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Liver Forum 14

Monitoring of treatment response with FibroScan-based biomarkers

Céline Fournier, PhD
Chief Medical Officer

Disclosures

- Full-time employee of Echosens.

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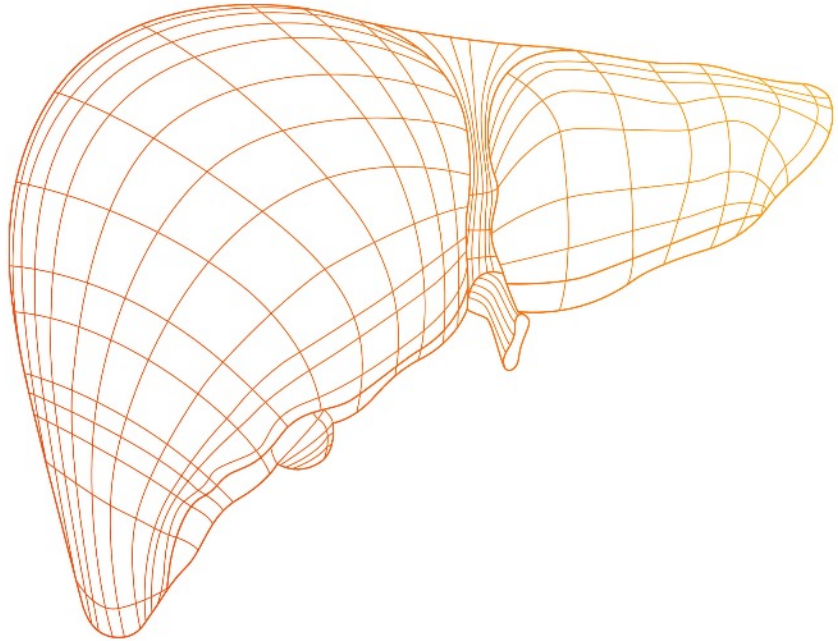
Content



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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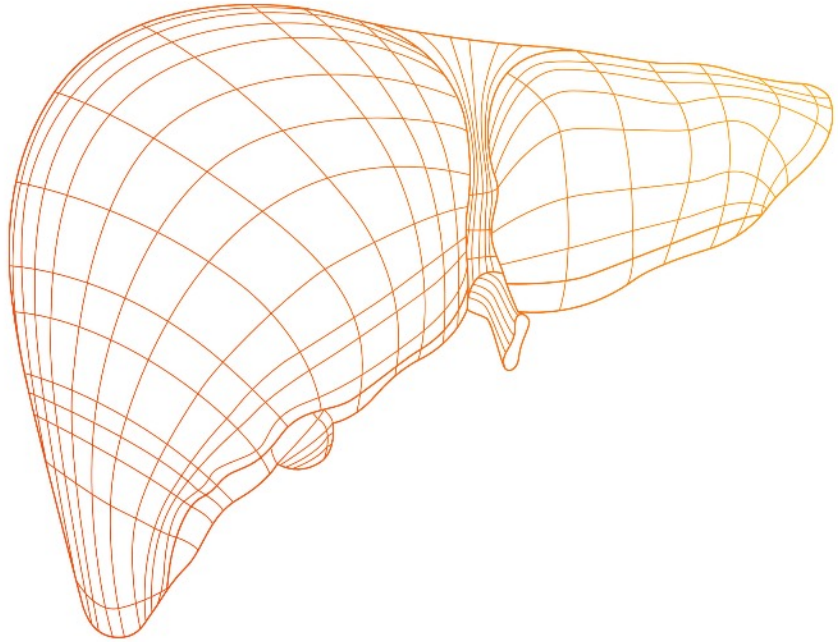

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Monitoring treatment response

- Definition from the BEST Resource – FDA/FNIH

A monitoring biomarker is a biomarker **measured repeatedly** for assessing status of a disease or medical condition or **for evidence of** exposure to (or **effect of**) **a medical product** or an environmental agent.

- In NASH drug development, the expected response may depend on:
  - the trial phase: early vs late
  - the mode of action of the compound: metabolic vs anti-fibrotic
  - the population of interest: non-cirrhotic vs compensated cirrhosis

Examples:

- Early phase proof of concept trial of a drug expected to have a metabolic effect -> monitoring change in steatosis
- Phase 3 trial in non cirrhotic of a drug with an antifibrotic effect -> improvement of fibrosis stage

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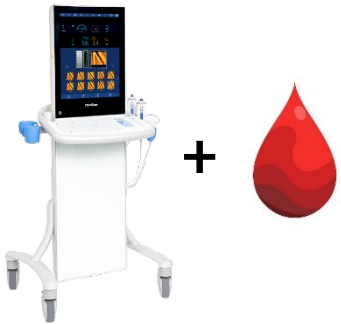
FibroScan-based biomarkers in NAFLD



LSM by VCTE	• Liver stiffness measurement in kPa @ 50Hz shear wave frequency • Assessment of liver fibrosis
CAP	• Measurement of ultrasound attenuation (in dB/m) • Assessment of liver steatosis
SSM by VCTE	• Spleen stiffness measurement in kPa @ 100Hz shear wave frequency • Assessment of portal hypertension
FAST	• Combines LSM by VCTE, CAP and AST • Probability of **at-risk NASH (NASH + NAS ≥ 4 + F ≥ 2)**
FibroMeter VCTE	• Combines LSM by VCTE, PLT, INR, AST, GGT, A2M, sex, age • Probability of **significant fibrosis (F ≥ 2)**
Agile 3+	• Combines LSM by VCTE, AST, ALT, PLT, diabetes status, sex, age • Probability of **advanced fibrosis (F ≥ 3)**
Agile 4	• Combines LSM by VCTE, AST, ALT, PLT, diabetes status, sex • Probability of **cirrhosis (F=4)**

A2M: alpha2-macroglobuline; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CAP: controlled attenuation parameter; GGT: gamma glutamyl transferase; INR: international normalized ratio; LSM: liver stiffness measurement; PLT: platelets count; SSM: spleen stiffness measurement; VCTE: vibration-controlled transient elastography.

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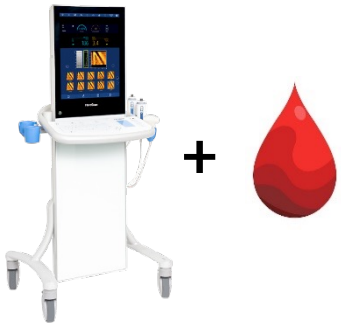
FibroScan-based biomarkers in NAFLD



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A2M: alpha2-macroglobuline; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CAP: controlled attenuation parameter; GGT: gamma glutamyl transferase; INR: international normalized ratio; LSM: liver stiffness measurement; PLT: platelets count; SSM: spleen stiffness measurement; VCTE: vibration-controlled transient elastography.

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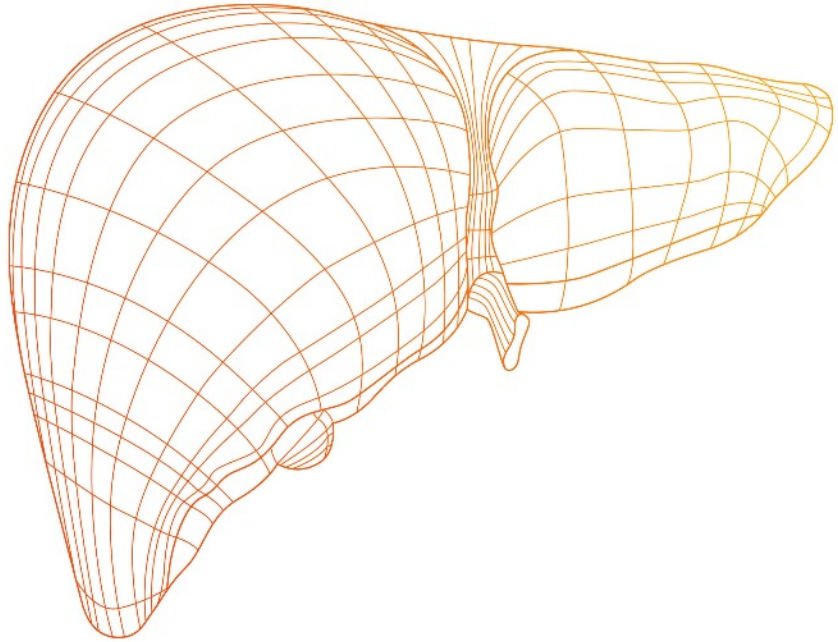

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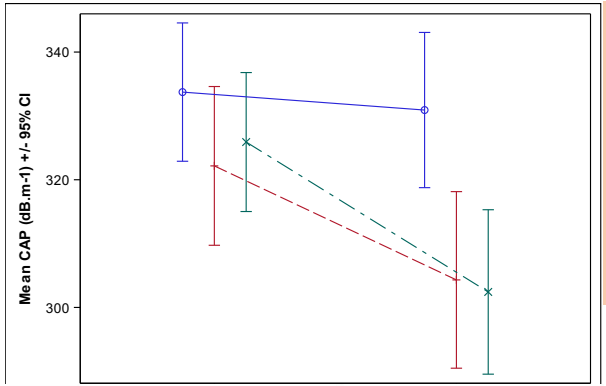
Monitoring change in steatosis with CAP

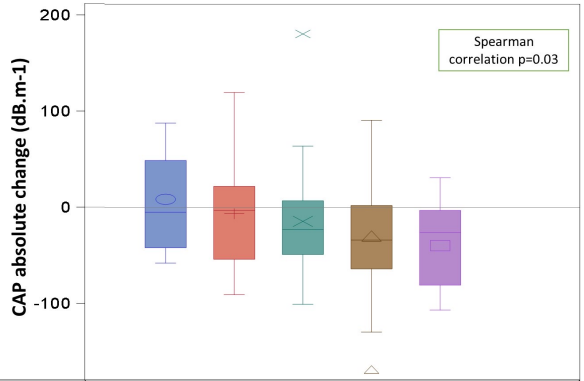
Phase 2b – Lanifibranor – 24 weeks



	Screening			End of treatment		
	Placebo	Lani 800mg	Lani 1200mg	Placebo	Lani 800mg	Lani 1200mg
N	60	60	54	68	67	64
Mean ± SD	335 ± 42	323 ± 48	326 ± 39	328 ± 47	309 ± 55	304 ± 50
Median	333	327	326	338	304	300
Min; Max	242; 400	192; 400	241; 400	213; 400	124; 400	177; 400
Pvalue* vs. Placebo	-	0.253 (NS)	0.226 (NS)	-	0.028 (S)	0.005 (S)

Lani=Lanifibranor, CI=Confidence Interval, * Wilcoxon-Mann-Whitney test

- CAP was comparable at baseline between treatment groups.
- Significant decreases of CAP were observed at Week 24 under lanifibranor compared to placebo.



	Histological steatosis change				
	Worsening	No change	Impr. (1pt)	Impr. (2pts)	Impr. (3pts)
N	9	19	27	33	7
Mean ± SD	8.6 ± 53.3	-6.5 ± 54.6	-14.5 ± 54.9	-29.7 ± 56.9	-39.7 ± 48.1
Median	-5	-3	-23	-34	-26
Min; Max	-58; 88	-91; 120	-101; 181	-169; 91	-107; 31

Impr(X)=Improvement of X points of histological steatosis

- Significant relationship between change in CAP and change in histological steatosis grade was observed at W 24.

Cooreman Hepatology 2021;74:1142A

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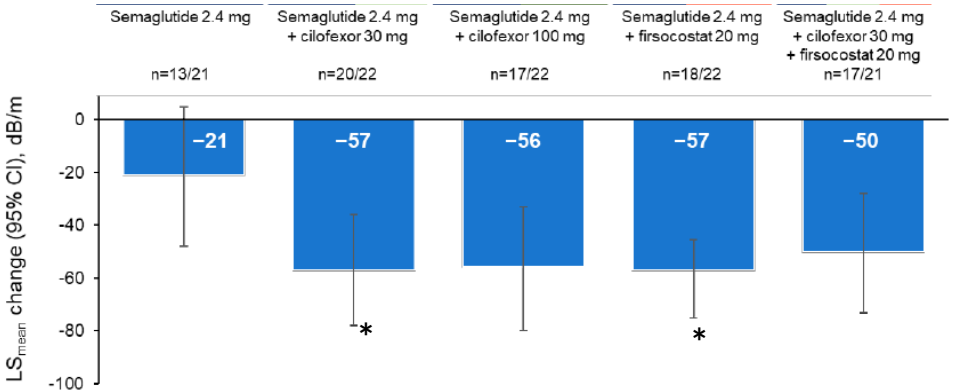
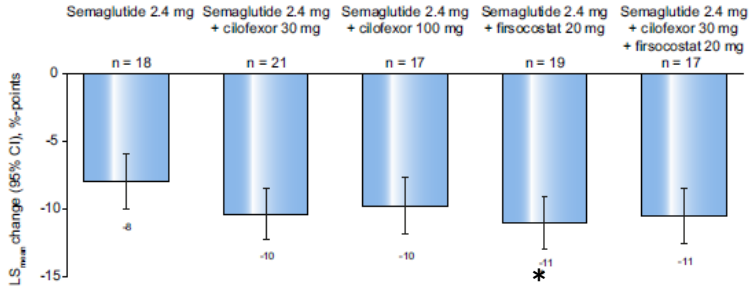
Monitoring change in steatosis with CAP

Phase 2 – SEMA/CILO/FIRS – 24 weeks (OL)

CAP



MRI-PDFF



LS mean: least-square mean change based on ANCOVA models adjusted for baseline and diabetes status. ANCOVA, analysis of covariance; CI, confidence interval; dB/m, decibels per meter.
*statistically significant compared to SEMA alone.

- Trends observed with CAP are similar to those observed with MRI-PDFF
- Two combinations showed significant improvement compared to SEMA alone

Alkhouri J Hepatology 2022;77:607-18

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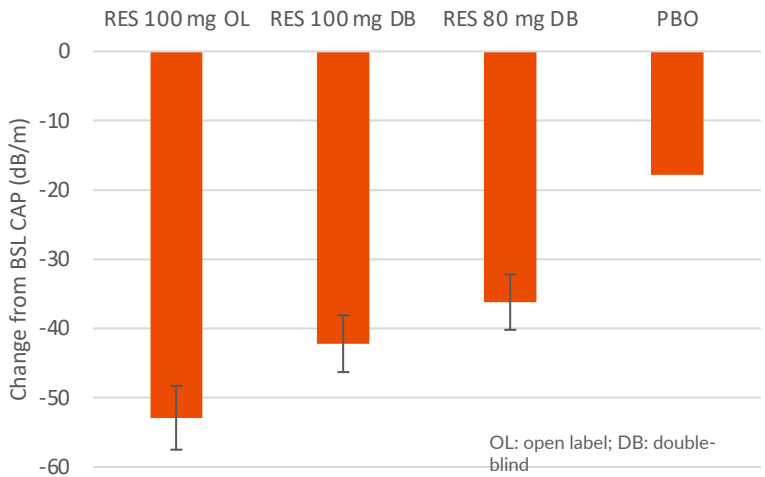
Monitoring change is steatosis with CAP

Phase 3 – Resmetirom – 52 weeks

MAESTRO-NAFLD-1*



- Significantly larger decrease of CAP at Week 52 in all active arms compared to PBO

MAESTRO-NASH**

"Reduction in […] imaging test (MRI-PDFF, CAP […] were observed in resmetirom treatment arms as compared to placebo."

- Awaiting additional results to be shared at EASL ILC 2023 and subsequent publications

*Harrison J Hepatology 2022;77(S1):S14
**Madrigal press release Dec 19, 2022

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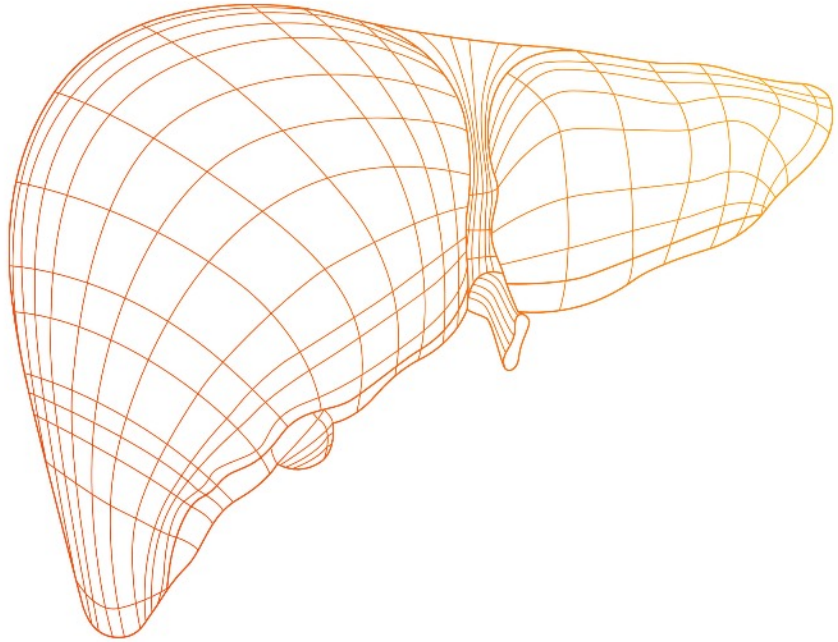

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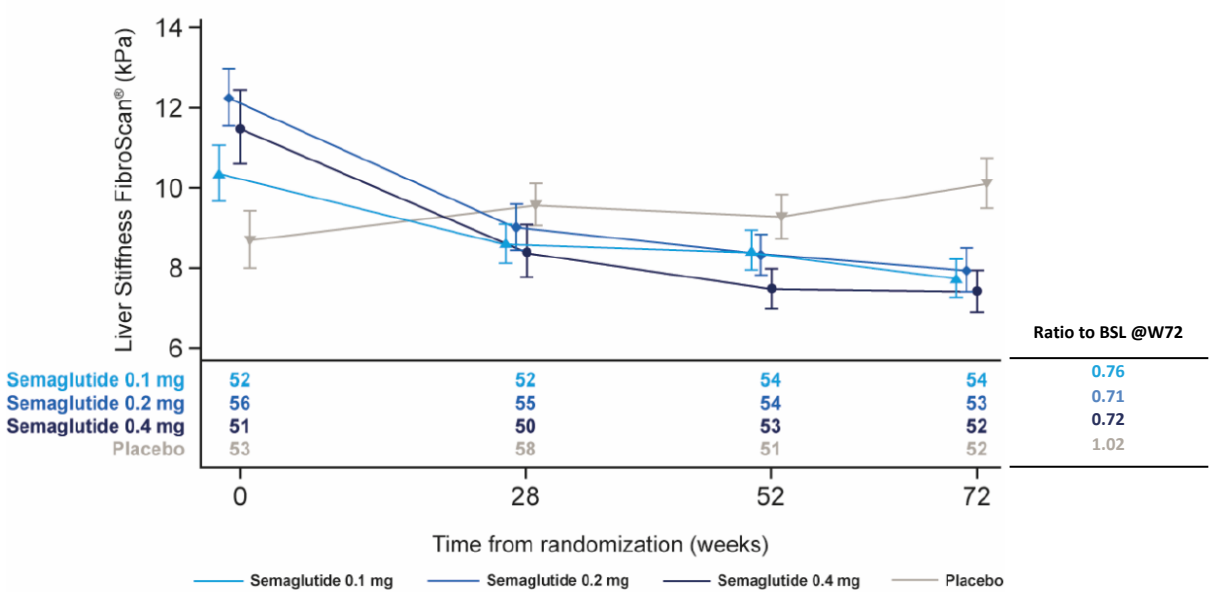
Monitoring change in fibrosis with LSM by VCTE

Phase 2b – Semaglutide – 72 weeks



- Decrease of LSM in active arms vs increase in PBO arm

Mean values from baseline to week 72 for patients assessed at sites with FibroScan® equipment available. Error bars: standard error of the mean.

Newsome NEJM 2020;384:1113-24

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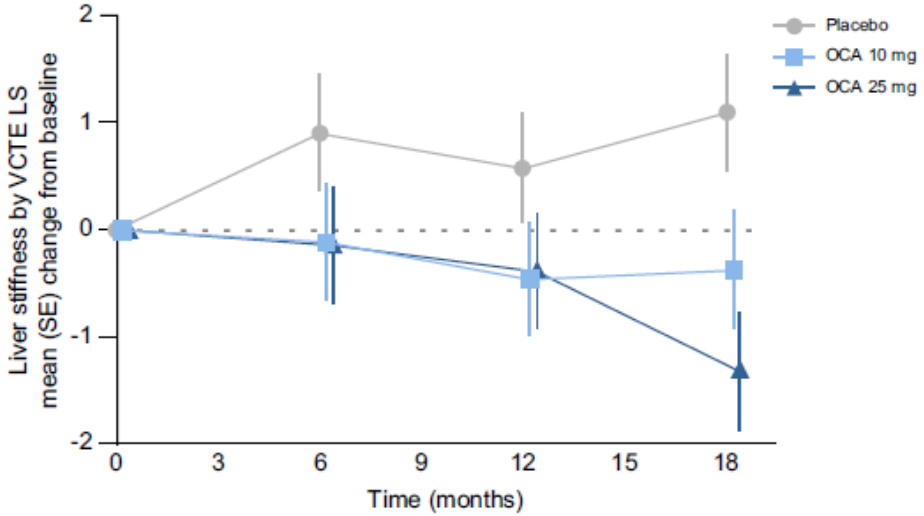
Monitoring change in fibrosis with LSM by VCTE

Phase 3 – Obeticholic acid – REGENERATE – 18 months



Placebo	225	203	199	183
OCA 10 mg	225	208	200	182
OCA 25 mg	228	206	184	171

Mean values from baseline to M18 for patients assessed at sites with FibroScan® equipment available. SE: standard error of the mean.

- At Month 18 in the ITT population, a decrease in LSM by VCTE was observed in patients treated with OCA

Rinella J Hepatology 2022;76:536-48.

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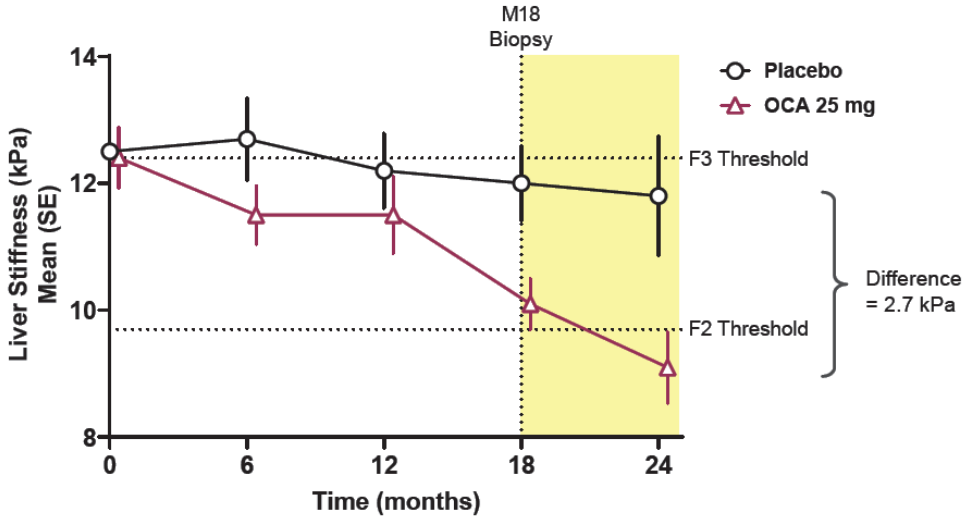
Monitoring change in fibrosis with LSM by VCTE

Phase 3 – Obeticholic acid – REGENERATE – 24 months



Placebo, n =	225	232	236	221	89
OCA 25 mg, n =	228	235	217	206	87

Mean values from baseline to M24 for patients assessed at sites with FibroScan® equipment available. SE: standard error of the mean.

- OCA treatment elicited durable improvements in LSM by VCTE at month 24, suggesting continued improvement beyond the categorical histologic benefit seen at 18 months

Loomba J Hepatology 2020;73:S133-4.

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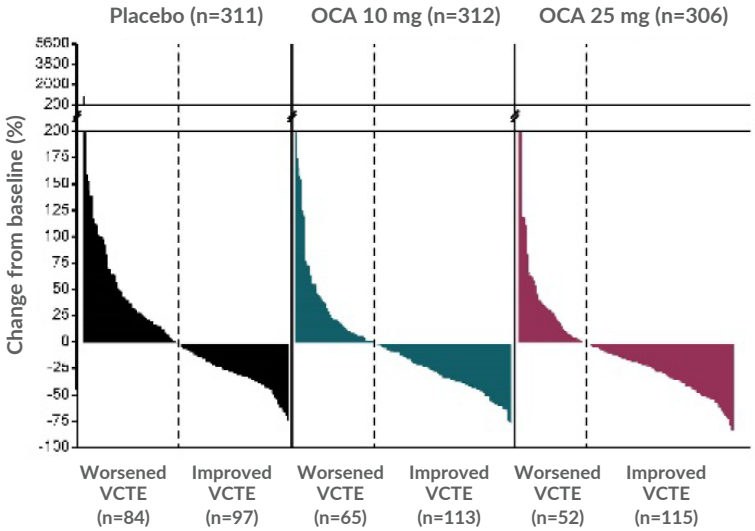
Monitoring change in fibrosis with LSM by VCTE

Phase 3 – Obeticholic acid - REGENERATE– 18 months

Individual patient shifts from baseline to M18



Patients with unchanged VCTE at M18: PBO, n=2; OCA 10 mg, n=4; OCA 25 mg, n=4

- Compared with placebo, more patients treated with OCA had reductions in VCTE from baseline to M18

Rinella J Hepatology 2022;76:536-48.

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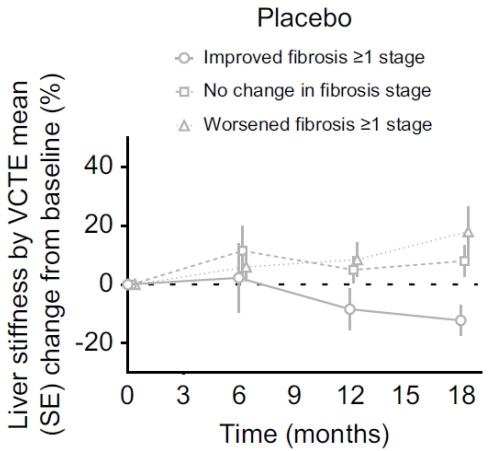
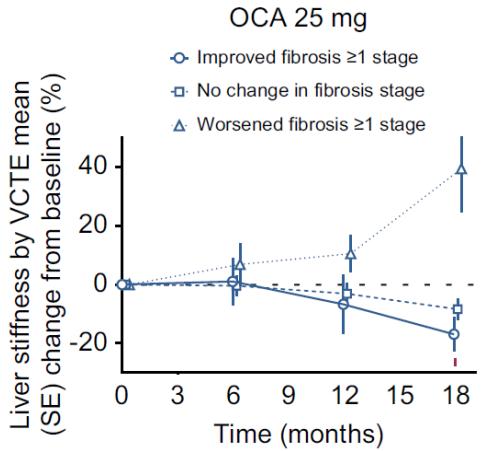
Monitoring change in fibrosis with LSM by VCTE

Phase 3 – Obeticholic acid - REGENERATE– 18 months

Change from baseline over time by treatment group and histological fibrosis improvement status



Improved, n =	40	38	38	37
No change, n =	111	100	104	100
Worsened, n =	42	41	40	39



Improved, n =	66	63	59	57
No change, n =	92	90	87	82
Worsened, n =	26	25	26	25

- In both PBO and OCA 25 mg arms, LSM by VCTE :
  - Increases in patients with worsening of fibrosis by histology
  - Decreases in patients with improvement of fibrosis by histology
- Among patient with stable fibrosis by histology, LSM by VCTE improved in patients receiving OCA 25 mg vs PBO

Mean (SE) percentage change for patients assessed at sites with FibroScan® equipment available. SE: standard error of the mean.

Rinella J Hepatology 2022;76:536-48.

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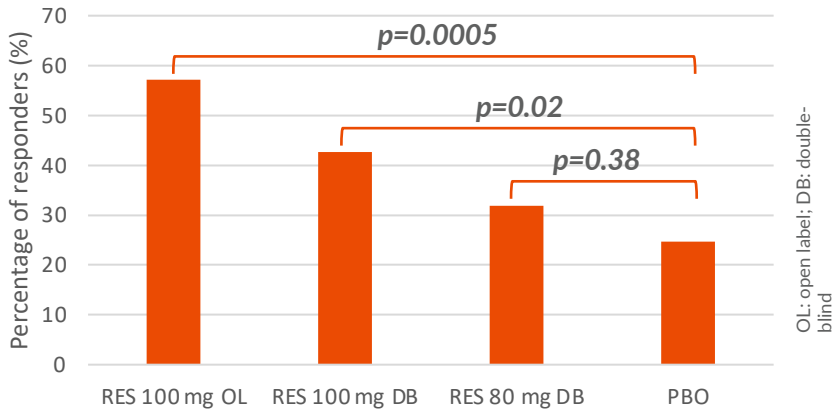
Monitoring change in fibrosis with LSM by VCTE

Phase 3 – Resmetirom – 52 weeks

MAESTRO-NAFLD-1*

Responder defined by:
BSL LSM ≥ 7.2 kPa AND ≥ 2 kPa reduction



- Comparative mean reduction in LSM by VCTE not significantly different between PBO and active arms
- Proportion of LSM-based responders significantly higher in the two RES 100 mg arms compared to PBO

MAESTRO-NASH**

"Reduction in […] imaging tests ([…] liver stiffness measures) were observed in resmetirom treatment arms as compared to placebo."

- Awaiting additional results to be shared at EASL ILC 2023 and subsequent publications

*Harrison J Hepatology 2022;77(S1):S14
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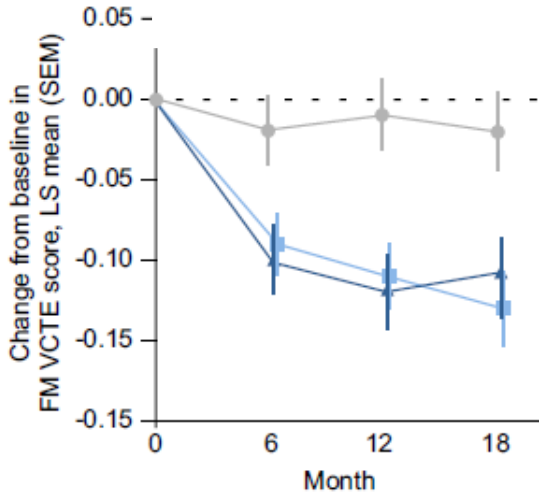
Monitoring change in fibrosis with FibroMeter VCTE

Phase 3 – Obeticholic acid - REGENERATE– 18 months



Placebo	129	104	102	89
OCA 10 mg	155	134	134	111
OCA 25 mg	131	109	93	85

LS mean: least-square mean using a mixed-effect repeated-measures model with treatment, baseline, visit, visit by treatment interaction, and stratification factors (baseline diabetes status and use of thiazolidinediones or vitamin E) as fixed effects; SEM: standard error of the mean; FM: FibroMeter; VCTE: vibration-controlled transient elastography.

- Compared with placebo, patients treated with OCA had meaningful reductions FibroMeter VCTE scores at Month 6 that were sustained through Month 18

Rinella J Hepatology 2022;76:536-48.

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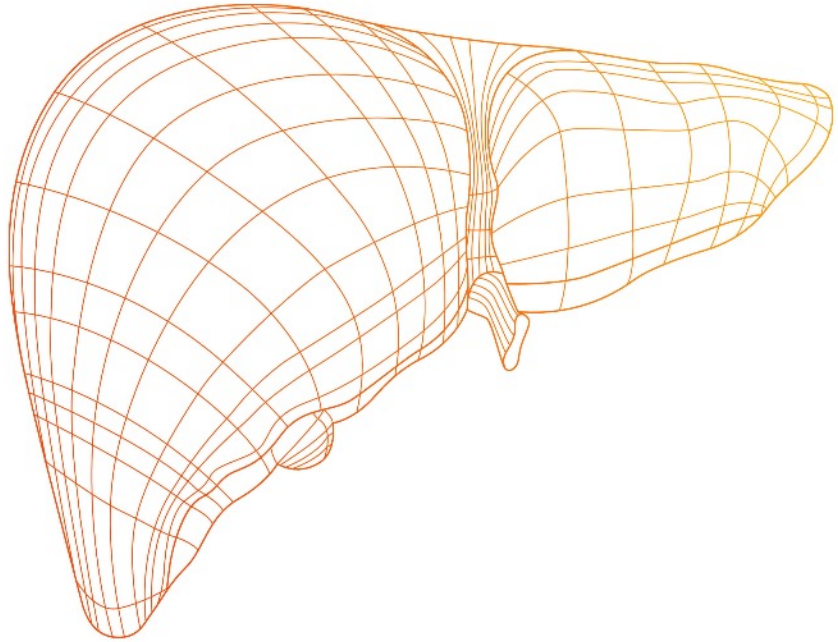

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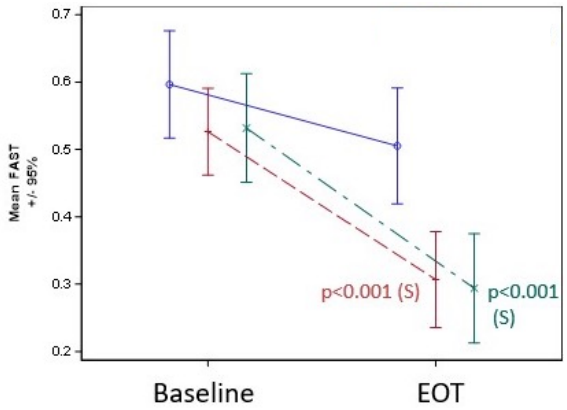
Monitoring change in at-risk NASH with FAST

Phase 2b – Lanifibranor – 24 weeks

Mean change over time

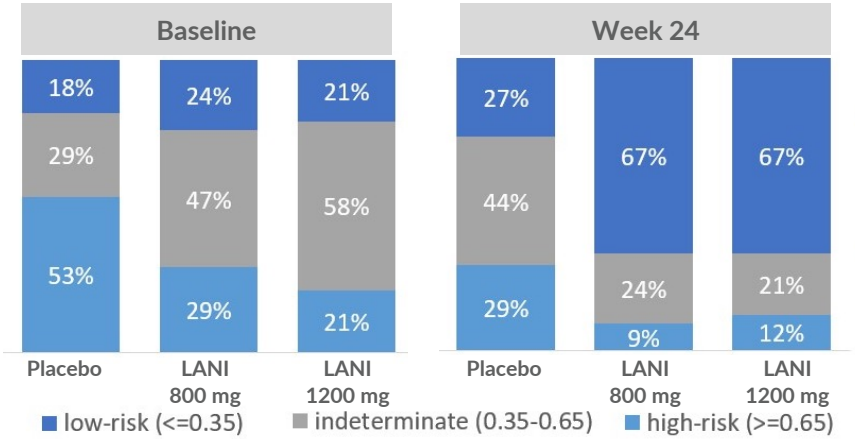


Placebo, Lanifibranor 800mg/d, Lanifibranor 1200mg/d

Mean change over time (95% confidence interval) in F2-F3 patients with available FAST data. P-values obtained from MMRM adjusted on baseline values, comparing each treatment group to placebo. MMRM: Mixed-Model-Repeated-Measures.

- Significant decreases of FAST score were observed at EOT under lanifibranor compared to placebo

Proportion of patients with low, intermediate and high probability of at-risk NASH



- At baseline, similar proportions of patients with low-risk probability were observed in all treatment arms
- At W24, 67% of patients under lanifibranor were at low-risk versus 27% under placebo

Cooreman J Hepatology 2022;77(S1):S722.

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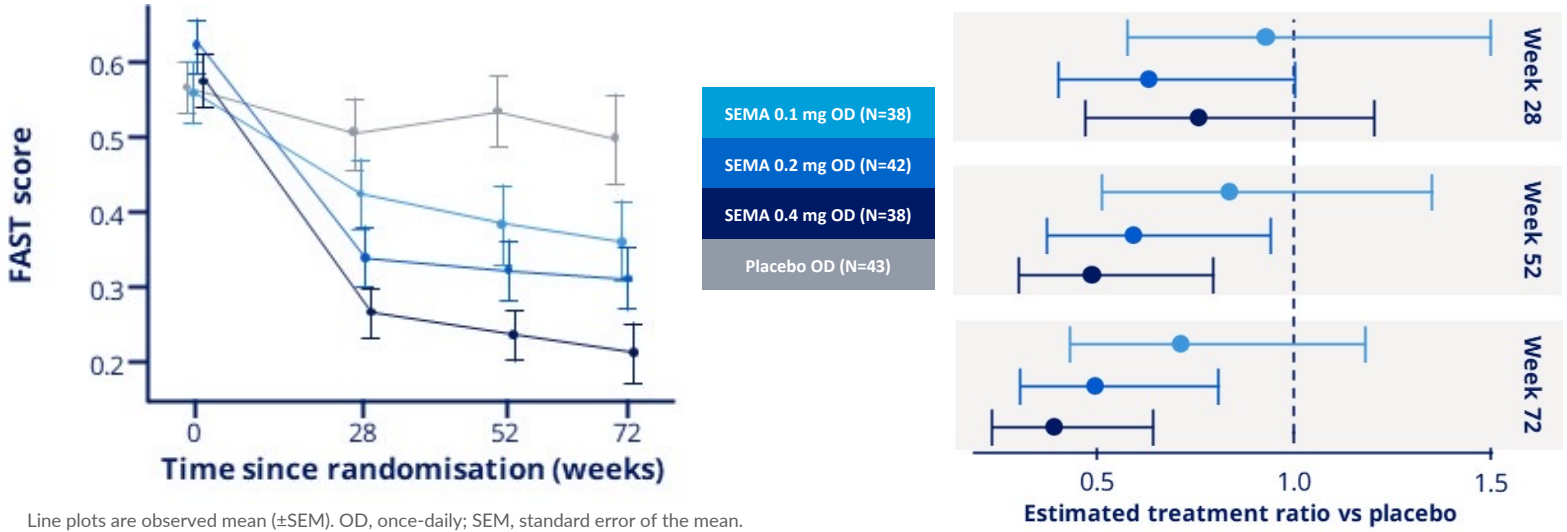
Monitoring change in at-risk NASH with FAST

Phase 2b – Semaglutide – 72 weeks

Change over time by treatment arms



Line plots are observed mean (±SEM). OD, once-daily; SEM, standard error of the mean.

➢ Dose dependent reduction in FAST at W28 and sustained until W72

Wong J Hepatology 2021;75(2):S257-8.
Courtesy of Novo Nordisk

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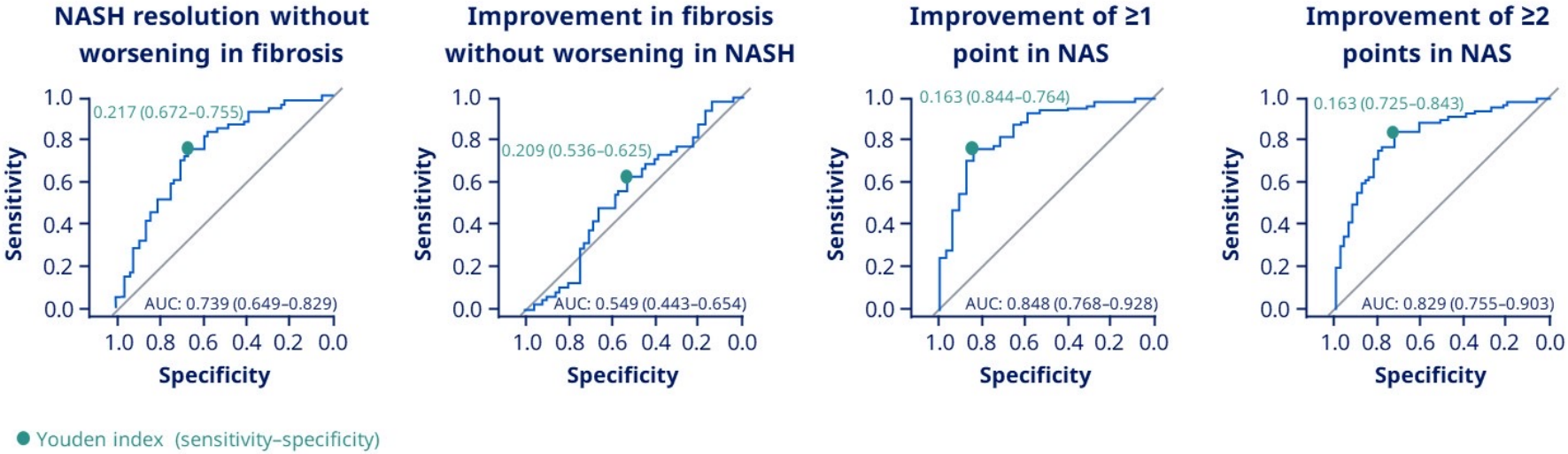
Monitoring change in at-risk NASH with FAST

Phase 2b – Semaglutide – 72 weeks

Accuracy of change in FAST between baseline and W72 to assess histological endpoints



Combining all treatment arms. AUC, area under the curve; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis.

➢ Reduction in FAST is associated with several histological endpoints

Wong J Hepatology 2021;75(2):S257-8.
Courtesy of Novo Nordisk

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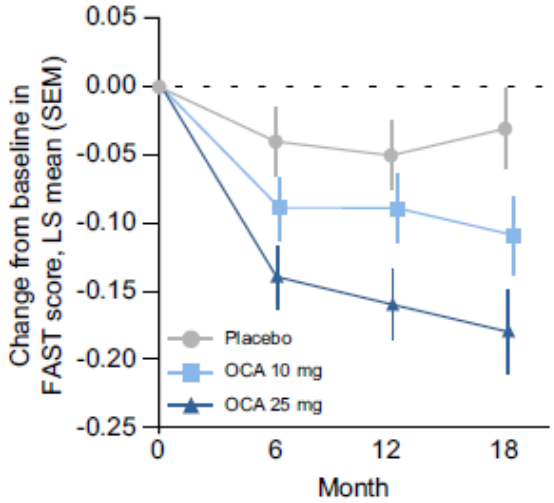
Monitoring change in at-risk NASH with FAST

Phase 3 – Obeticholic acid - REGENERATE– 18 months



Placebo	100	83	80	68
OCA 10 mg	107	92	86	73
OCA 25 mg	103	90	76	61

LS mean: least-square mean using a mixed-effect repeated-measures model with treatment, baseline, visit, visit by treatment interaction, and stratification factors (baseline diabetes status and use of thiazolidinediones or vitamin E) as fixed effects; SEM: standard error of the mean.

- Compared with placebo, patients treated with OCA had meaningful dose dependent reductions in FAST at Month 6 that were sustained through Month 18

Rinella J Hepatology 2022;76:536-48.

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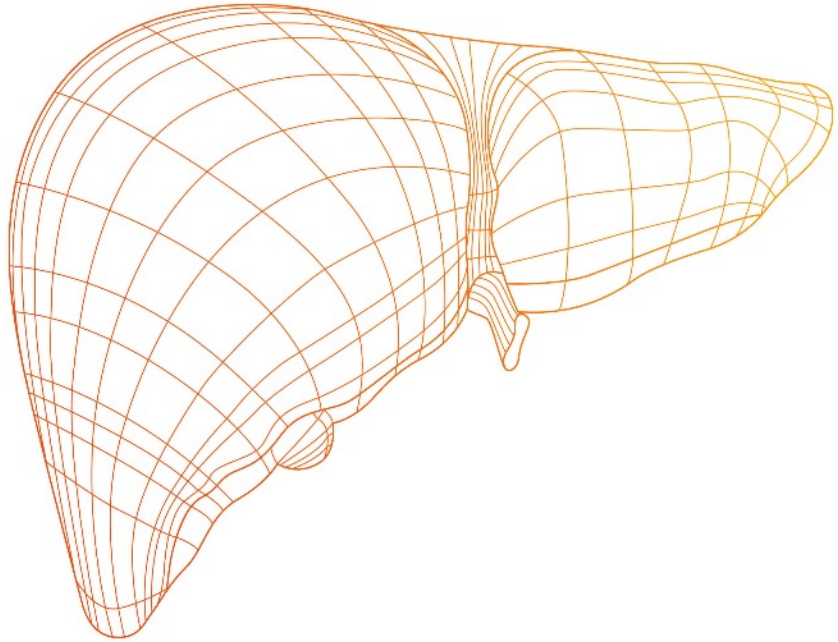

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Take home messages

- FibroScan-based biomarkers allow monitoring several types of treatment response depending on the trial setting and mode of action of the compound
- Changes in CAP over time can be used to monitor treatment effects and are associated with steatosis changes assessed by MRI-PDFF and histology
- Changes in LSM by VCTE over time can be used to monitor treatment effects and are associated with fibrosis improvement and worsening assessed by histology
- Fewer data on FibroMeter VCTE but seems promising at monitoring treatment response from M6
- By combining biomarkers of fibrosis, steatosis and inflammation, and providing the probability of at-risk NASH, FAST is able to monitor dose-dependent treatment response from M6 and change in FAST is associated with several histological endpoints such as NASH resolution without worsening of fibrosis
- More data expected at the upcoming EASL ILC meeting in June
- Longitudinal data show that worsening in LSM by VCTE is associated with increased risk of poor clinical outcomes in NAFLD patients with advanced fibrosis[1,2]
- Progression to (regression from) LSM-defined cirrhosis independently increases (decreases) the risk of poor clinical outcomes in biopsy-proven NAFLD patients[3]

1. *Petta CGH 2021; 19(4):806-815*
2. *Loomba Gut 2022; 72(3):581-9*
3. *Gawrieh Hepatology 2022;76(S1):S64*

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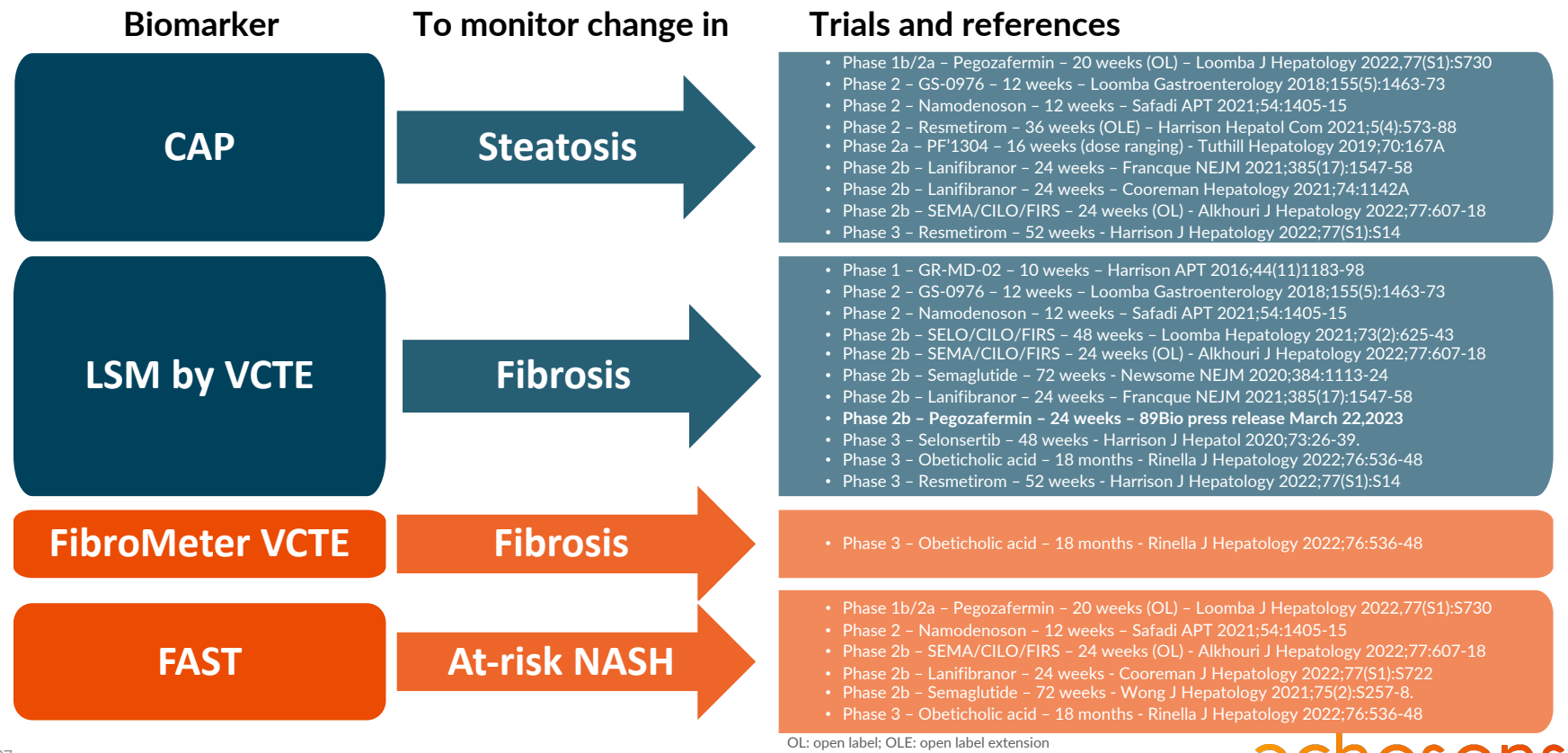
Literature recap



OL: open label; OLE: open label extension

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because liver health matters