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Liver Forum 17
LSM by VCTE as a Reasonably Likely Surrogate Endpoint:
Review of the latest clinical evidence

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Disclosures

- Full-time employee of Echosens.

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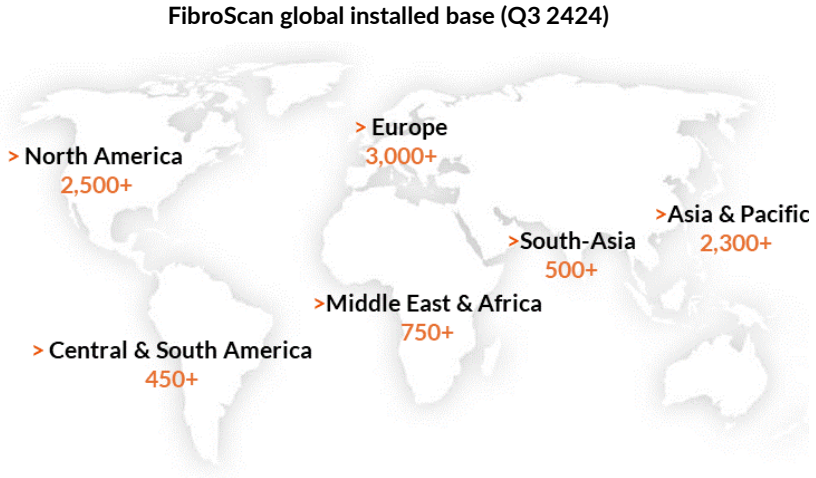
Background and scope

- LSM by VCTE is a well-established biomarker used in routine clinical practice
- Widely available globally
- Large body of clinical evidence on its usefulness for the for the management of patients with MASLD
- Recommended in numerous guidelines (AGA, ACEE, AASLD, APASL, EASL, EASD, EASO, ALEH, …)



- Goal of today's presentation is to review the latest clinical evidence supporting the use LSM by VCTE as a Reasonably Likely Surrogate Endpoint in MASLD by focusing on:
  - Prognosing clinical outcomes
  - Monitoring clinical outcomes
  - Monitoring treatment response

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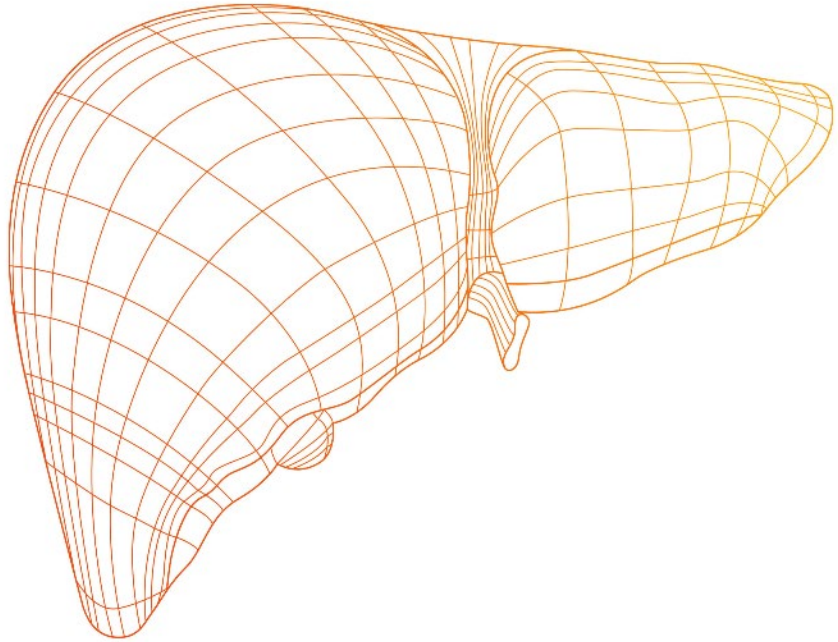

1. Introduction
2. **Prognosing risk of clinical outcomes**
3. Monitoring risk of clinical outcomes
4. Monitoring treatment response
5. Take home messages

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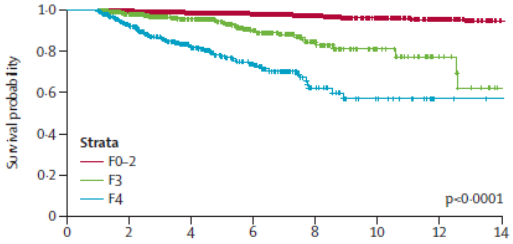
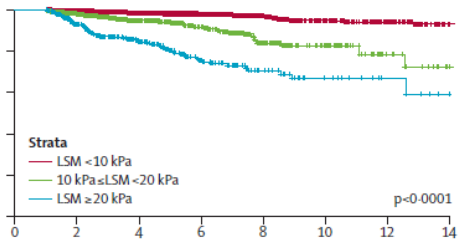
LITMUS: individual patient data meta-analysis

Aggregated survival probabilities

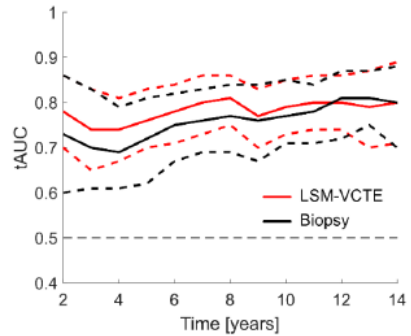


Number at risk (number censored)								
F0–2	1698	1488	1019	696	415	252	134	49
	(0)	(209)	(668)	(979)	(1256)	(1412)	(1530)	(1612)
F3	511	434	281	177	92	43	18	6
	(0)	(70)	(215)	(310)	(390)	(437)	(461)	(471)
F4	310	256	164	101	38	21	8	5
	(0)	(34)	(101)	(151)	(205)	(220)	(233)	(236)



Number at risk (number censored)								
LSM <10 kPa	1527	1346	923	628	386	236	124	44
	(0)	(177)	(594)	(880)	(1121)	(1262)	(1374)	(1451)
10 kPa≤LSM <20 kPa	718	614	393	261	127	66	29	14
	(0)	(96)	(299)	(421)	(544)	(604)	(640)	(654)
LSM ≥20 kPa	274	218	148	85	33	15	7	2
	(0)	(40)	(91)	(139)	(186)	(202)	(210)	(214)

Time-dependent AUC (95% CI)



	3 years	5 years	10 years
N	1816	1193	316
Fibrosis stage by histology	0.70 (0.61-0.83)	0.72 (0.62-0.81)	0.77 (0.71-0.85)
LSM by VCTE	0.74 (0.65-0.83)	0.76 (0.70-0.83)	0.79 (0.73-0.85)

Mozes LGH 2023 [PMID: 37290471]	
N	2518
Median [IQR] follow-up	57 [33-91] months
Endpoint composition	all-cause mortality, HCC, liver transplantation, or cirrhosis complications (ie, ascites, variceal bleeding, hepatic encephalopathy, or progression to a MELD score ≥15)
Endpoint rate	5.8%

In this real-world evidence cohort from tertiary care centers:

- Patients with LSM by VCTE ≥ 10 kPa have higher the risk of all cause mortality and major liver related outcomes
- LSM by VCTE provides similar prognostic information to fibrosis stage assessed by histology

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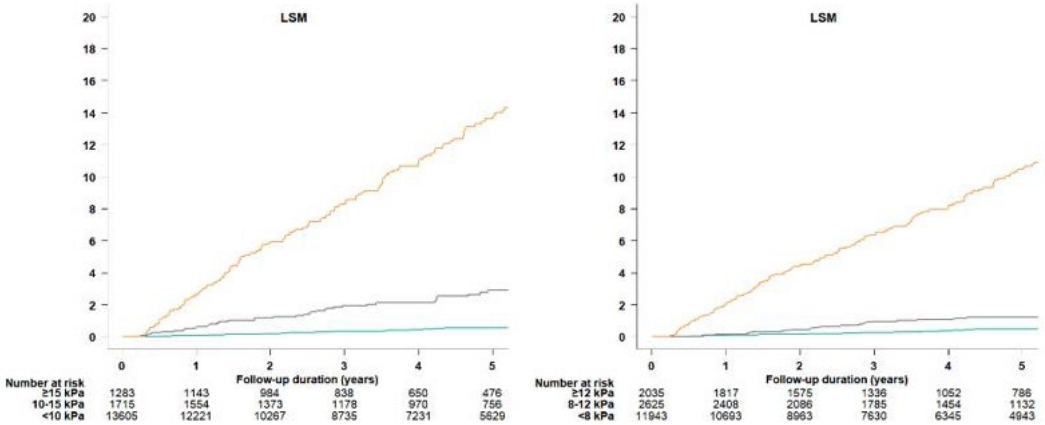
VCTE-Prognosis cohort: global natural history cohort

Cumulative incidence



Lin JAMA 2024 [PMID: 38512249]	
N	16,603
Median [IQR] follow-up	52 [25-85] months
Endpoint composition	HCC, hepatic decompensation (ascites, variceal hemorrhage, hepatic encephalopathy, or hepatorenal syndrome), liver transplant, and liver-related deaths
Endpoint rate	1.9%

Time-dependent AUC (95% CI)

	Integrated	3 years*	5 years*
Fibrosis stage by histology	0.82 (0.77-0.86) [n=3532]	0.85 (0.81-0.88)	0.86 (0.83-0.89)
LSM by VCTE	0.85 (0.82-0.88) [n=16,603]	0.86 (0.81-0.90)	0.86 (0.82-0.89)

*Head-to-head comparison in 3,532 patients - not significantly different
Unpublished - Courtesy of Pr V. Wong

In this largest to date, global natural history cohort:

- Baseline LSM by VCTE is associated with the risk of major liver related outcomes, and the risk significantly increase when ≥ 10 kPa
- Baseline LSM by VCTE provides similar prognostic information to fibrosis stage assessed by histology

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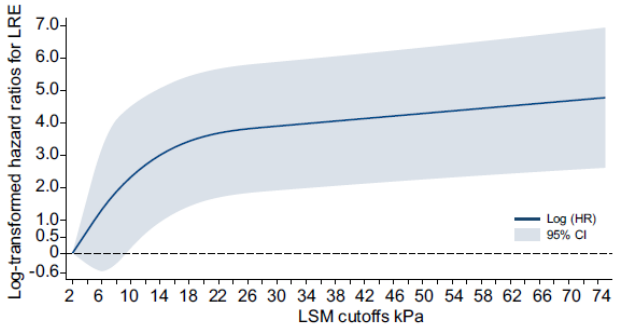
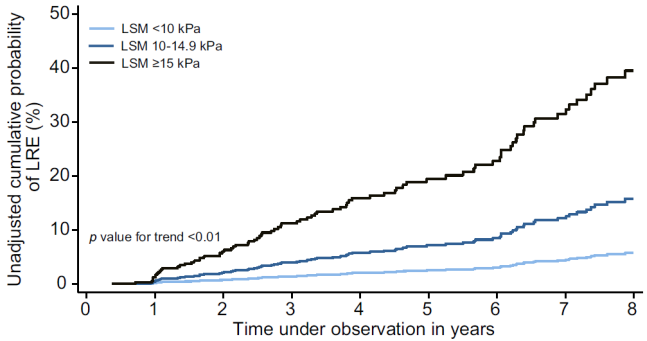
NASH CRN: large prospective study

- Dose-dependent association between first LSM and risk of LREs



- Cumulative probability



Gawrieh J Hepatol 2024 [PMID: 38762169]	
N	1,403
Mean [range] follow-up	53 [5-114] months
Endpoint composition	liver-related death, liver transplant, hepatocellular carcinoma, MELD >15, development of varices, or hepatic decompensation
Endpoint rate	6.3%

In this prospective study with longitudinal follow-up of patients with biopsy proven NAFLD:

- the inflection point at which LRE risk begins to significantly increase was an LSM of 10 kPa
- Compared with LSM <10 kPa, the risk of LREs was increased by about 2- and 8-fold in persons with LSM 10-14.9 and ≥ 15 kPa, respectively

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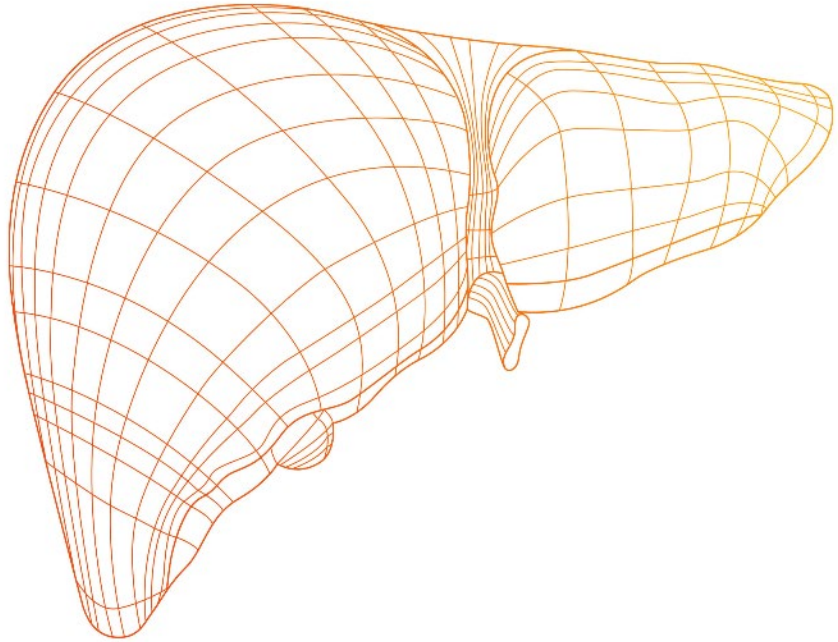

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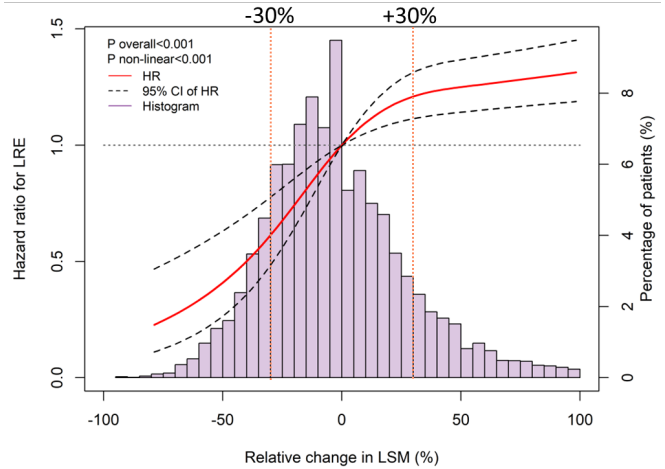
VCTE-Prognosis cohort: global natural history cohort

Association between the relative change of LSM and risk of LRE



First VCTE	% change	% of patients	LRE per 1,000 py
Low risk (LSM <10 kPa) N=9,009	>30% ↓	10%	1.4
	Stable	75%	0.7
	>30% ↑	15%	2.4
Intermediate risk (LSM 10-15 kPa) N=1,120	>30% ↓	37%	0.7
	Stable	52%	7.4
	>30% ↑	11%	17.2
High risk (LSM ≥15 kPa) N=791	>30% ↓	45%	16.1
	Stable	45%	33.3
	>30% ↑	10%	55.9

Lin JAMA 2024 [PMID: 38512249]	
N	10,920 (with LSM at two time-points)
Median [IQR] time interval between LSM	15 [11-28] months
Median [IQR] follow-up	34 [12-56] months
Endpoint composition	HCC, hepatic decompensation (ascites, variceal hemorrhage, hepatic encephalopathy, or hepatorenal syndrome), liver transplant, and liver-related deaths
Endpoint rate	1.1%

In this largest to date, global natural history cohort:

- In patients with a baseline LSM ≥ 10 kPa, a +/-30% change in LSM reflects disease progression and regression and is predictive of LREs

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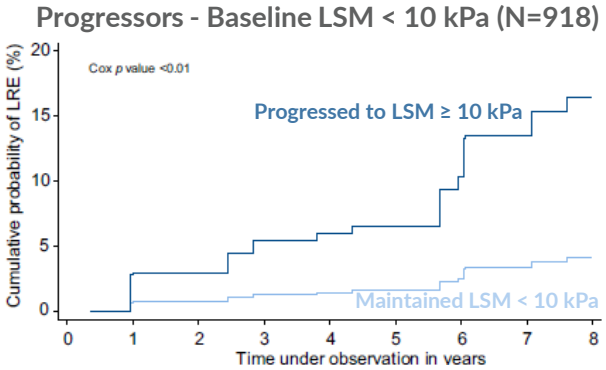
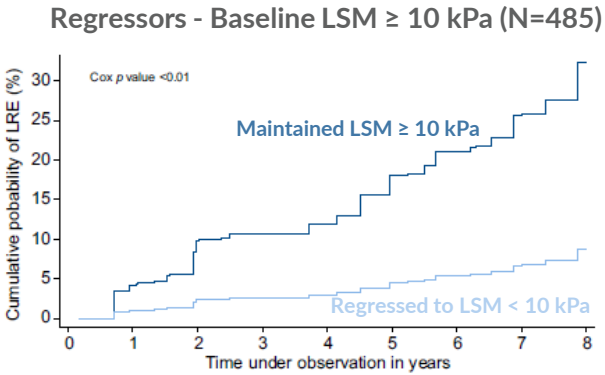
NASH CRN: large prospective study

- Cumulative proportion of patients with of LRE by change in LSM status





Gawrieh J Hepatol 2024 [PMID: 38762169]	
N (NAFLD spectrum)	1,403 (F0 → F4)
Region	USA
Mean [range] follow-up	53 [5-114] months
Endpoint composition	liver-related death, liver transplant, hepatocellular carcinoma, MELD >15, development of varices, or hepatic decompensation
Endpoint rate	6.3%

In this prospective study with longitudinal follow-up of patients with biopsy proven NAFLD:

- Progression to cACLD (LSM by VCTE ≥ 10 kPa) is associated with a 4-fold increase in LRE risk, whereas regression from cACLD is associated with a 75% decrease in this risk
- Same was also observed in sensitivity analyses evaluating 30% changes in LSM from different baseline LSM thresholds

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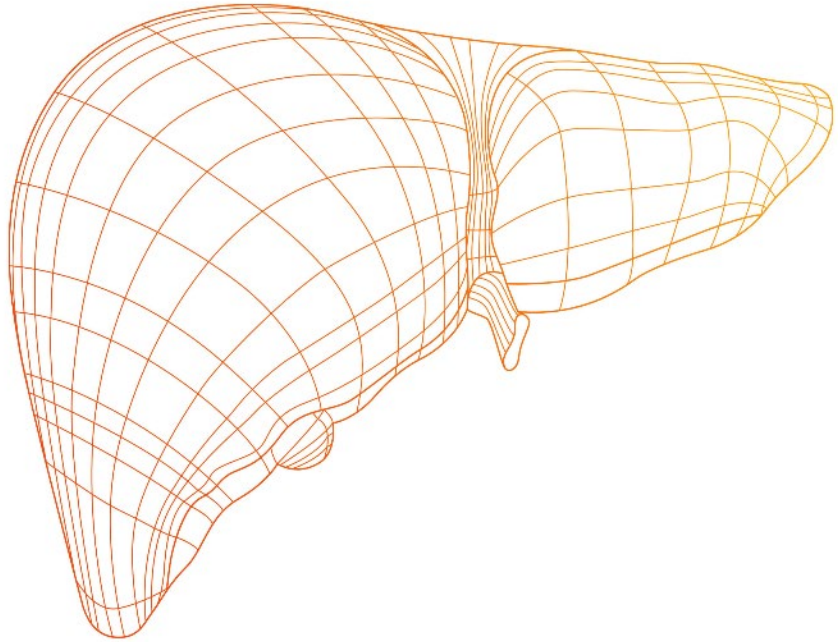

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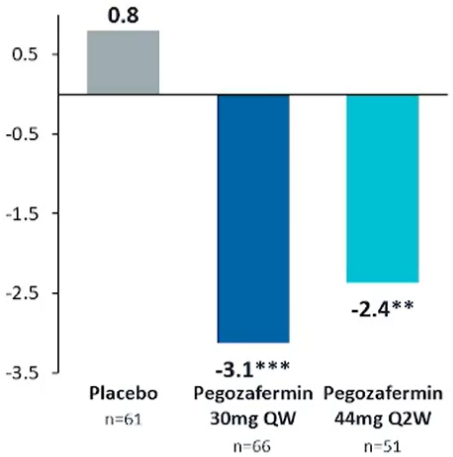
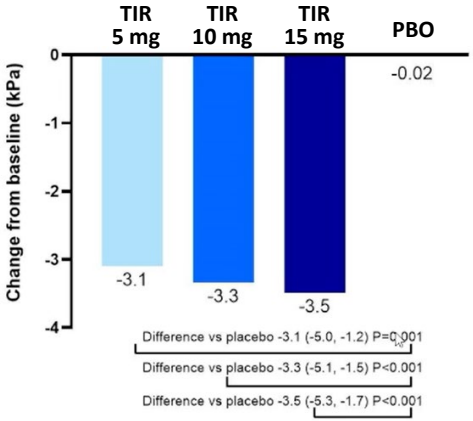
Changes in LSM by VCTE in recent Phase 2b trials

ENLIVEN
Pegozafermin – 24 weeks
Loomba NEJM 2023 [PMID: 37356033]

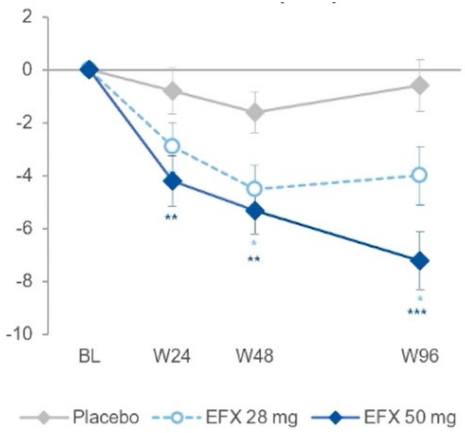


**p<0.01, *** p<0.001 versus placebo

SYNERGY-NASH
Tirzepatide – 52 weeks
Loomba NEJM 2024 [PMID: 38856224]



HARMONY
Efruxifermin – 96 weeks
Harrison EASL ILC 2024 – LBO 002



*p<0.05, **p<0.01, *** p<0.001 versus placebo

- LSM by VCTE absolute change from baseline is significantly different in the active arms compared to placebos in trials involving drugs with different mode of actions (FGF21 analogue, GLP-1/GIP dual receptor agonist) regardless of study duration

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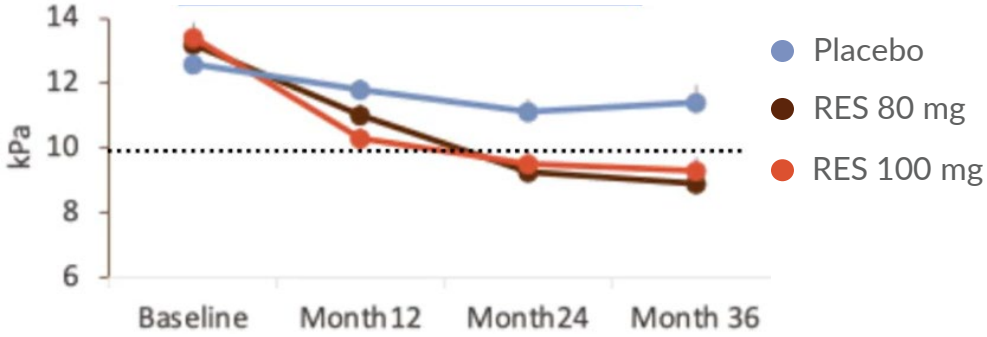
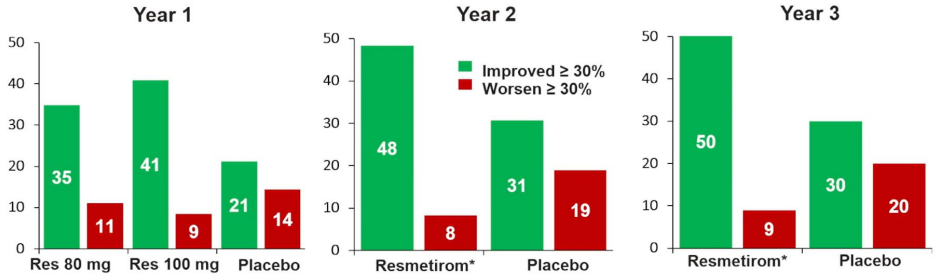
MAESTRO-NASH

Phase 3 – Resmetirom – 36 months

- LSM by VCTE over time across the three treatment arms



- LSM by VCTE responder analysis



In this on-going Phase 3 trial:

- LSM by VCTE decreases in the treated arms is sustained until 3 years of follow-up compared to PBO and going below 10 kPa
- Responder analyses (using a +/- 30% change from baseline) also reflects improvement relative to PBO with LSM-worsening in less than 10% of patients in RES-treated patients

Schattenberg EASL ILC 2024 – OS 117

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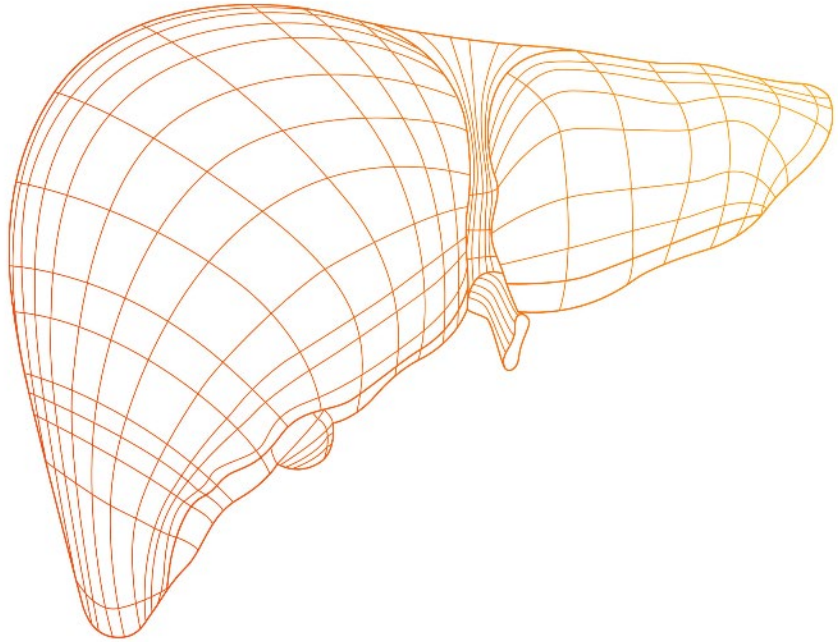

1. Introduction
2. Monitoring changes in liver steatosis
3. Monitoring changes in liver fibrosis
4. Monitoring changes in at-risk NASH
5. **Take home messages**

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Take home messages

There is now strong and converging clinical evidence showing that:

- The risk of liver-related events (LRE) is significantly increased in MASLD patients with LSM by VCTE ≥ 10 kPa
- The higher LSM is, the higher the risk of LRE is
- When assessed serially, a 30%-decrease in LSM by VCTE is associated with a decreased risk of LRE, while a 30%-increase in LSM is associated with an increased-risk of LRE in MASLD patients.
- LSM by VCTE absolute change from baseline is significantly different in the active arms compared to placebos in trials involving drugs with different mode of actions (FGF21 analogue, GLP-1/GIP dual-RA) confirming what has already been reported with FXR, GLP-1 RA, THR-β agonist…
- In the on-going Phase 3 trial, after 3 years of treatment, compared to placebo, patients receiving Resmetirom show:
  - A sustained decrease in LSM by VCTE
  - LSM values reaching less than 10 kPa
  - A higher proportion of patients with a 30% LSM improvement
  - A lower proportion of patients with a 30% LSM worsening

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because liver health matters