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Patient Monitoring Using the ELF™ Test

The evidence so far…

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Disclaimer

The information presented herein reflects a potential context of use (COU) for monitoring in clinical trials and drug development.
For U.S. clinical practice, the ELF Test is currently limited to prognostic use.

U.S. Intended Use:
The ELF Test is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to non-alcoholic steatohepatitis (NASH) to assess the likelihood of progression to cirrhosis and liver-related clinical events.

My misadventures with AI-generated art…

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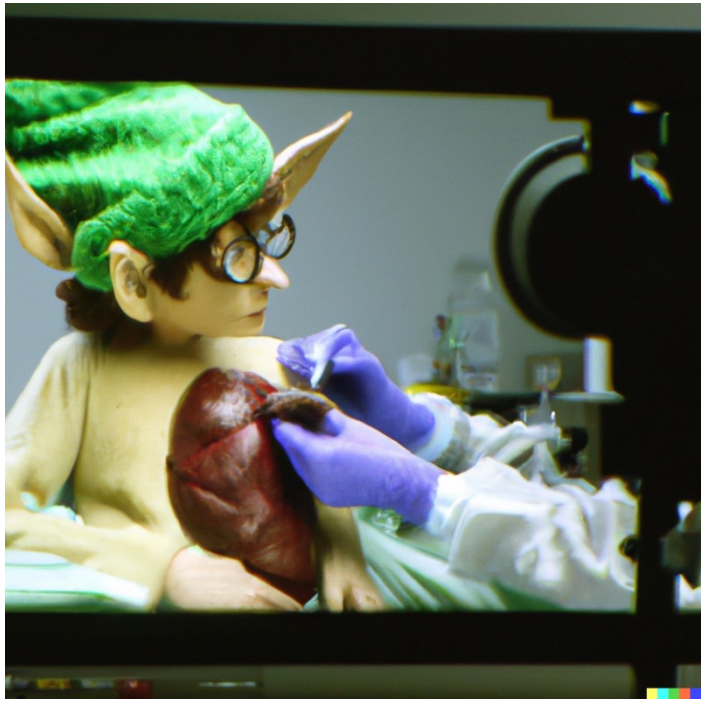
Keywords: ELF & evaluate & liver

These images were created with the assistance of DALL·E 2.

My misadventures with AI-generated art…



AI solution to reduce biopsies:
Grow liver externally

Unrecognized liver-related event?
Hepatic foliation

AI makes connections…
Association between cigarette smoking and progression of fibrosis

AI is learning at a rapid pace.

A potential monitoring* utility of the ELF Test is also emerging rapidly.

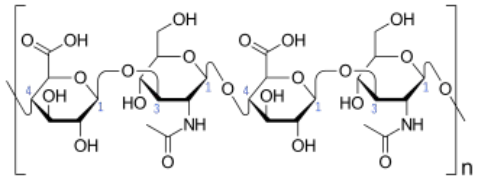
* This claim has not been reviewed by the FDA and is not available in the U.S. for routine clinical use
These images were created with the assistance of DALL·E 2.

Overview of the Enhanced Liver Fibrosis (ELF) Test

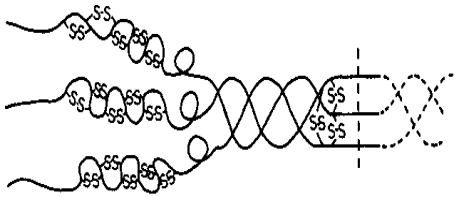
ELF Test: Background

ELF Test:

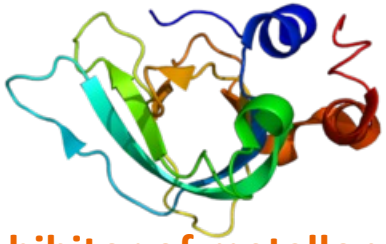
- Serum-based non-invasive test (NIT)
- Multianalyte assay with algorithmic analysis (MAAA)
- Measures direct markers of fibrosis: HA, PIIINP and TIMP-1
- Combines quantitative measurements into a unitless ELF score



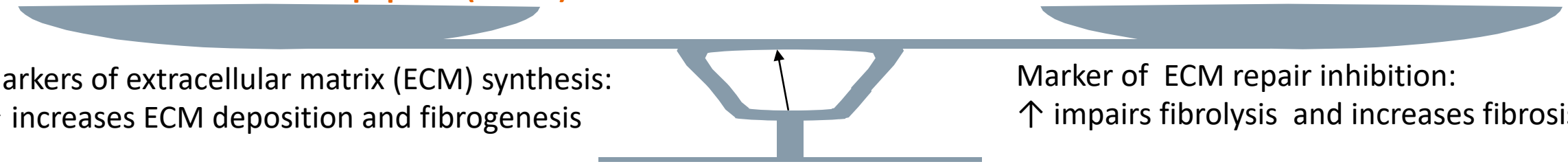
Hyaluronic acid (HA)



Procollagen III amino terminal peptide (PIIINP)



Tissue inhibitor of metalloproteinase-1 (TIMP-1)



Markers of extracellular matrix (ECM) synthesis:
↑ increases ECM deposition and fibrogenesis

Marker of ECM repair inhibition:
↑ impairs fibrolysis and increases fibrosis

Arpino V, Brock M, Gill SE. The role of TIMPs in regulation of extracellular matrix proteolysis. Matrix Biol 2015;44-46:247-54.
Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology 2004;127:1704-13.

Applicable immunoassay instruments from Siemens Healthineers

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ADVIA Centaur® XP

ADVIA Centaur® XPT

ADVIA Centaur® CP*

$$ELF = 2.278 + 0.851 \times \ln(C_{HA}) + 0.751 \times \ln(C_{PIIINP}) + 0.394 \times \ln(C_{TIMP\text{-}1})$$

$$ELF = 2.494 + 0.846 \times \ln(C_{HA}) + 0.735 \times \ln(C_{PIIINP}) + 0.391 \times \ln(C_{TIMP\text{-}1})$$

Atellica® IM

Atellica® Solution

* Not yet available for use on ADVIA Centaur CP in the U.S. Future availability cannot be guaranteed.

The right reagent/instrument/algorithm combination is essential

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Reagents:
ADVIA Centaur or Atellica IM

+

Instrument:
ADVIA Centaur (XP, XPT, CP) system or Atellica IM Analyzer

+

Algorithm:
ADVIA Centaur XP/XPT, Atellica IM

$$ELF = 2.278 + 0.851 \times \ln(C_{HA}) + 0.751 \times \ln(C_{PIIINP}) + 0.394 \times \ln(C_{TIMP\text{-}1})$$

or ADVIA Centaur CP

$$ELF = 2.494 + 0.846 \times \ln(C_{HA}) + 0.735 \times \ln(C_{PIIINP}) + 0.391 \times \ln(C_{TIMP\text{-}1})$$

The ELF™ Test is only offered by Siemens Healthineers

* Not yet available for use on ADVIA Centaur CP in the U.S. Future availability cannot be guaranteed.

Why monitor patients using the ELF Test?

Potential utility of the ELF Test for a monitoring COU

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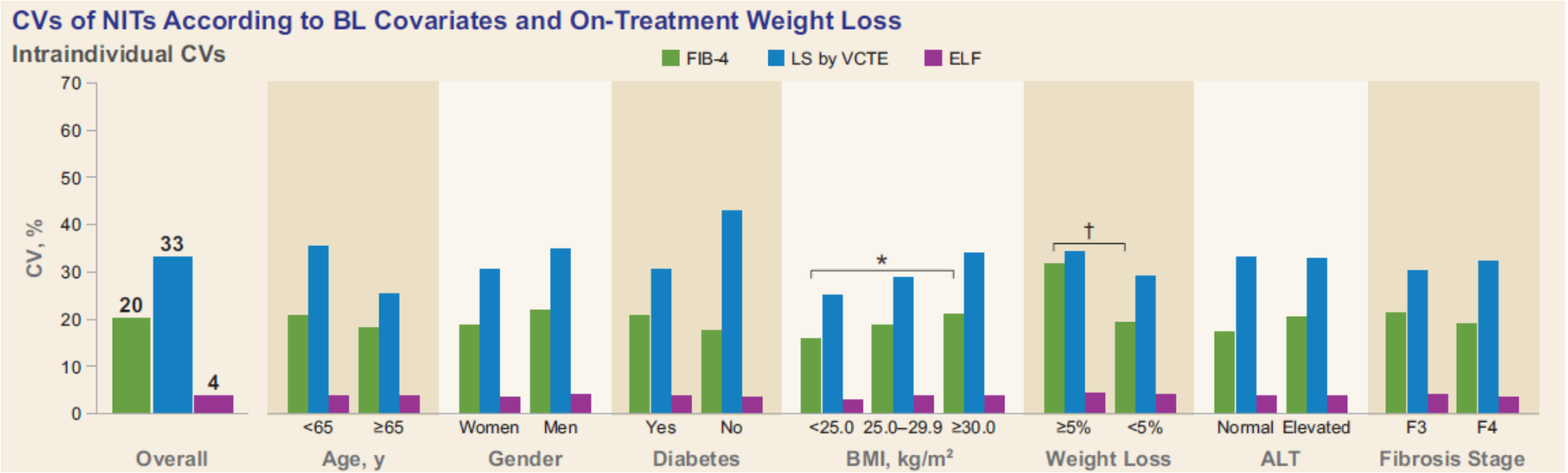
1. Several Phase 2&3 drug trials in NASH are on-going.
   Surrogate endpoints using NITs are valuable to support drug development efforts.

2. Two drug candidates are in FDA review or near submission.
   Clinical management of patients undergoing NASH treatment necessitates monitoring.

3. The ELF Test predicts clinical events in NASH patients.
   Currently, no other NIT has this FDA-reviewed claim in label.

Preliminary evidence for a monitoring context of use for ELF

ELF is the among the most precise of NITs



ELF precision: 3.8% CV

"In NASH patients with stable, advanced fibrosis…ELF may have greater precision for disease monitoring in NASH."

Anstee Q et al. J Hepatol. 2021;75(S2):S575-S576. **Presented at ILC 2021**

What is a meaningful change in ELF?

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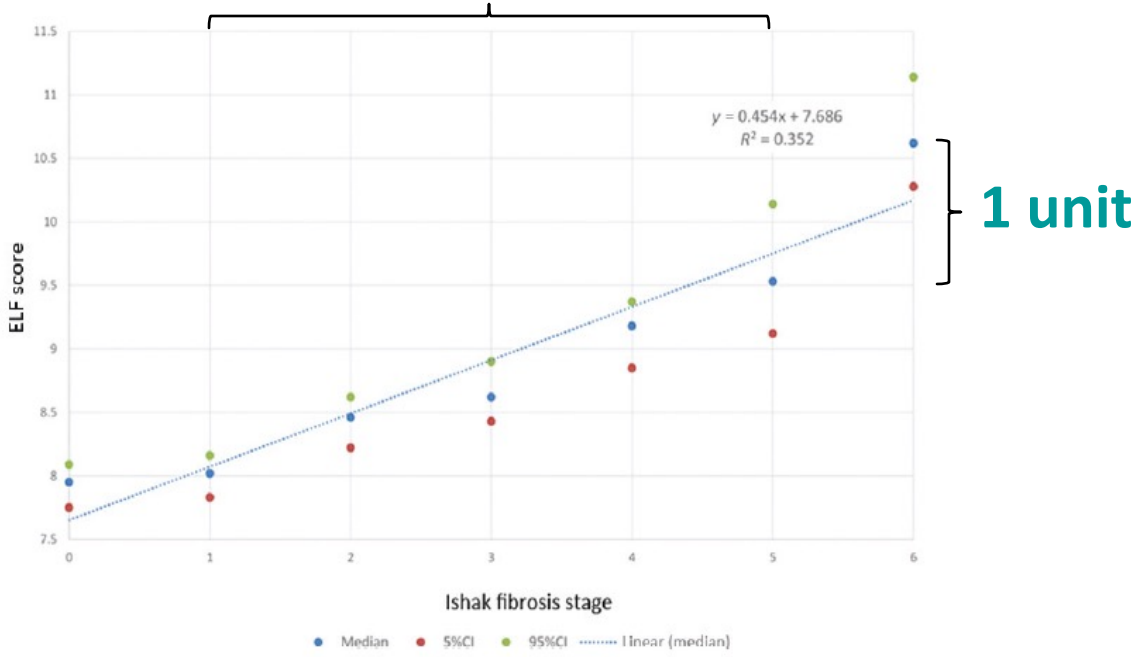
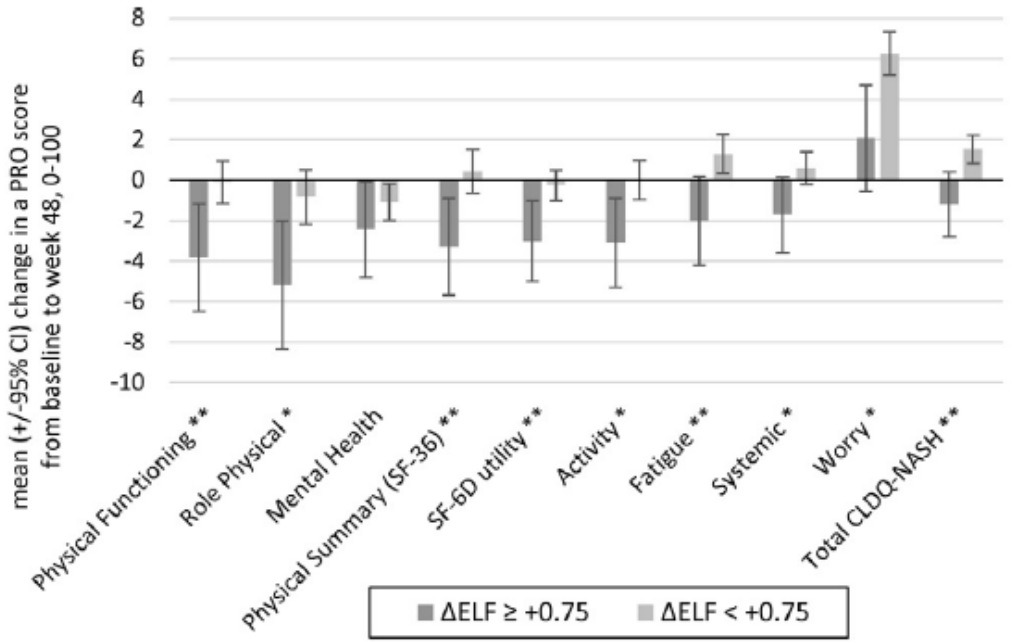
0.50 units



An increase of approximately 0.5 in ELF corresponds to an increase in fibrosis of 1 Ishak stage in the midrange from S1 to S5.

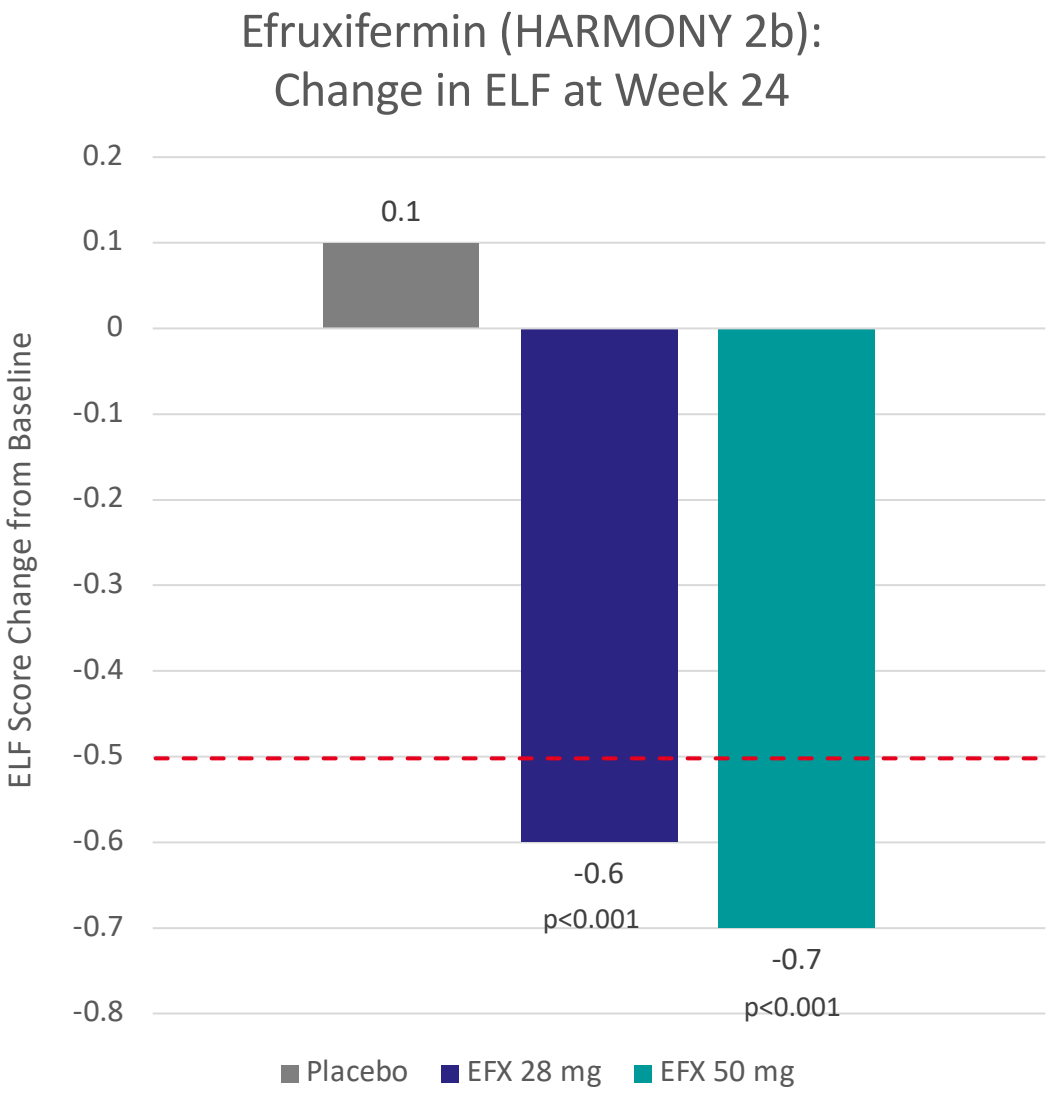
0.75 units



Patients with an ELF score increase of ≥ 0.75 units experienced a worsening of patient reported outcomes

Day J et al. J Appl Lab Med. 2019;3(5):815–826.
Younossi ZM et al. Gastroenterology. 2021 Apr;160(5):1608-1619.e13.

Some drug studies show mean ELF change ≥ 0.50 units



Dose-dependent mean ELF reductions correlate with biopsy endpoints (fibrosis improvement and/or resolution of NASH)

Measure (mean)	Placebo (N=41)	EFX 28mg (N=38)	EFX 50mg (N=34)
≥ 1-stage improvement in fibrosis without worsening of NASH (%)	20	39*	41*
NASH resolution without worsening of fibrosis (%)	15	47**	76***
NASH resolution AND ≥ 1-stage improvement in fibrosis (%)	5	29**	41***

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

Source: Akero Therapeutics' Phase 2b HARMONY Study Press Release (2022-11-13).
https://ir.akerotx.com/news-releases/news-release-details/akero-therapeutics-phase-2b-harmony-study-both-50mg-and-28mg-efx

In other drug studies mean ELF change is less than 0.50 units

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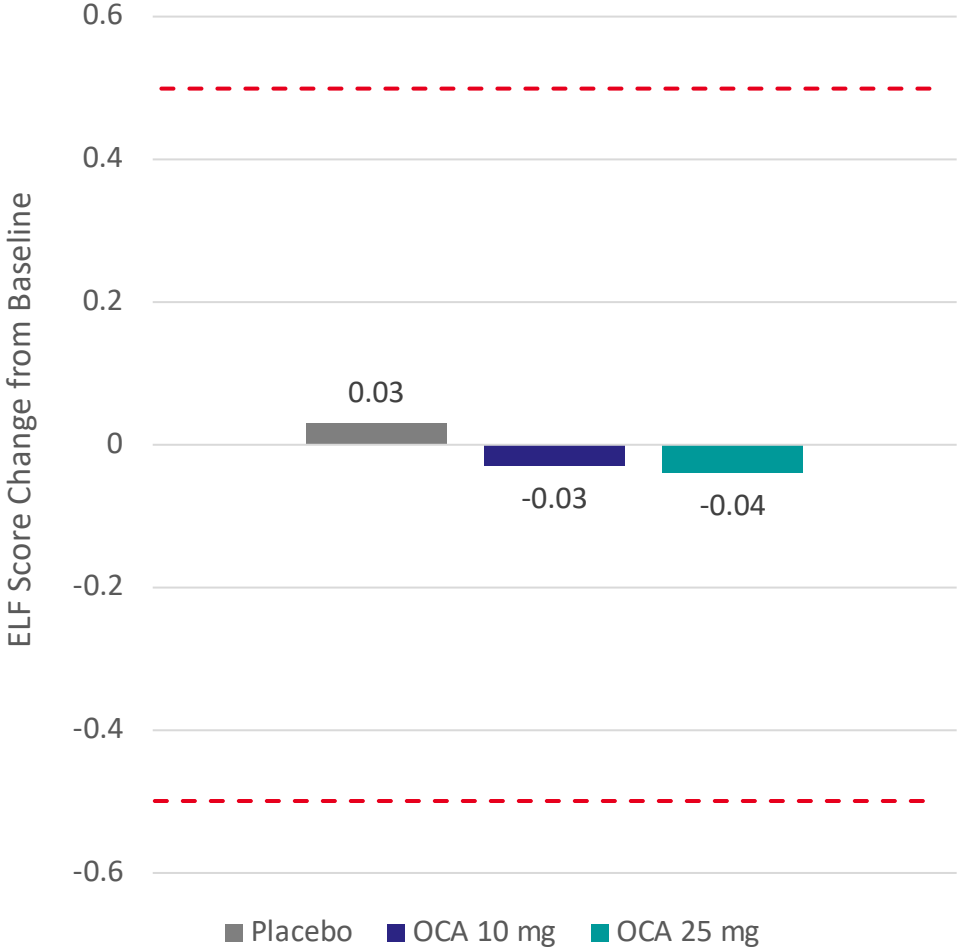
Obeticholic acid (REGENERATE):
Change in ELF at Month 18

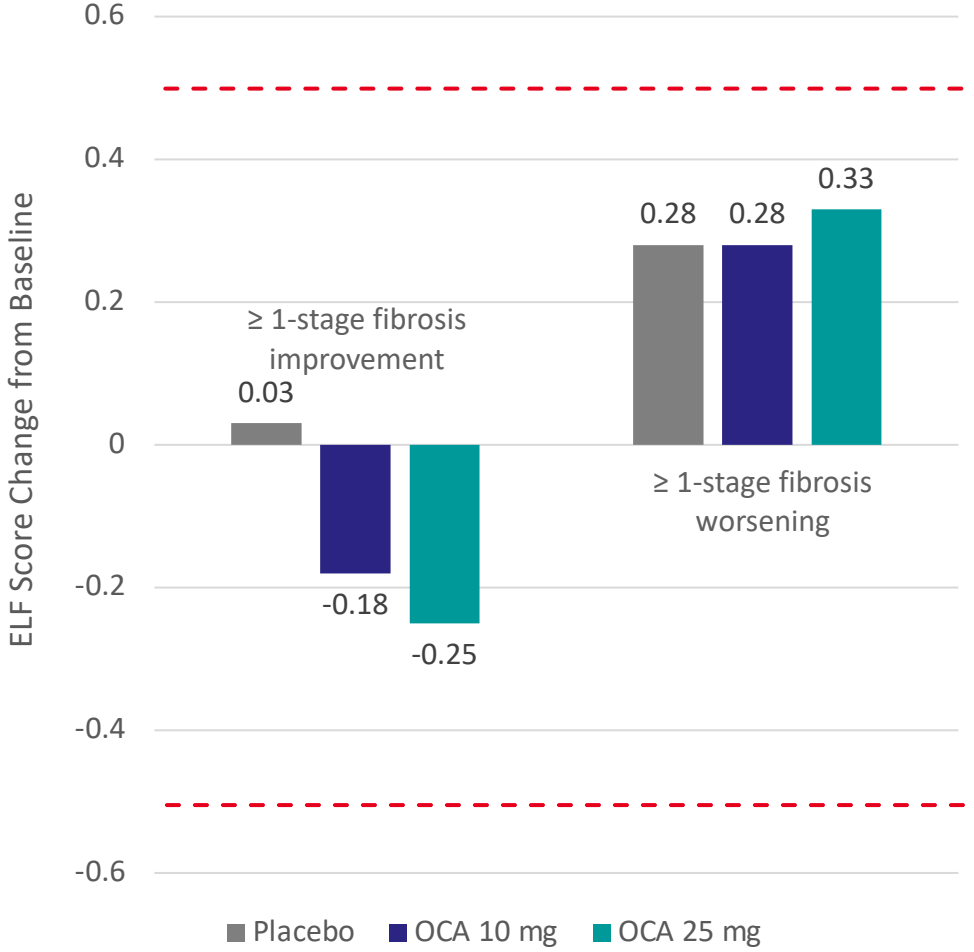


Minimal change in mean ELF seen at 18 months

Sub-population analysis gives more information

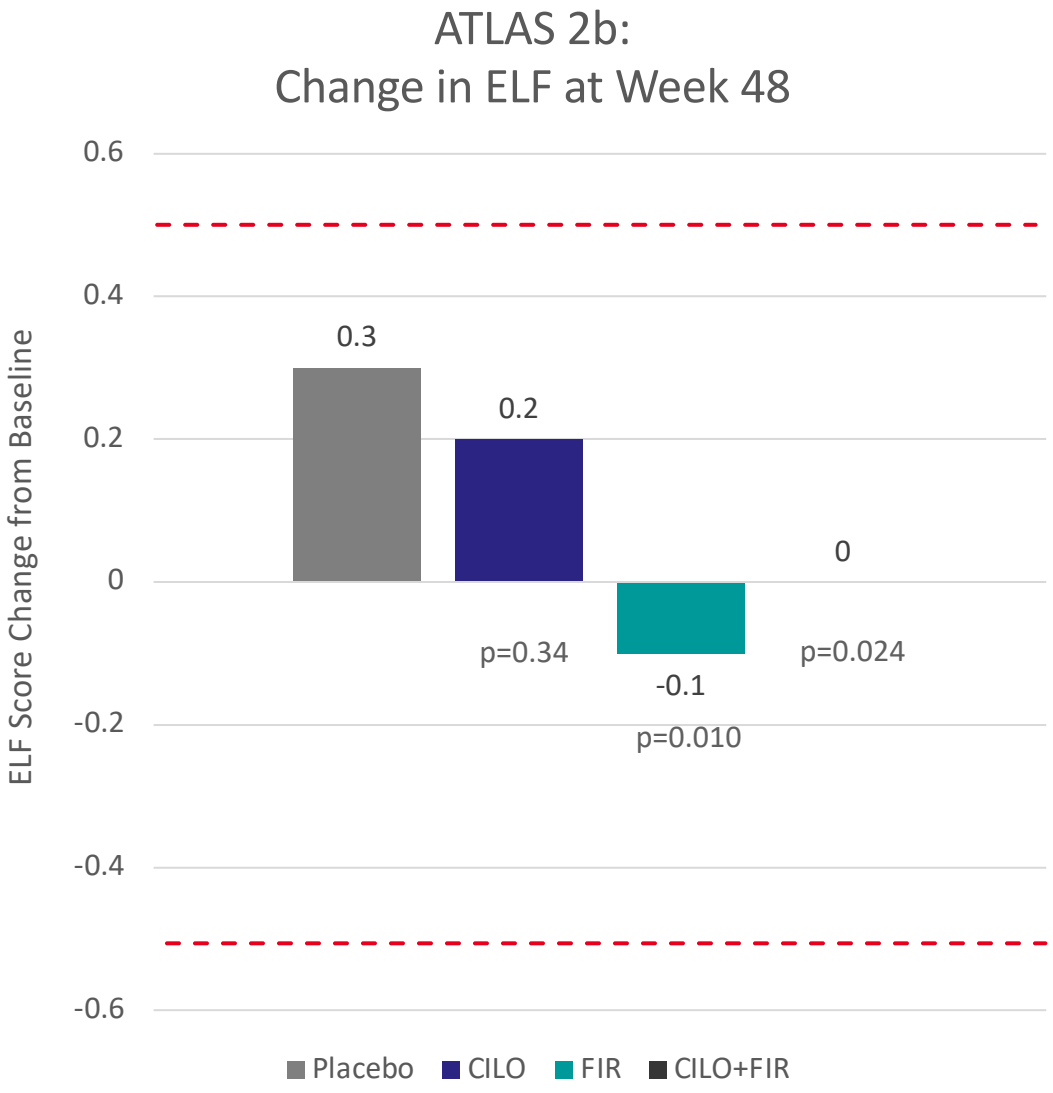
No population reaches mean ELF change ≥ 0.50 units

Obeticholic acid (REGENERATE):
Change in ELF at Month 18



Rinella ME et al. J Hepatol. 2022;76(3):536-548.

Is mean ELF change useful to assess efficacy?



Firsocostat arm:

- Highest mean ELF reduction
- Most ELF responders (≥ 0.50 unit reduction)

Correlation between mean ELF change and ELF responders

	ELF Response (%)
Placebo (N=39)	19
CILO (N=40)	24
FIR (N=40)	44*
CILO+FIR (N=78)	31

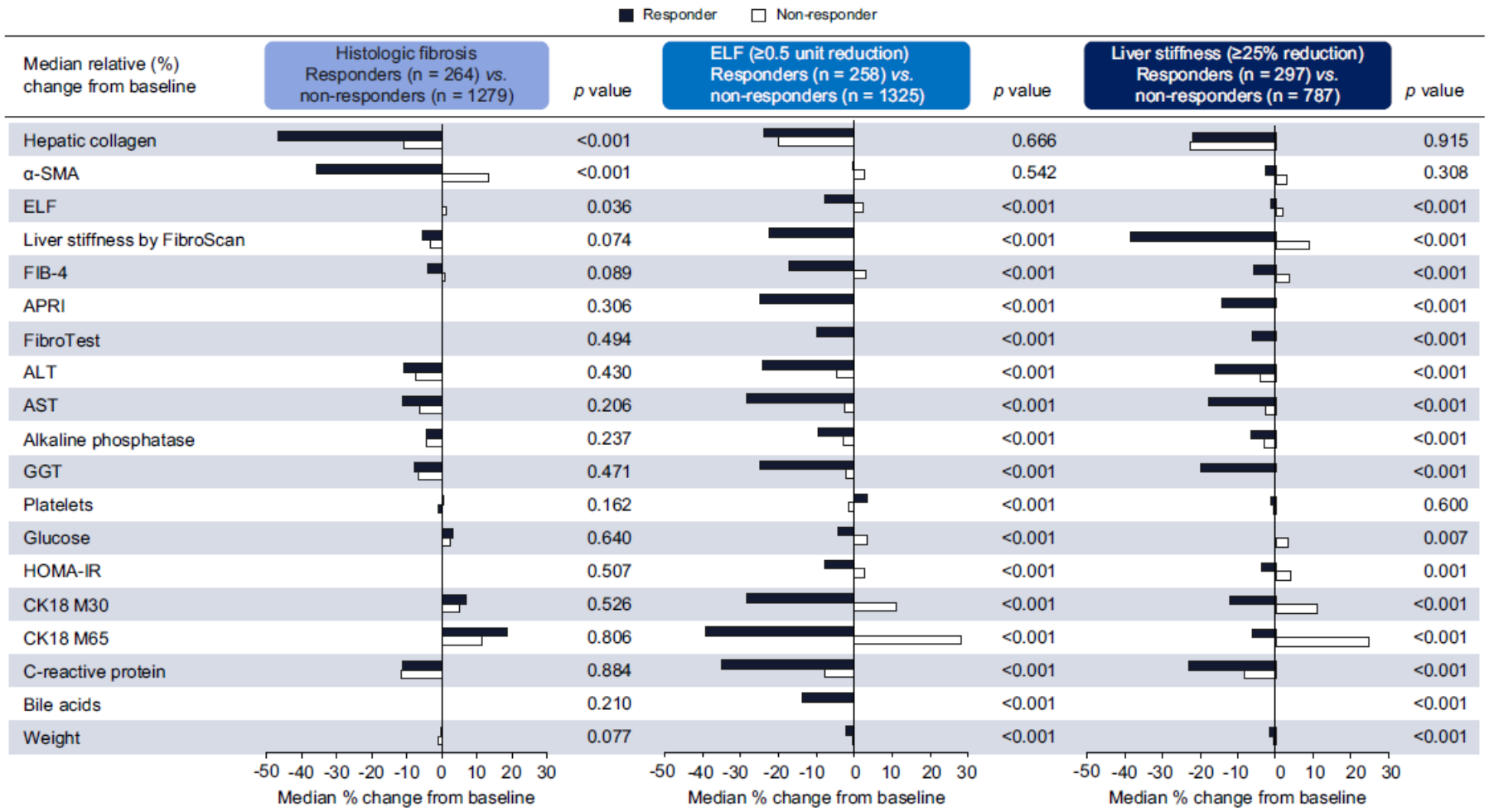
* p<0.05 versus placebo

QUESTION:
Is ELF response (≥0.50 unit decrease) a more useful metric than mean ELF change?

Loomba R et al. J Hepatol. 2020;73(S1):S116-S117. **Presented at ILC 2020**

Treatment response based on ELF reduction of ≥ 0.50

ELF reduction of ≥ 0.5 to identify responders



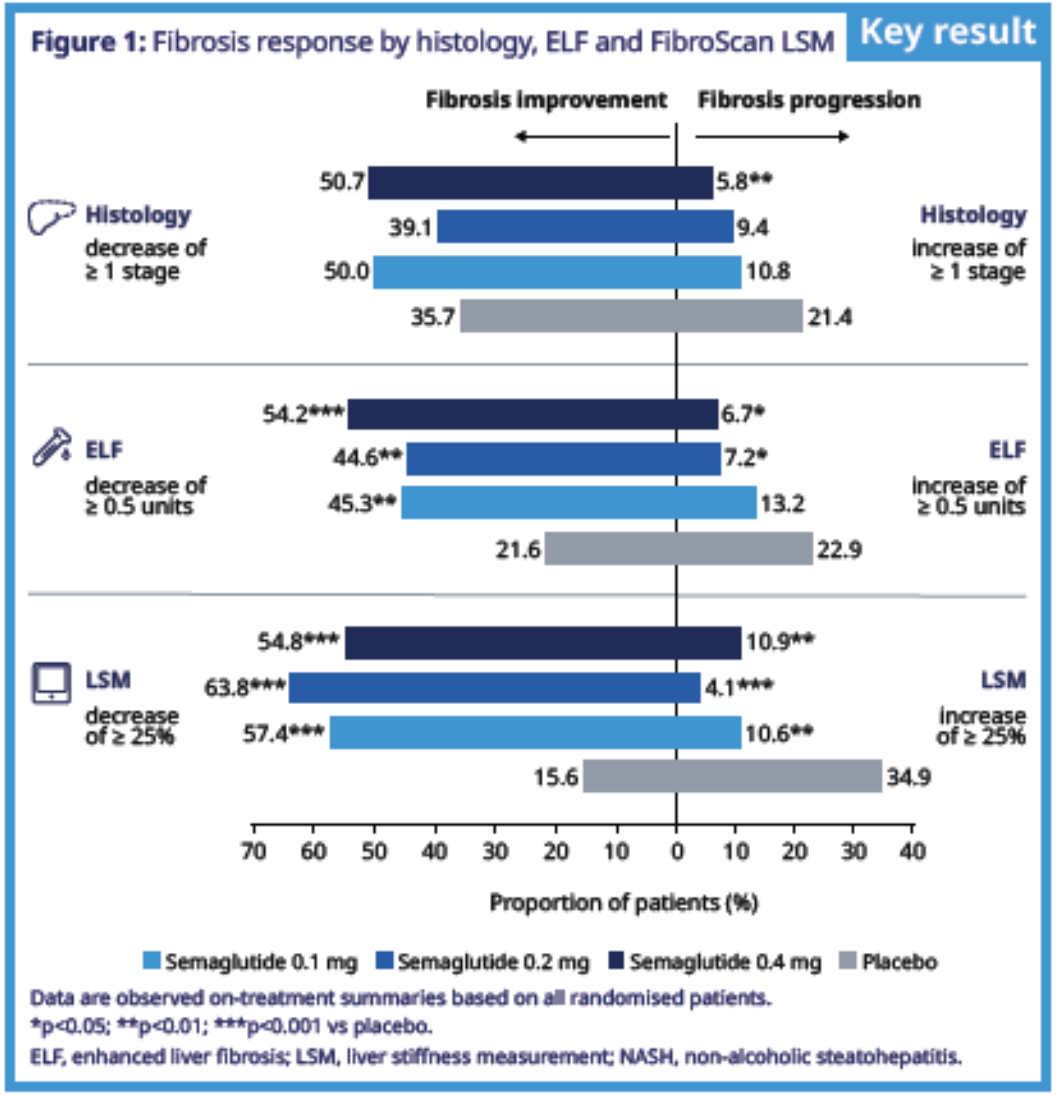
Improvement in ELF (≥ 0.50 unit reduction) correlated with a variety of clinical parameters

ELF and LSM showed similar trends (responders vs. non-responders)

Data from selonsertib phase 3 trials (NCT03053050, NCT03053063): NASH patients F3 (N = 802) and F4 (N = 877)

Harrison SA et al. J Hepatol. 2020;73(1):26-39

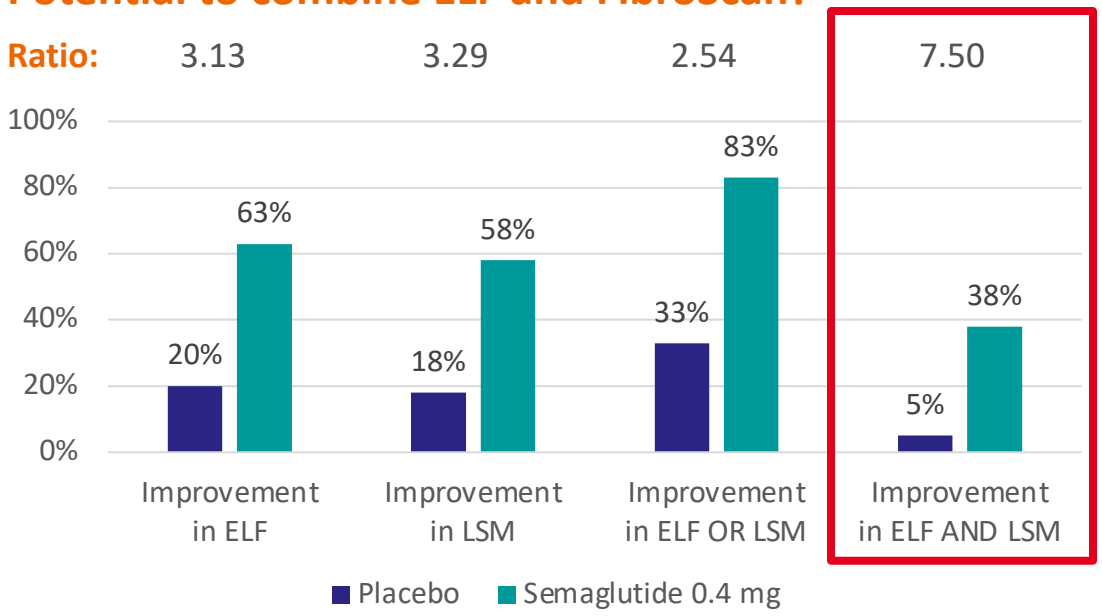
ELF change of ±0.50 to identify improvement or progression



Data from semaglutide phase 2 trial (NCT02970942):
320 NASH patients with F1-F3

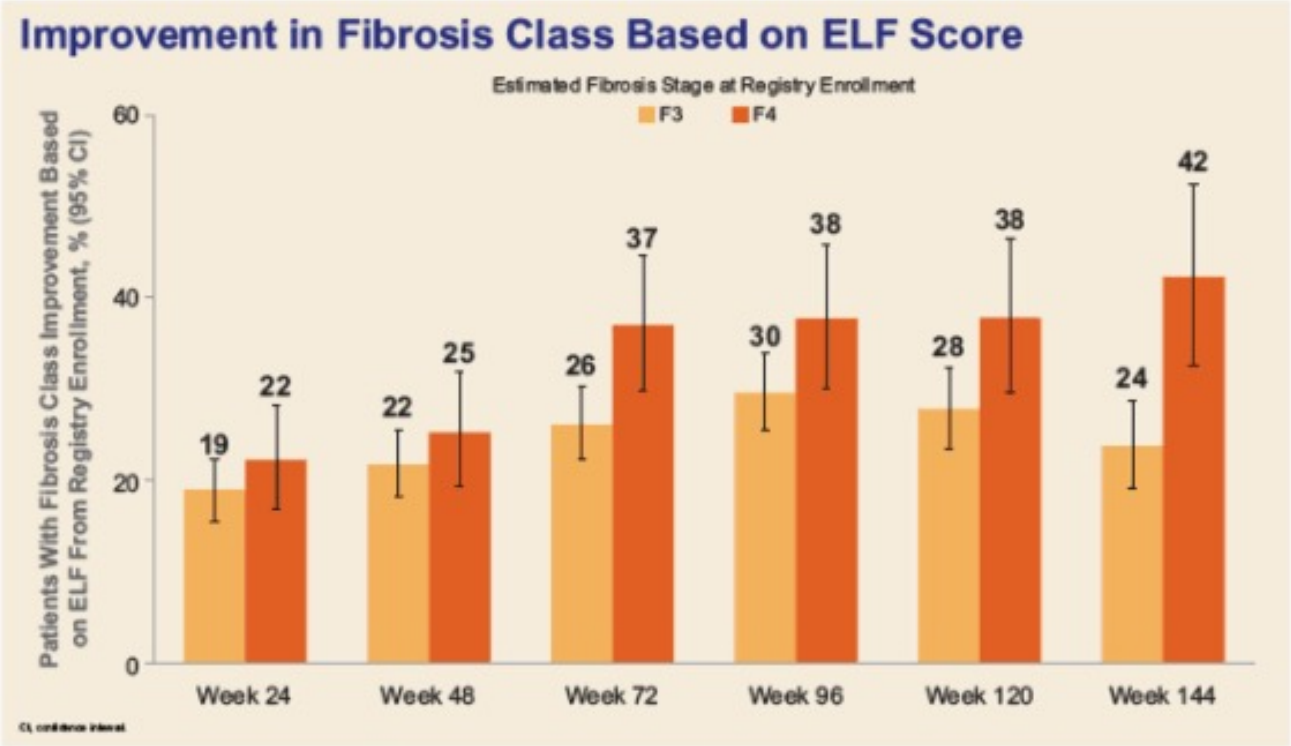
ELF change (± 0.50 units) shows dose-dependent trend. Mirrors similar trends seen with changes in LSM and histology.

Potential to combine ELF and FibroScan?



Anstee Q et al. J Hepatol. 2021;75(S2):S576-S577. **Presented at ILC 2021**

Lessons from chronic hepatitis C



- At registry enrollment, 594 (38%) and 247 (16%) patients had ELF scores consistent with F3 and F4 fibrosis, respectively
- By Week 144 of follow-up, 24% and 42% with F3 and F4 fibrosis, respectively, at registry enrollment had improvements in fibrosis class based on ELF

Elimination of underlying cause of liver disease leads to ELF improvement (≥ 0.5 units)

In patients with ELF > 11.3 at baseline (i.e. F4)… 42% of patients had ELF decrease by ≥ 0.5 units by Week 144

ELF improvement was progressive and sustained…

…but it took until Week 144 for some patients to reach ELF response

Will we see a similar pattern in NASH when effective treatments are available?

Jacobson IM, et al. Hepatol. 2019;70(Suppl 1):537. **Presented at The Liver Meeting (AASLD) 2019**

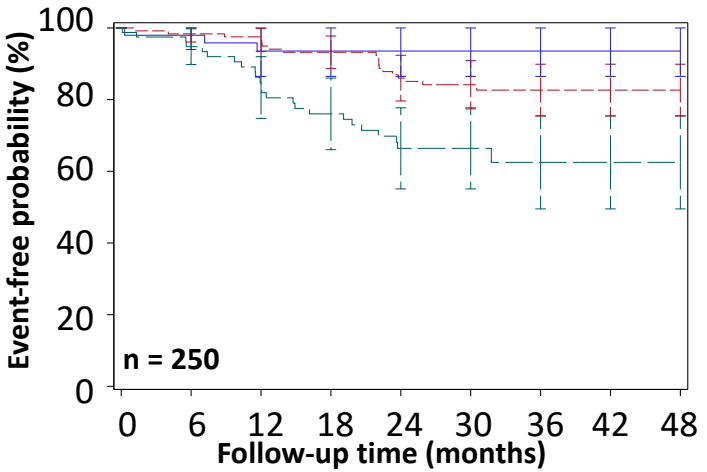
Does ΔELF correlate to changes in event risk?

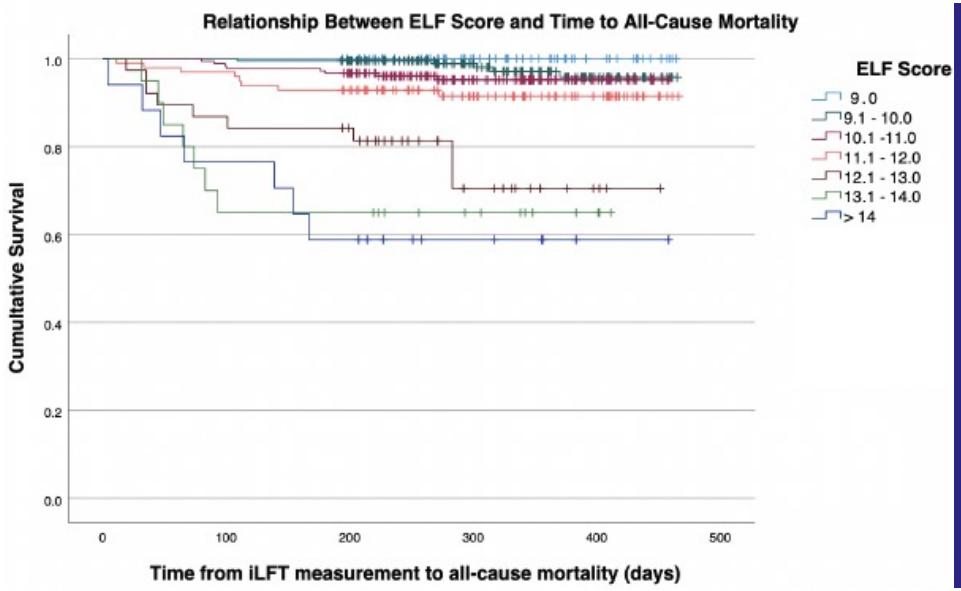
Translation of prognostic data to monitoring use

Progression to Liver Related Events

Score	n	Events	Risk	Hazard Ratio
<9.80	49	3	6.1%	1.00
≥9.80 to <11.30	122	7	15.6%	2.42
≥11.30	79	24	30.4%	6.13

Data pooled from 3 treatment and placebo arms of simtuzumab F4 Phase 2b study*





iLFT Pathway Study (NHS Tayside; N = 634)

"[I]n patients with ELF scores >13, >20% have died within 3 months…, and by 6 months from measurement nearly 40% have died."

(Pearson M et al. J Hepatol. 2022;71(S1):S495-S496)

"A unit change in ELF is associated with a doubling of risk of liver-related outcome."

(Parkes J et al. Gut. 2010;59(9):1245–1251)

"[T]he relative risk of events increased 68% per 0.5-unit increase in ELF score (HR, 1.68; 95% CI, 1.50, 1.88)."

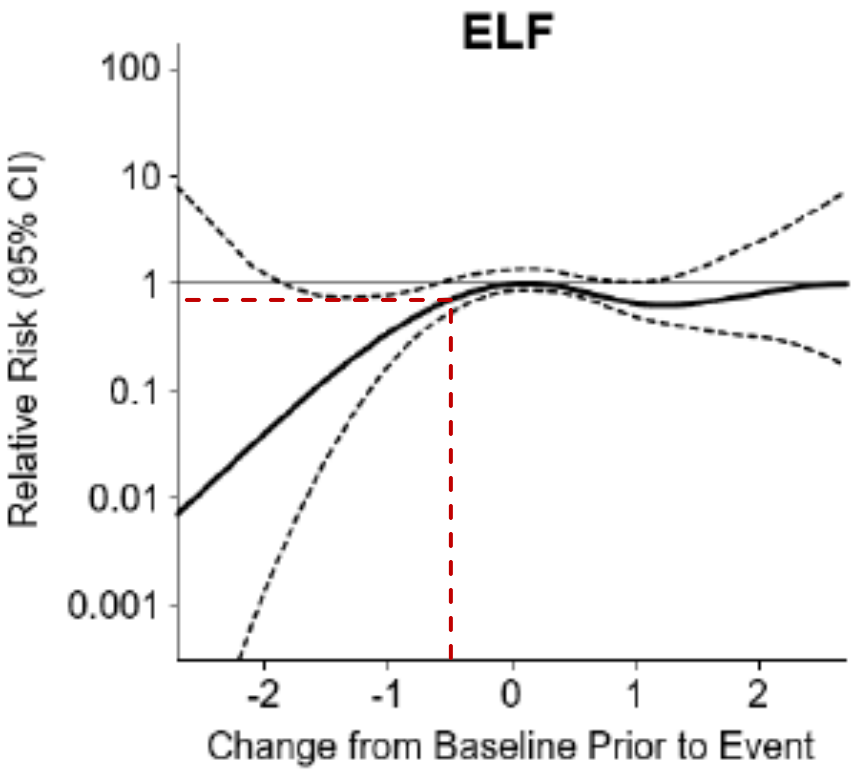
(Sanyal AJ et al. Hepatology. 2022;75(5):1235-1246)

QUESTION:
Do changes in ELF correlate to changes in clinical outcomes?

* Data from the placebo arm of this study is included in the pooled study analyses in the U.S. Instructions for Use. Data on file at Siemens Healthineers. See also: Sanyal AJ et al. Hepatology. 2019;70(6):1913–1927

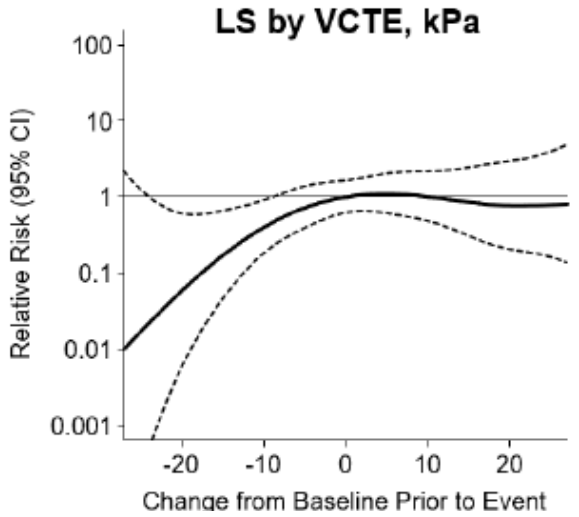
What might be optimal delta to identify a change in clinical risk?

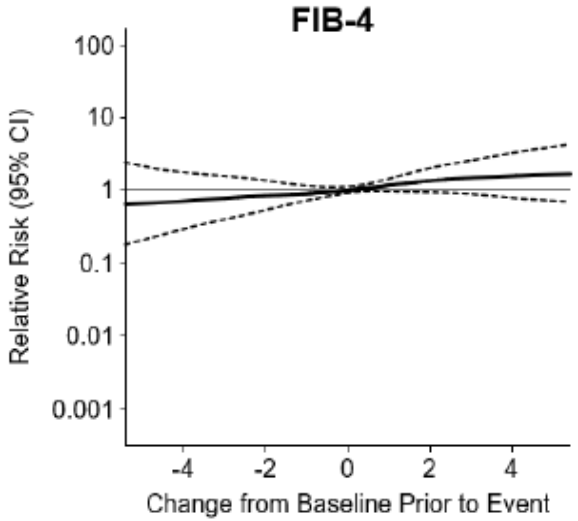
Data pooled from F4 simtuzumab (Phase 2b) and selonsertib (Phase 3) studies



QUESTION:
Is a decrease of 0.50 ELF units too little to substantially reduce risk of clinical outcomes?

For comparison…





Sanyal AJ et al. Hepatology. 2022;75(5):1235-1246.

Could a 0.50-unit ELF reduction lead to fewer clinical events*?

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EXAMPLE 1:
Baseline ELF: 8.00
0.50 unit increase at 1 year

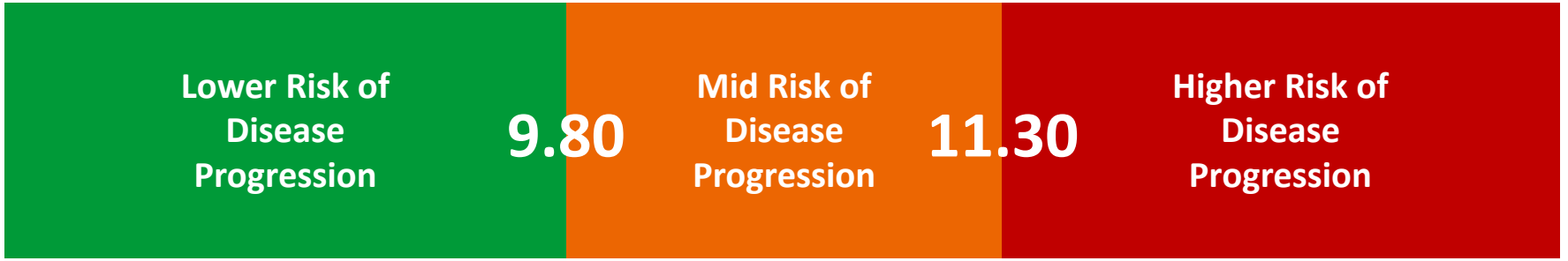
8.00 → 8.50

Patient remains in lower risk category

EXAMPLE 3:
Baseline ELF: 12.00
0.50 unit decrease at 1 year

11.50 ← 12.00

Although patient remains in higher risk category, considerable improvement seen.



9.50 ← 10.00

EXAMPLE 2:
Baseline ELF: 10.00
0.50 unit decrease at 1 year

Patient drops to lower risk category

Internal analysis (≥0.50-unit reduction of ELF at 48 weeks)

- For patients with Baseline ELF < 9.80:
  - Does not alter risk of events
  - These patients already are at lower risk of events
- For patients with Baseline ELF ≥ 9.80:
  - ELF responders show approx. 50% reduction in events
  - Trend only (dataset not statistically significant)
  - These patients may be most relevant to evaluate ELF changes

* This claim has not been reviewed by the FDA and is not available in the U.S. for routine clinical use.

Open questions

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1. How do we confirm that a decrease of ELF by ≥0.50 corresponds to approximately 50% fewer clinical events*?

   To validate, we need:
   - Larger sample size
   - Effective drug with many ELF responders (≥ 0.50 unit reduction in ELF)
   - Sufficient follow-up time (up to 3 years)

2. What is the timeframe for subsequent ELF testing?

   In a natural history cohort (i.e. spontaneous regression): 48-52 weeks?

   If patients are treated by efficacious anti-fibrotic drugs: as low as 24 weeks?

* This claim has not been reviewed by the FDA and is not available in the U.S. for routine clinical use.

What is the optimal timing for ELF measurement?

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Drug	Mechanism of Action	Study (Phase)	Duration	Treatment Arms	Estimated Treatment Difference (Mean ΔELF) Tx Arm A	Tx Arm B	Tx Arm C
Efruxifermin	FGF21 mimic	HARMONY (2b)	24 weeks	A: 28 mg (N=38) B: 50 mg (N=36)	-0.7	-0.8	---
Semaglutide Cilofexor Firsocostat	GLP-1R agonist FXR agonist ACC inhibitor	NCT03987074 (2)	24 weeks	A: SEMA (N=21) B: SEMA+CILO (N=22) C: SEMA+FIR (N=22)	-0.56*	-0.47*	-0.59*
PXL065	PPARγ modulator	Destiny 1 (2)	36 weeks	A: 7.5 mg (N=25) B: 15 mg (N=32) C: 22.5 mg (N=30)	-0.06	-0.13	-0.28
Resmetirom	THR-β agonist	NCT02912260 (2)	36 weeks	A: 80 mg (N=84)	-0.48**	---	---
Cilofexor Firsocostat	FXR agonist ACC inhibitor	ATLAS (2b)	48 weeks	A: CILO (N=40) B: FIR (N=40) C: CILO+FIR (N=78)	-0.1	-0.4	-0.3
Semaglutide	GLP-1R agonist	NCT02970942 (2)	72 weeks	A: 0.1 mg (N=80) B: 0.2 mg (N=78) C: 0.4 mg (N=82)	-0.35	-0.40	-0.57
Obeticholic acid	FXR agonist	REGENERATE (3)	144 weeks	A: 10 mg (N=311) B: 25 mg (N=308)	-0.06	-0.07	---

* No placebo arm for this study; ** Patients with baseline ELF > 9.00

Rate of ELF change may be influenced by drug mechanism of action

Sources:
Akero Therapeutics' Phase 2b HARMONY Study Press Release (2022-11-13); Alkhouri N et al. J. Hepatol. 2022;77(3):607-618; poxel SA (https://www.poxelpharma.com/en_us/pipeline/nash);
Harrison SA et al. Lancet. 2019;394(10213):2012-2024; Loomba R et al. J Hepatol. 2020;73(S1):S116-S117;
Newsome PN et al. N Engl J Med. 2021;384(12):1113-1124; Rinella ME et al. J Hepatol. 2022;76(3):536-548

In summary…

1. Validation of the ELF Test for a monitoring context of use* is a work in progress.
2. A reduction of ELF by ≥ 0.50 units shows promise as a surrogate endpoint for treatment response
3. Deltas may be more helpful in patients with Baseline ELF ≥ 9.80
4. Early data suggests that a decrease in ELF ≥ 0.50 is roughly correlated to 50% fewer liver-related clinical events, but more studies are needed.
5. Decreases in ELF ≥ 0.50 may be seen as early as 24 weeks, but likely dependent on drug mechanism of action – more studies are needed

Siemens Healthineers is open to partnerships:

1. To address the above questions
2. To potentially develop recommendations for clinical practice (if use is sufficiently validated)

* This claim has not been reviewed by the FDA and is not available in the U.S. for routine clinical use.

Thank You

Keyword: liver doctor

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