Madrigal

Endpoints in MASH Cirrhosis Trials

Liver Forum March 2026

Pam, patient advocate

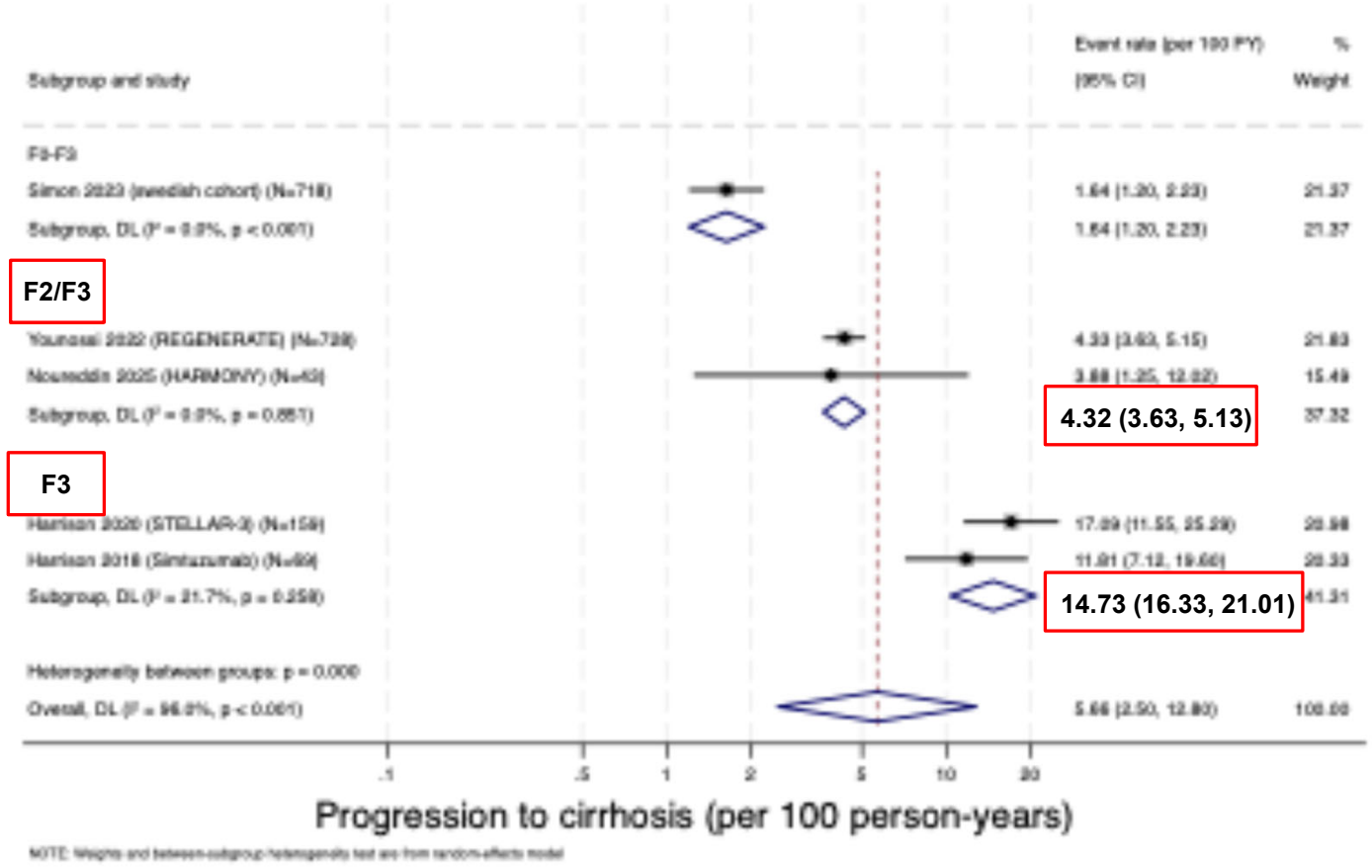
Biomarker Identification of Patients with Cirrhosis

- F2/F3 trials with histologic progression to cirrhosis at 4-5 years such as Regenerate, MAESTRO-NASH and Essence evaluated many serial biomarkers
  - Biomarkers assessed during these trials may allow prediction of progression to cirrhosis for subsequent trials
  - Caveats include issues related to identifying F4 on biopsy, early cirrhosis

- Biomarkers may be used to identify patients with cirrhosis to enroll in cirrhosis outcome studies
  - Examples of these trials include FGF21, MAESTRO trials
  - Patients who are F4 (with or without biopsy) with evidence of clinically significant portal hypertension based on biomarkers/imaging

- F4c trials- clinical outcomes and surrogates of decompensation, progression or regression

Meta-Analysis: Progression to Cirrhosis - Annual Rate



- Selection criteria:
  - MASH only
  - Biopsy-proven
  - Natural history or placebo group of clinical trials
- Methodology
  - Random-effects model (DerSimonian–Laird method) applied to estimate pooled event rates
  - Weights assigned by study sample size and variance

External Data : Month 48 Regenerate Outcome Events

	Placebo N=728	OCA 10 mg N=729	OCA 25 mg N=730
Any event	137	115	107
Event rate (95% CI)	18.8 (16.0 – 21.9)	15.8 (13.2 – 18.6)	14.7 (12.2 – 17.4)
Mean rate difference (95%CI)		-3.0 (-6.9 to 0.8)	-4.2 (-8.0 to -0.4)
Stratified log-rank test P value vs pbo		0.103	0.044
Stratified hazard ratio vs placebo (95%Ci)		0.814 (0.635 – 1.043)	0.772 (0.600 – 0.994)
Death	9 (1.2%)	7 (1.0%)	11 (1.5%)
Liver transplant	0	1 (0.1%)	1 (0.1%)
MELD progression	2 (0.3%)	4 (0.5%)	2 (0.3%)
Hospitalization for complications of hepatic decompensation	0	1 (0.1%)	2 (0.3%)
Ascites secondary to cirrhosis requiring medical intervention	0	3 (0.4%)	4 (0.5%)
Progression to cirrhosis	**126 (17.3%)**	**99 (13.6%)**	**87 (11.9%)**

- **87% of events are histologic conversion**
- **Progression to cirrhosis for placebo was 17%, with any outcome event 19%**
  - **40% event rate in F3 population which represented ~55% of patients in Regenerate**
  - **4.33% event per year (likely not evenly distributed)**
- **We assume discontinuations are censored**

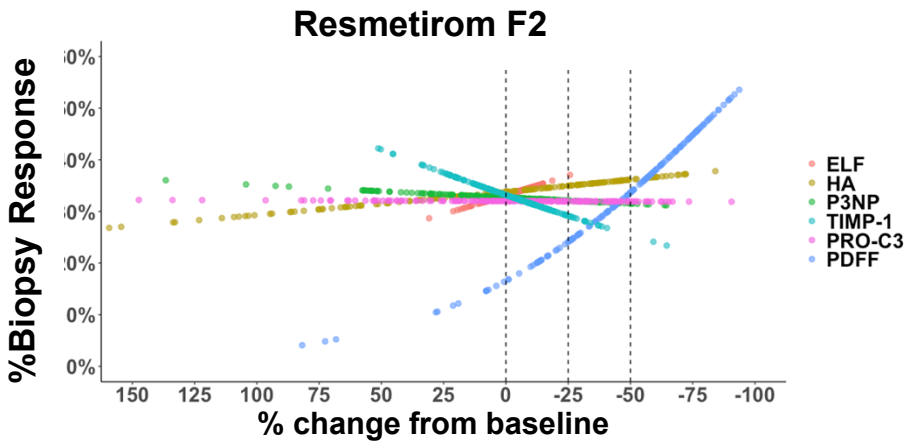
Serial Biomarkers in MAESTRO-NASH (F2/F3), Link to Fibrosis MAESTRO-NASH Progression to F4 and Clinical Outcomes

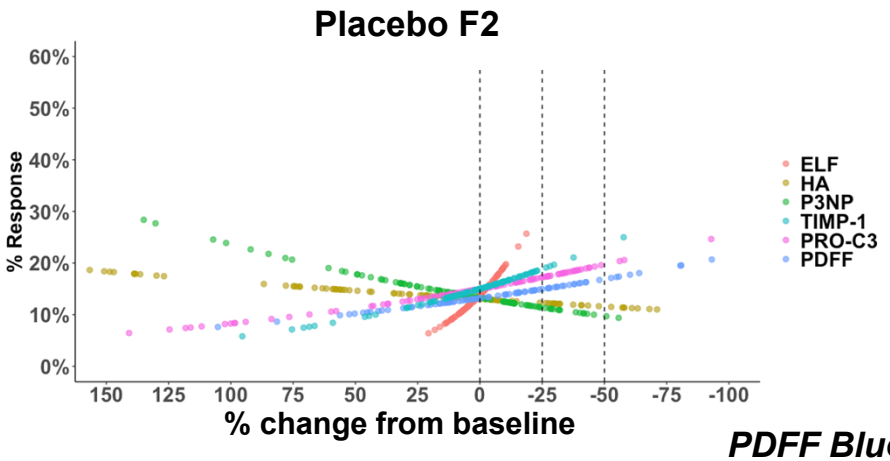
- Target specific serial biomarkers that show relationship to resmetirom mediated reduction in both MASH resolution and fibrosis improvement, liver and CV outcomes
  - MRI-PDFF
  - CAP
  - SHBG
  - Lipids

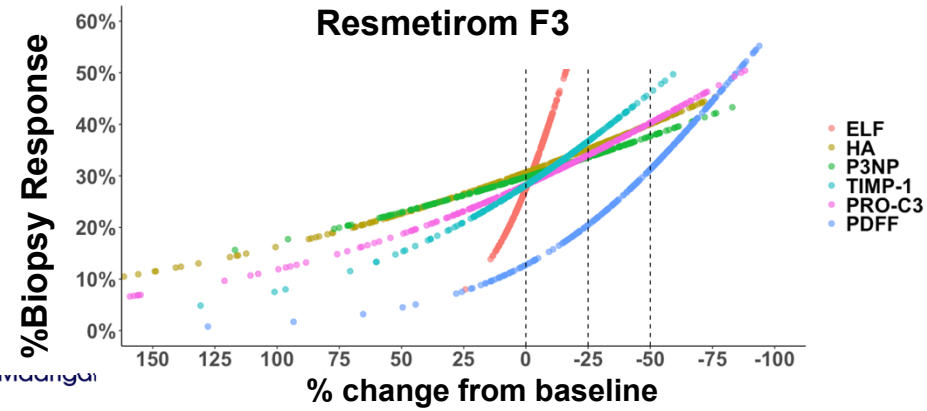
- Potential target-agnostic MASH imaging and fibrosis biomarkers
  - Liver Stiffness (MRE, VCTE)
  - Fibrosis synthesis biomarkers (ELF and components, PRO-C3)
  - Liver enzymes, adiponectin, CK-18 components
  - Genetic tests
  - Novel biomarkers

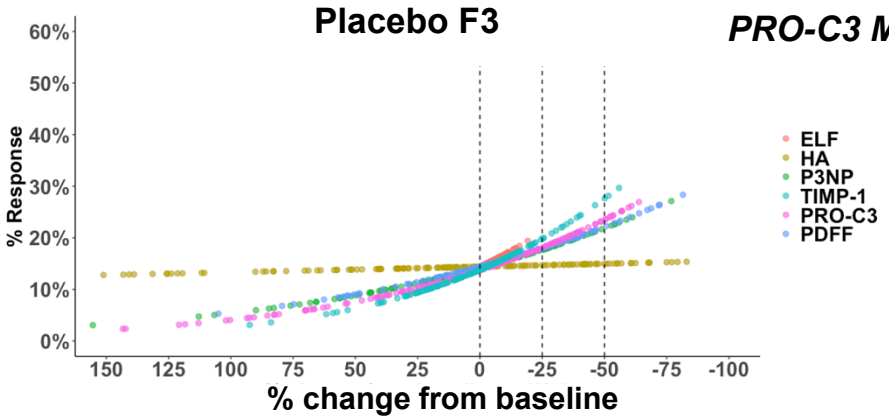
Correlation of Biomarker Responses with Fibrosis Improvement on Biopsies at Week52-MAESTRO-NASH

Regression analyses and machine learning to explore the full range of biomarker and % fibrosis improvement response









PDFF Blue
ELF Red
PRO-C3 Magenta

Clinical Trials- MASH Cirrhosis---Current Endpoints

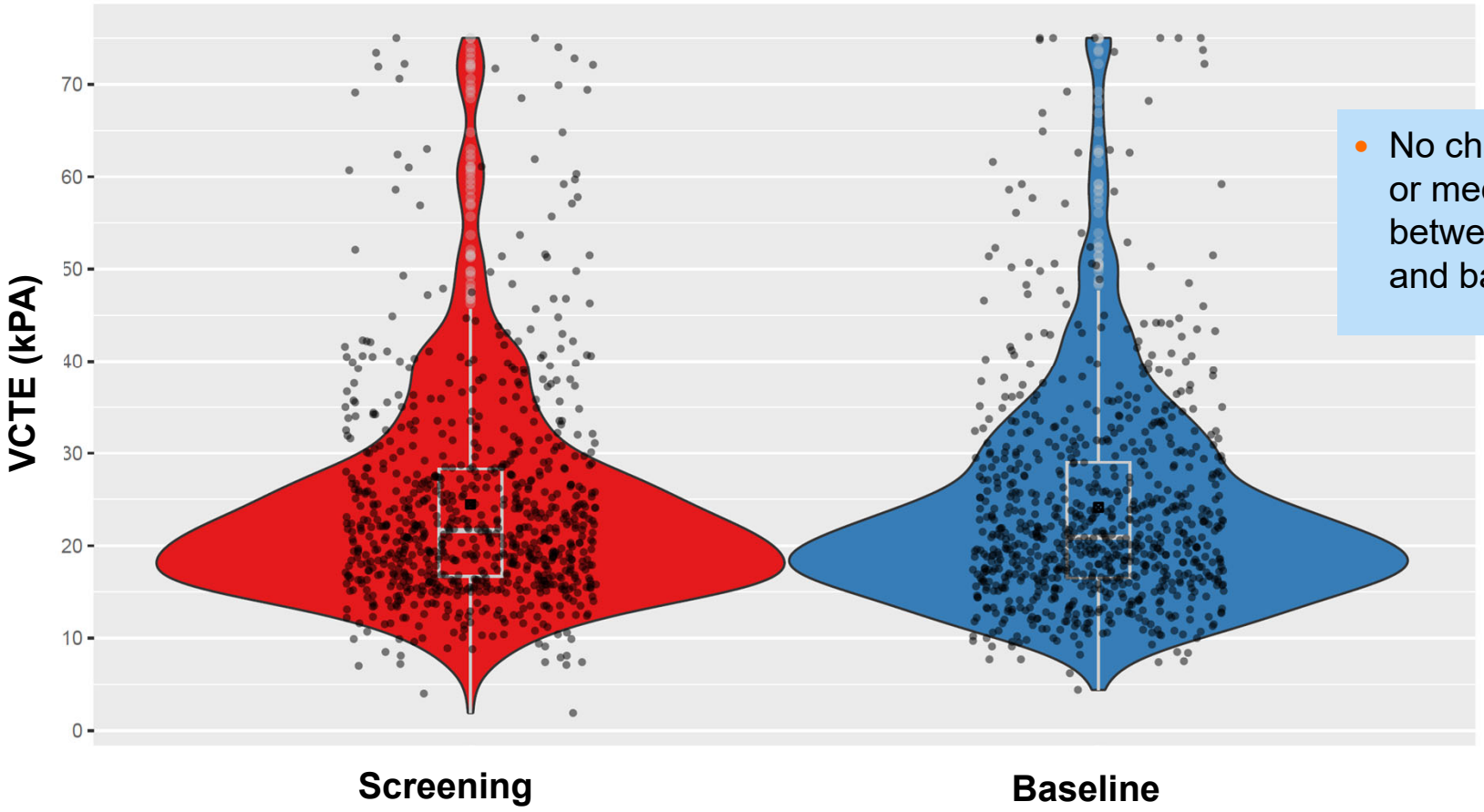
- Ongoing clinical trials in patients with MASH cirrhosis have several design types
- MAESTRO-NASH OUTCOMES-resmetirom
  - Time to liver related events (decompensation, liver transplant, all cause mortality)
  - Monitoring imaging and biomarkers
  - Liver biopsy not required at baseline (approximately half of F4 patients had a biopsy)or during study
- Navigate (Belapectin)
  - To prevent the formation of esophageal varices in patients with MASH cirrhosis and clinical signs of portal hypertension.
  - Requires serial esophogastropathy
- FGF21 serial biopsy F4c trials
  - 2 year serial liver biopsy to demonstrate regression from F4c to F3 (Symmetry)
  - Phase 3, Serial liver biopsy at Year 2, followed by clinical outcomes portion of trial

Key Features of MASH F4c -Patient Identification

MAESTRO-NASH Outcomes

- 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



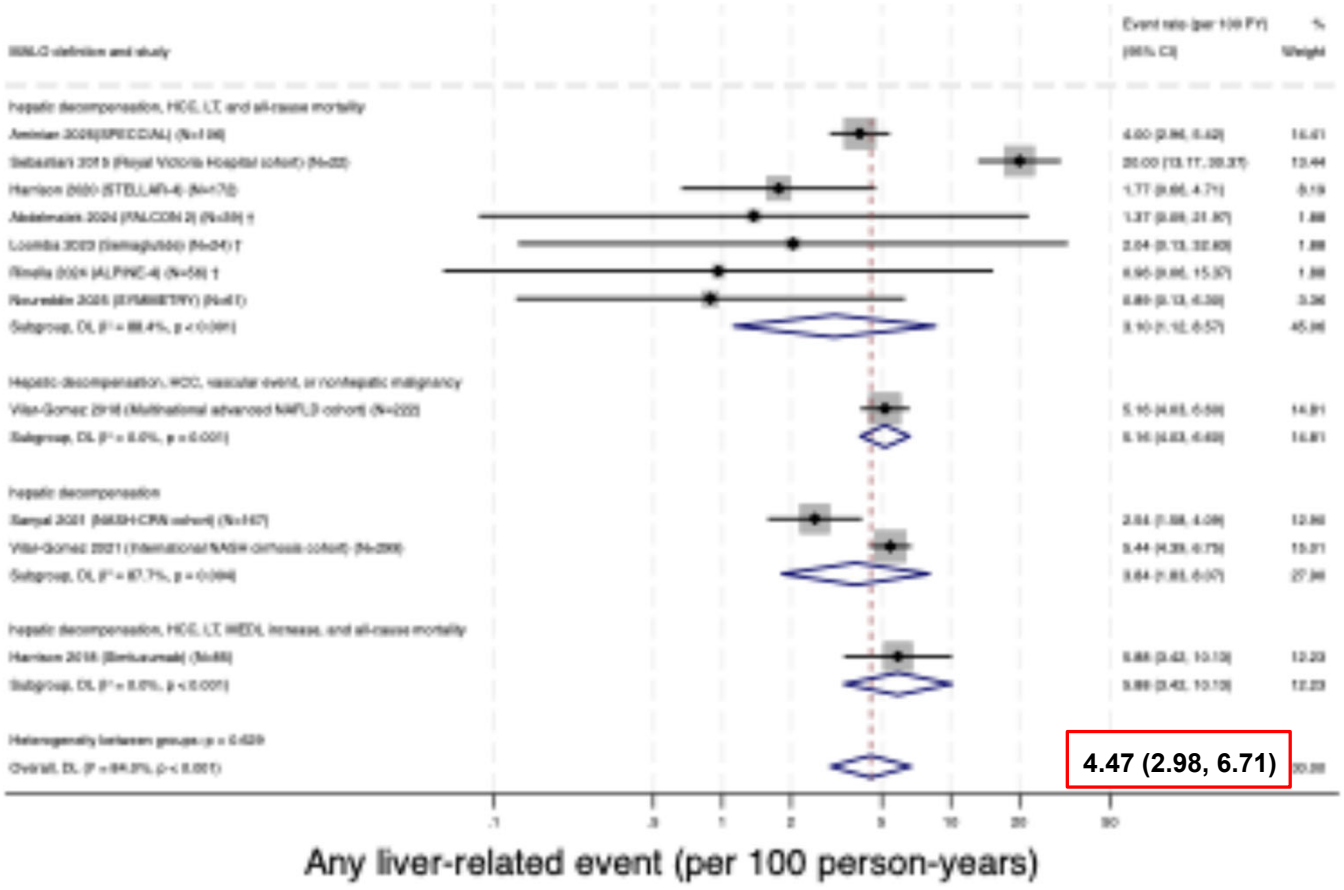
- No change in mean or median kPa between screening and baseline VCTEs

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)

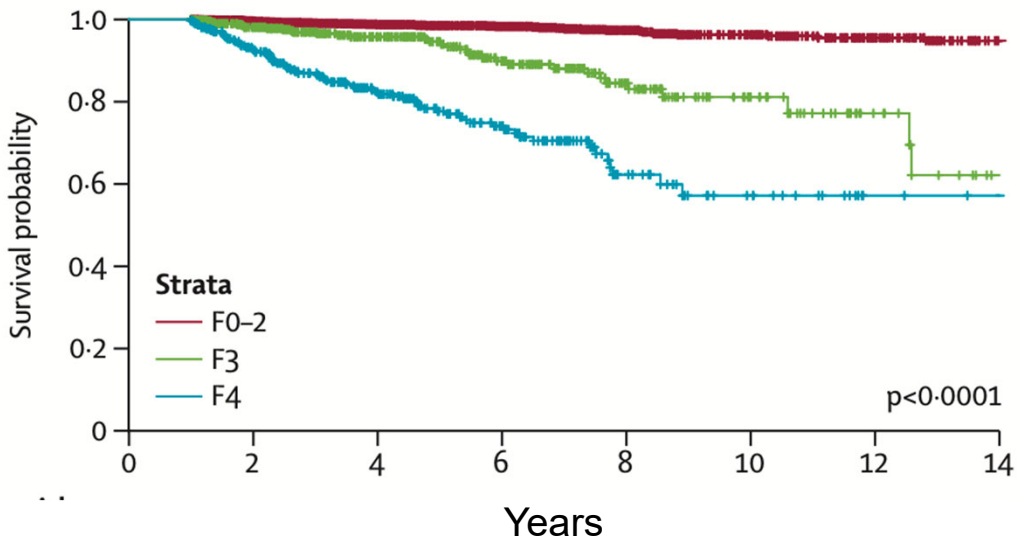
Liver-related Events in F4c - Annual Rate



- Selection criteria:
  - MASH F4c only
  - Biopsy-proven
  - Natural history or placebo group of clinical trials
- Methodology
  - Random-effects model (DerSimonian–Laird method) applied to estimate pooled event rates
  - Weights assigned by study sample size and variance
  - Zero-event studies included with 0.5 continuity correction for CI

Madrigal

Published Individual Patient Data Analysis from 25 MASLD/MASH Studies



- Study population: 2,518 NAFLD, of which 310 F4 (biopsy-confirmed)
- Median FU: 57 months (IQR 33–91)
- F4 events:
  - **71/310 (22.9%) reached the composite endpoint at Year 4**
    - All-cause mortality
    - Liver transplantation
    - HCC
    - decompensation (ascites, hepatic encephalopathy, or variceal bleeding)
    - Progression to MELD ≥15
  - **≈ 4.8–5.0% per year**

Mózes FE et al. Lancet Gastroenterol Hepatol. 2023 Aug;8(8):704-713

Regression Versus Progression in F4c-Simtuzumab/Selosertib

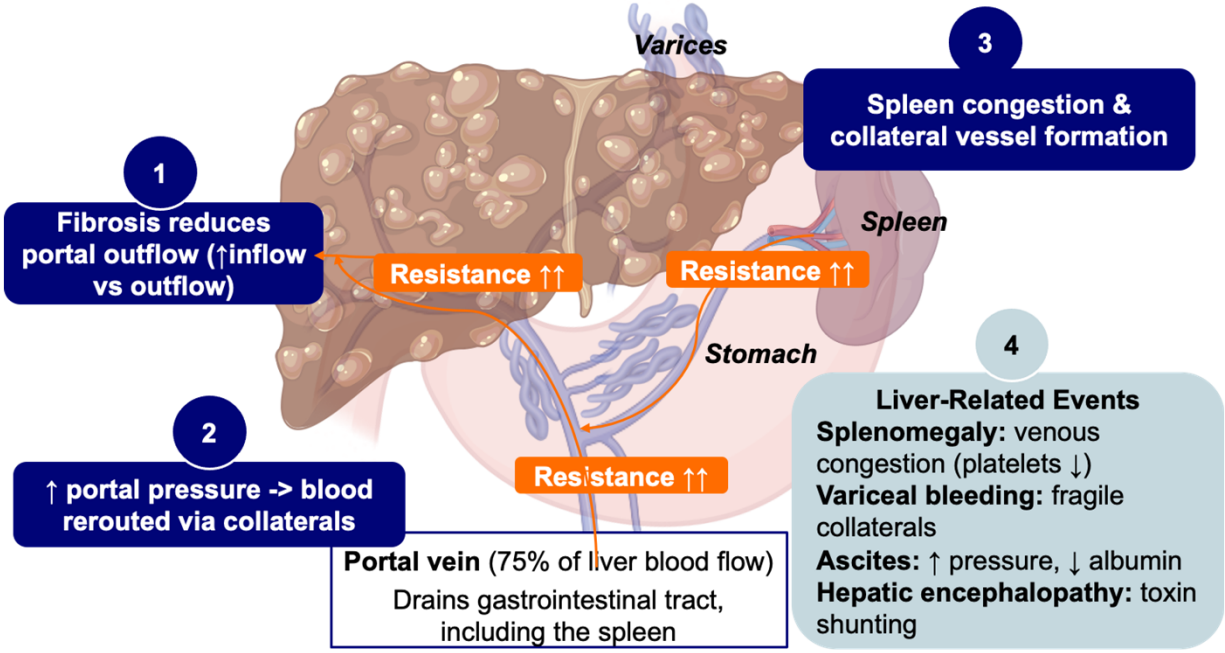
TABLE 2 Baseline factors and changes in clinical parameters associated with cirrhosis regression

	Baseline (median [Q1, Q3])			LS mean change from baseline (95% CI)[a]		
	Cirrhosis regression (n = 176)	No regression (n = 957)	p value	Cirrhosis regression (n = 176)	No regression (n = 957)	p value
NITs						
ELF score	10.06 (9.40, 10.74)	10.77 (10.13, 11.45)	**<0.0001**	0.12 (0.00, 0.24)	0.29 (0.23, 0.34)	**0.0076**
PIIINP	9.86 (7.86, 13.82)	13.21 (9.78, 17.49)	**<0.0001**	0.66 (−0.34, 1.66)	1.40 (0.94, 1.85)	0.1601
TIMP-1	263.3 (223.2, 307.2)	311.2 (260.3, 388.9)	**<0.0001**	−8.2 (−22.4, 6.1)	11.6 (5.0, 18.2)	**0.0087**
Hyaluronic acid	90.41 (51.57, 159.59)	154.65 (90.08, 272.78)	**<0.0001**	64.15 (14.71, 113.58)	121.56 (98.43, 144.70)	**0.0275**
FIB-4	2.03 (1.28, 2.69)	2.70 (1.90, 4.00)	**<0.0001**	0.23 (−0.01, 0.46)	0.45 (0.34, 0.56)	0.0645
NFS	0.26 (−0.74, 1.15)	0.90 (0.02, 1.83)	**<0.0001**	0.24 (0.12, 0.35)	0.31 (0.26, 0.36)	0.2188
Liver stiffness by VCTE, kPa[b]	14.0 (10.9, 20.2)	21.8 (15.7, 31.6)	**<0.0001**	−3.9 (−6.5, −1.4)	0.4 (−1.3, 2.2)	**<0.0001**
HVPG, mm Hg[c]	8.3 (6.0, 10.0)	12.5 (9.5, 17.0)	**<0.0001**	−1.4 (−3.0, 0.1)	0.2 (−0.2, 0.7)	**0.0454**

- Data from two large, randomized, placebo-controlled studies of simtuzumab (NCT01672879) and selonsertib (STELLAR-4,NCT03053063) in compensated cirrhosis due to NASH. Sanyal et al, DOI: 10.1002/hep.32204
- Patients with and without regression on biopsy were assessed for baseline and changes in measures of portal hypertension including hepatic venous pressure gradient (HVPG) and serial biomarkers
- Reduction in VCTE was correlated with regression, including reduction of CSPH as measured on HPVG

Non-invasive Measures of Clinically Significant Portal Hypertension (CSPH)

CSPH is Responsible for the Most Severe and Fatal Complications of Cirrhosis[1]

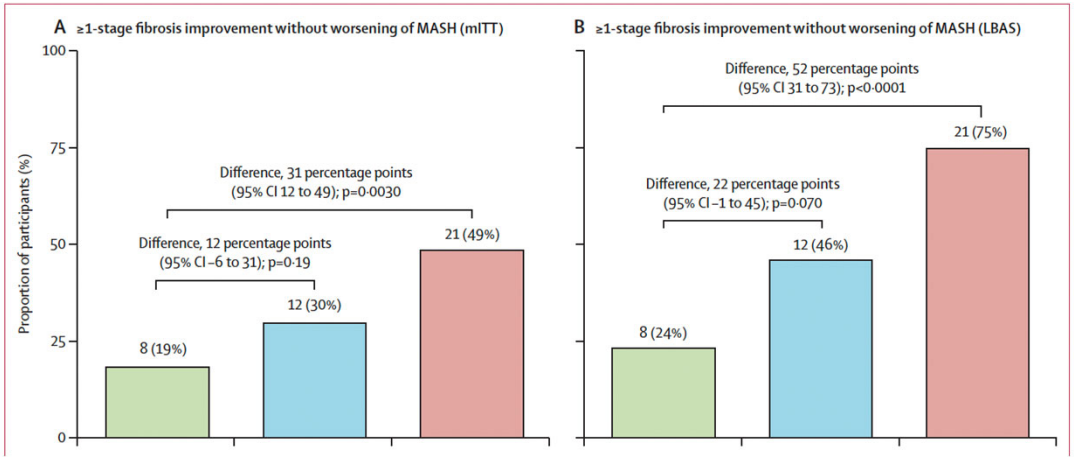


Risk of CSPH	Baveno	Anticipate-NASH
CSPH	VCTE ≥ 25	Logit = −3.9529402 + 2.2835809 × ln(LSM) – 0.033777725 × BMI – 0.014490895 × Platelet count.
Probable CSPH	20 ≤ VCTE < 25 & PLT < 150 **or** 15 ≤ VCTE < 20 & PLT < 110	
No/Low CSPH	Not meeting above criteria	

Key Details of the Formula:
Log(LSM): Liver Stiffness Measurement in kPa using transient elastography (e.g., FibroScan). BMI: Body Mass Index; Platelet count

- Baveno is used to estimate probability of CSPH and liver events
  - Highly dependent on liver stiffness measure (and platelet count)
- Baveno criteria for high BMI patients may need adjustment for BMI which increases the liver stiffness
- The Anticipate-NASH score predicts a continuous percentage likelihood of CSPH

Symmetry F4c Study with Efruxifermin

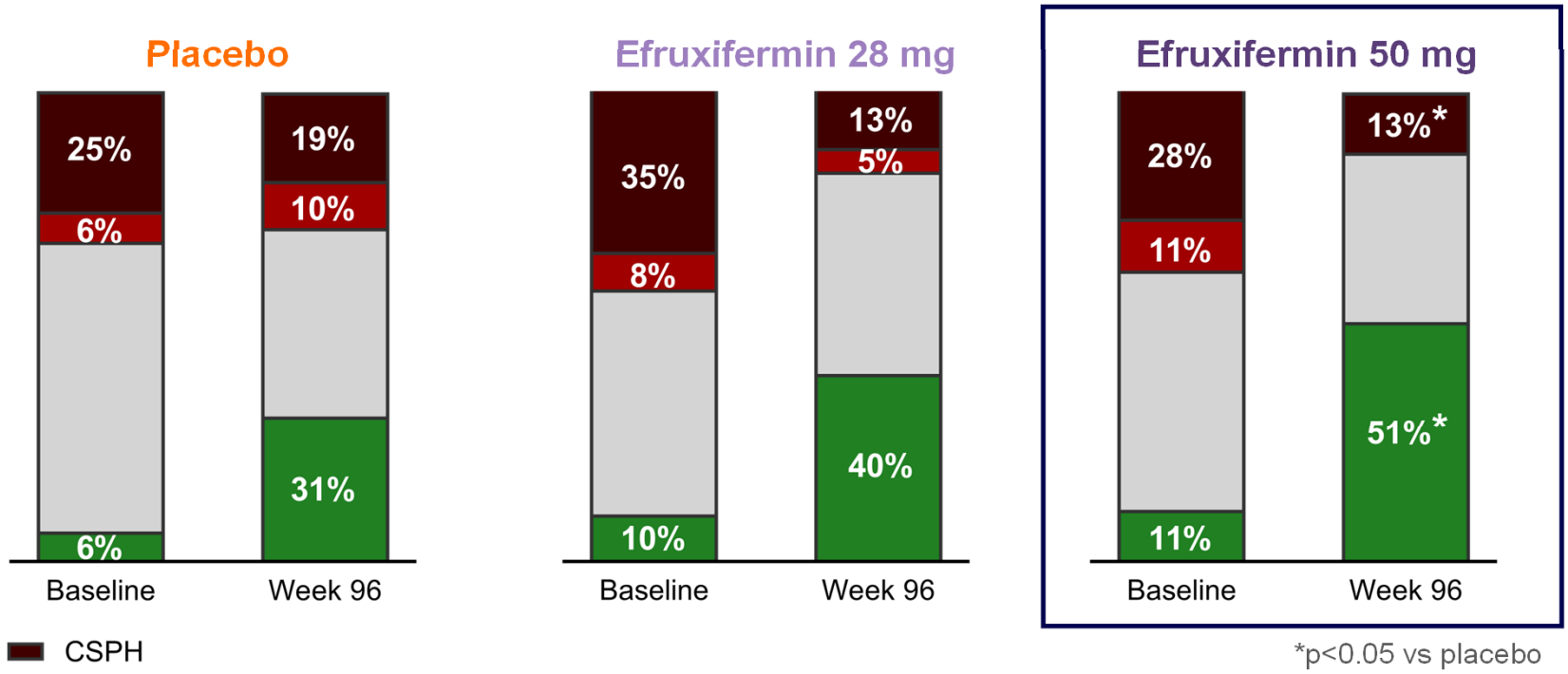


	Placebo (n=43)	Efruxifermin 28 mg (n=40)	p value	Efruxifermin 50 mg (n=43)	p value
Liver stiffness, kPa					
Absolute change from baseline	−0·6 (1·0)	−4·0 (1·1)	..	−7·2 (1·1)	..
LSM difference versus placebo (95% CI)	..	−3·4 (−6·2 to −0·5)	0·021	−6·6 (−9·4 to −3·7)	<0·0001

- Serial liver biopsy at 96 weeks in F4c showed reduction in fibrosis and improvement in biomarkers, including VCTE and measures of CSPH using Baveno criteria (NEJM 2025)
- Few clinical outcomes in serial biopsy F4c trials

Efruxifermin Significantly Improved CSPH Risk Profile
Overall Population

CSPH Could be Ruled Out for Over Half of Efruxifermin 50 mg Participants at Week 96



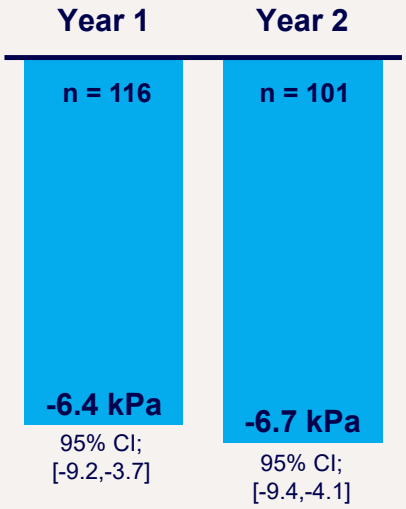
*p<0.05 vs placebo

*p<0.05 for proportion of participants at Week 96 in given CSPH category (CSPH or Probable CSPH; Rule Out CPSH).
Includes participants with paired Baseline and Week 96 data (N=135).

Madrigal

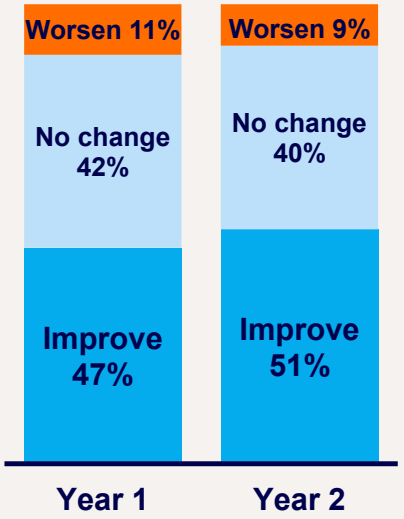
122 Patients with F4c Treated with Resmetirom for Two Years—Change in Liver Stiffness Measures

Mean Change from Baseline of 6.7 kPa

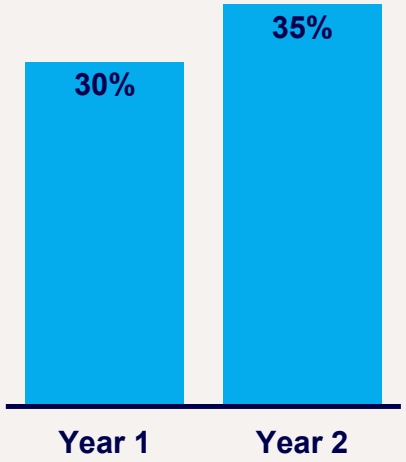


Statistically significant compared to baseline

>50% of Patients Achieved ≥25% Reduction in Liver Stiffness

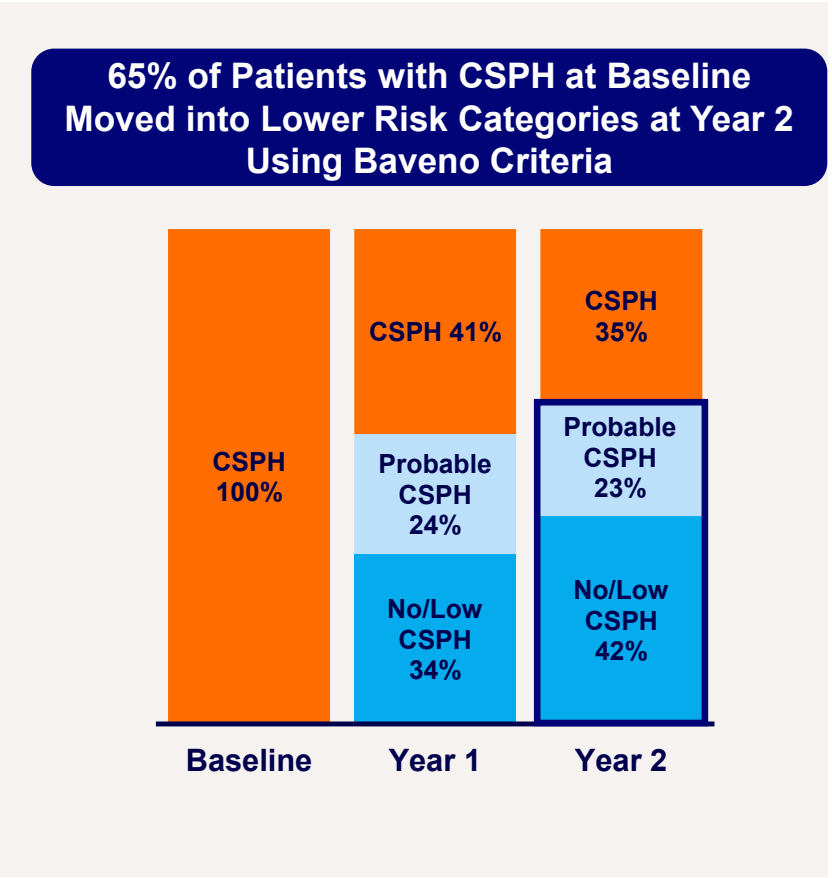


35% of Patients Met Criteria for Regression from F4 to F3[1]



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

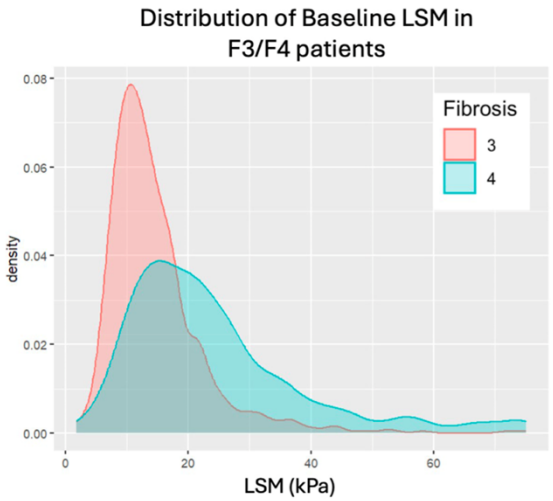
Potential Benefit of Resmetirom in F4c-Reduction in Clinically Significant Portal Hypertension (CSPH) Risk- Baveno Criteria



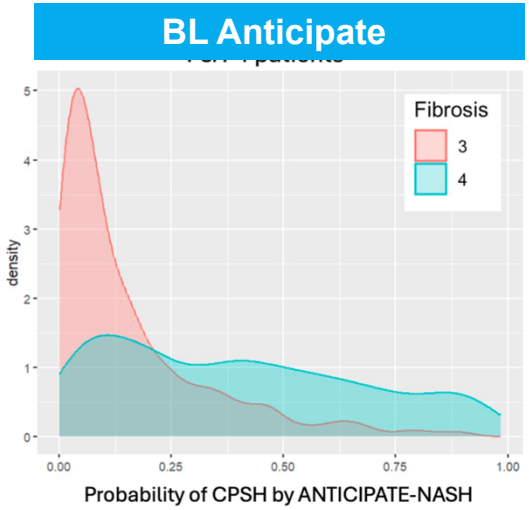
1. de Franchis R, et al. Baveno VII - Renewing consensus in portal hypertension. J Hepatol. 2022;76(4):959-974; image adapted from Mayo Clinic: Esophageal varices - Symptoms and causes - Mayo Clinic.

Anticipate-NASH Outcome Data

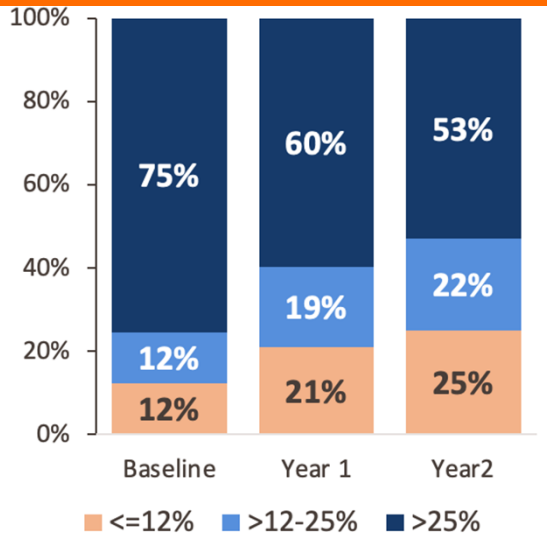
Baseline (BL) VCTE



BL Anticipate



Resmetirom-F4c (ANTICPATE %CSPH)



- Anticipate-NASH adjusts for BMI that tends to increase liver stiffness
- Validation: Anticipate CSPH Probability of <25% predicted lack of clinical outcomes in patients with F3 and F4 Gastroenterology 2025; :1–10
- Resmetirom shifted patients into lower Anticipate risk categories in a two year F4c study; patients with clinical events had higher CSPH prediction based on Anticipate-NASH scores at baseline

Summary/Next steps

- Biomarkers may be used to predict progression to F4c in long-term studies of F2/F3 patients-data from ongoing serial biopsy studies
- Biomarkers effectively identify patients with cirrhosis including biomarker evidence of CSPH in F4c trials
- Measures of CSPH and improvement in CSPH may be a potential “reasonably likely surrogate endpoint” to predict clinical outcomes (decompensation events) in patients with MASH and compensated cirrhosis