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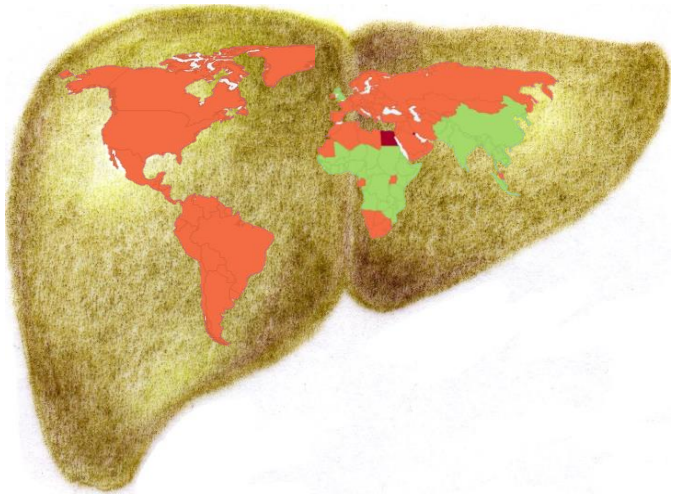

Lessons learned from NASH clinical trials

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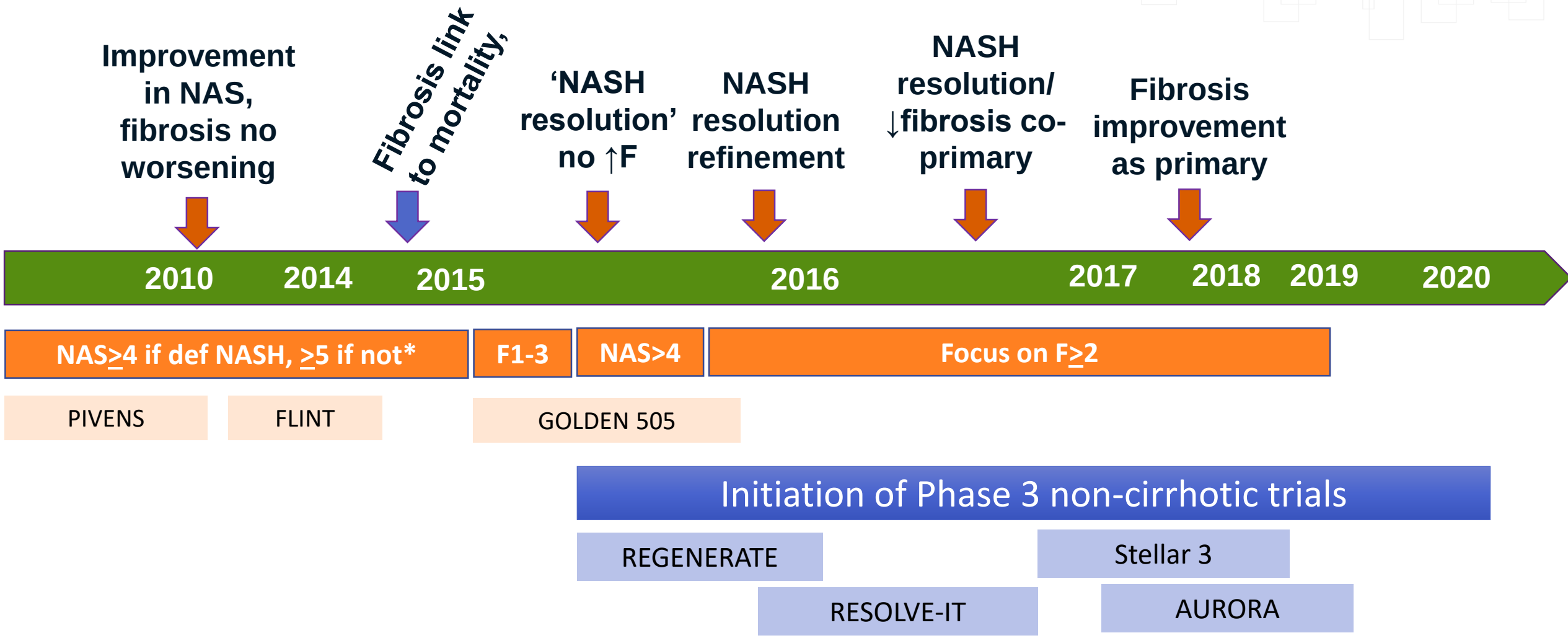
Professor of Medicine, Division of Gastroenterology & Hepatology

Northwestern University Feinberg School of Medicine

Berkeley Public Health

Evolution of NASH inclusion criteria and histological endpoints



Lessons learned in published placebo controlled Phase 2 studies

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PIVENS	FLINT	GOLDEN	NGM	Centaur
High screen fail rate…50%				
Central pathology critical	First trial to show fibrosis can improve with metabolic MoA ALT can predict histological response	Higher Placebo response: milder disease, looser endpoint Fibrosis improves when NASH improves Center effect	Steatosis and ALT can improve quickly and dramatically	Appealing MoA may have been offset by redundant pathways or limited target engagement

Resolution of NASH strongly tracks with fibrosis improvement (Brunt, Hepatology 2019)

Endpoints in early stage disease: ALT and PDFF – is one enough?

Endpoints in early phase 2 development

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ALT

- **↑ALT associated with ↑ mortality**
- **Every 10 U/L ↓ in ALT: OR 1.3** for histological improvement or resolution of NASH
- ≥17 U/L ALT ↓ predicted response in FLINT

MRI PDFF

- **≥ 5% absolute** reduction*
- **≥ 30% relative** reduction*
- Associates with histological improvement

* Targets for efficacy are based on limited data

Validity of ALT and MRI PDFF to assess efficacy is MoA dependent

(PIVENS, TONIC)

Ruhl and Everhart Gastroenterology 2009; Lee et al. Hepatology 2008, Ruhl et al. Hepatology 2016; Vuppalanchi et al. CGH 2014; Patel et al. Therap Adv Gastro 2016; Middleton et al. Gastroenterology 2017; Loomba et al. Gastroenterology 2019

Steatosis as an endpoint

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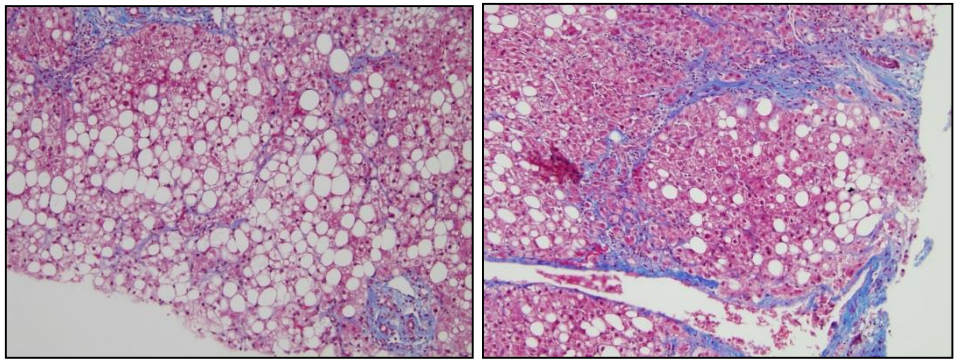
Pros

- Easy to measure
  - Good agreement on histology
  - Accurate non-invasive measurement
- Degree of steatosis associated with increased metabolic risk
- ?Link to fibrosis progression [1]

Cons

- Improvement not linked to outcomes
- Steatosis lessens as disease progresses



Stage 2-3 Stage 3-4

[1] Ajmera et al baseline PDFF and fibrosis progression. Gastroenterology 2018

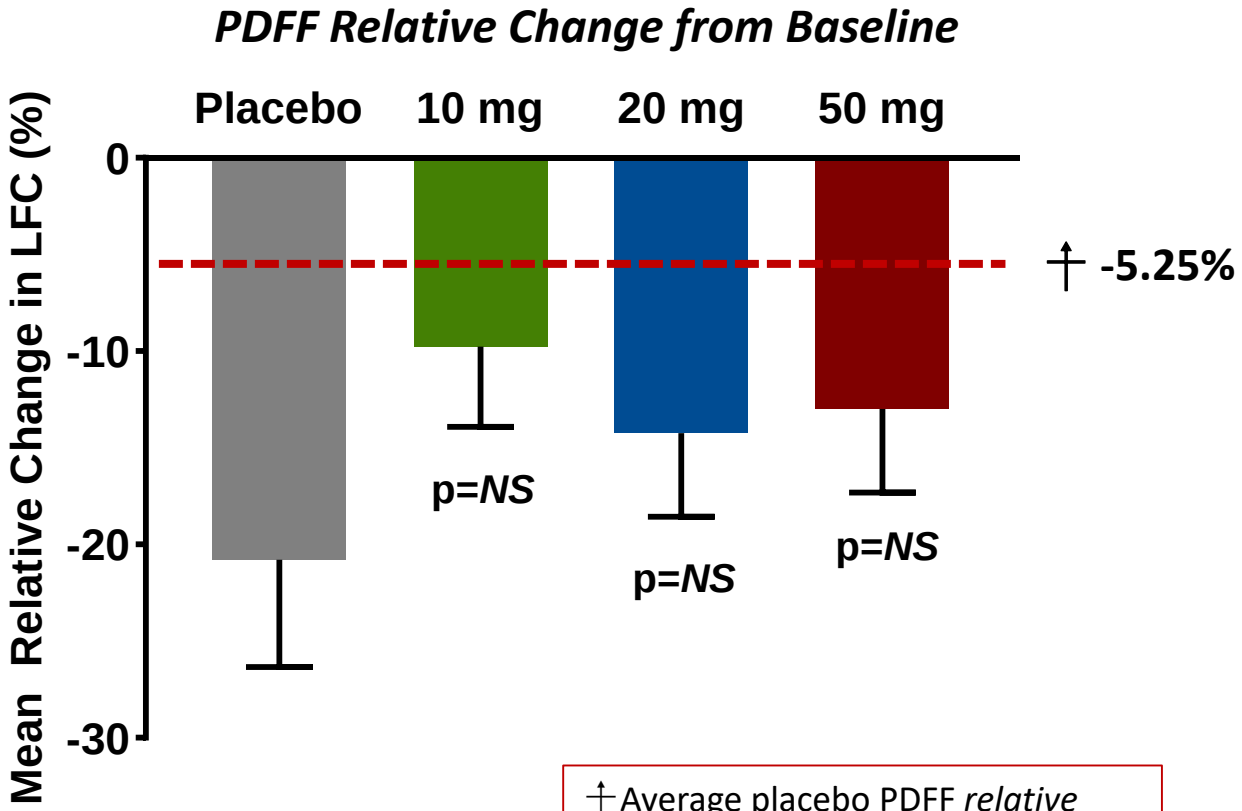
Association between significant improvements in liver fat, ALT and histology in NASH trials

Study	Drug/MoA	Steatosis	ALT	GGT	NASH res	Fibrosis
Wt loss	N/A	+	+	+	+	+
PIVENS	Pio/PPARγ	+	+	+	+*	+
PIVENS	Vit E	+	+	+	Trend,p=0.05	-
FLINT	OCA/FXR	+	+	+	Trend,p=0.08	+
LEAN	Liraglutide/GLP-1	-	**+ (trend)**	+	+	+
REGENERATE	OCA/FXR	-	+	+	+*	+
GOLDEN	Elafibranor/PPARα,δ	+/-	+	+	**+ (NAS≥4)**	
Madrigal	THRβ	+	+	+	+	+**
NGM (no Pbo)	NGM282/FGF19	+	+	+	+	+
ARREST	Aramchol/SCD-1 modulator	+	+		+	-

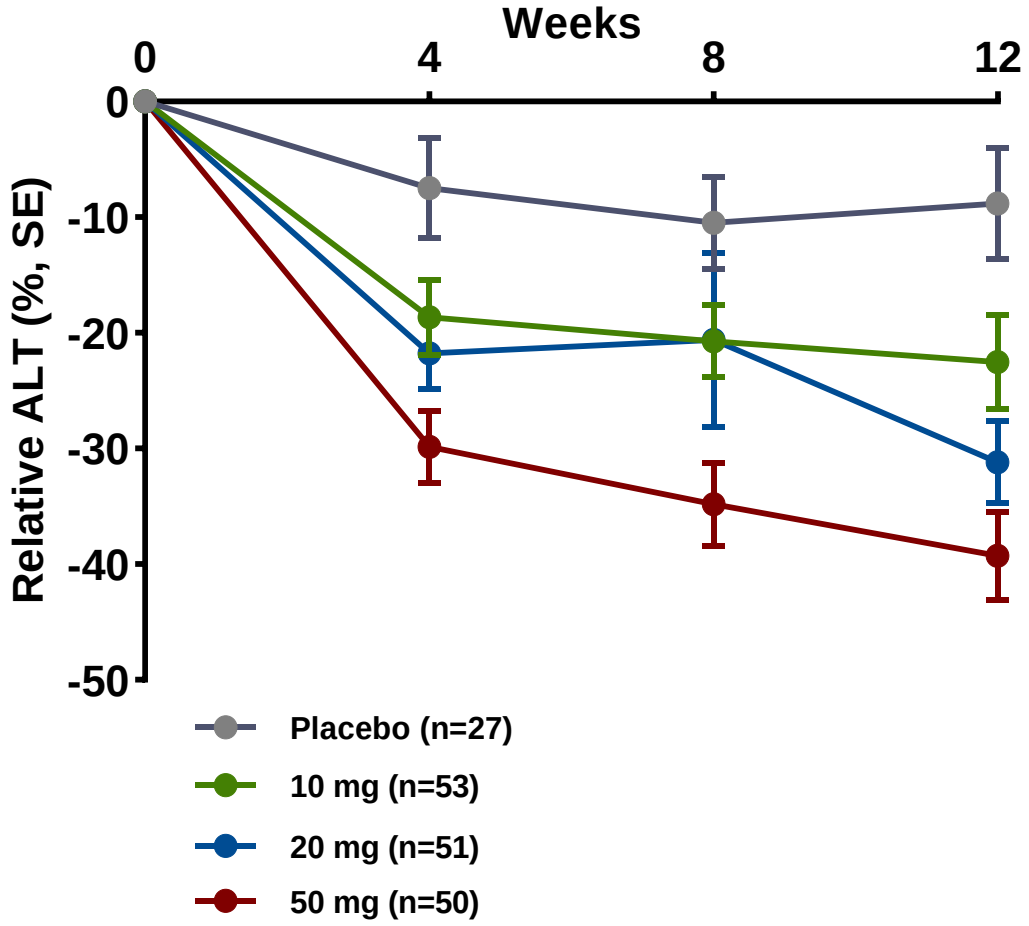
*By gestalt diagnosis
** By Histoindex only

Seladelpar Phase 2b Study in NASH

Discordance between PDFF response and ALT

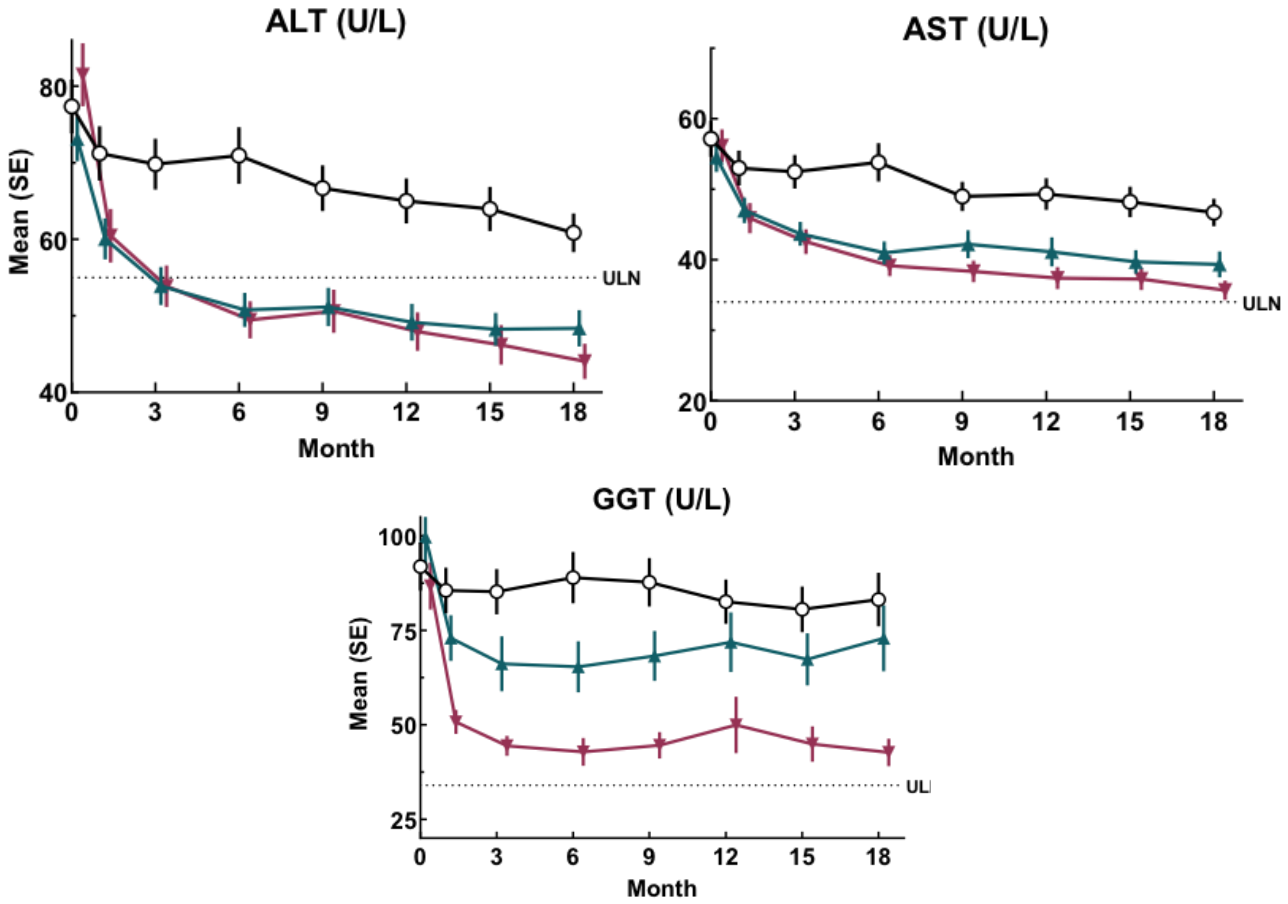


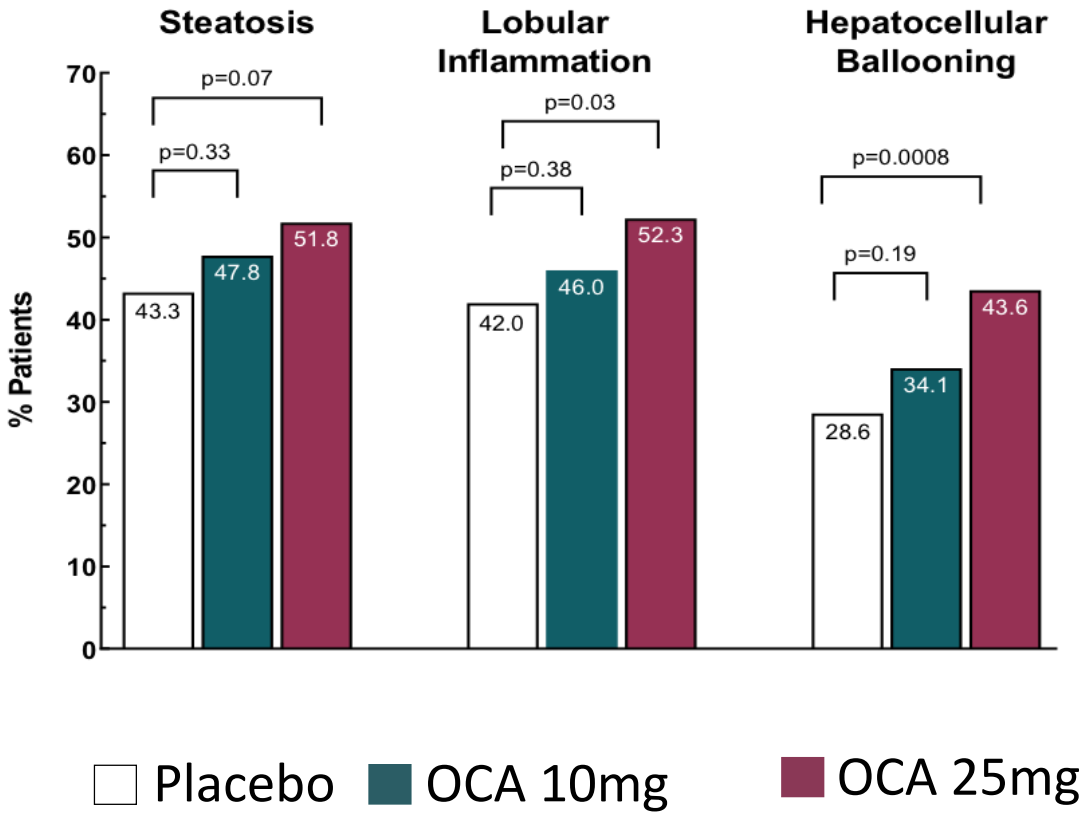
†Average placebo PDFF *relative* change (Viking, MGL, Pegbelfermin, GS4997, Aramchol): -5.25%



Cymabay Press release, June 11, 2019

Precedent for liver chemistry improvement independent of steatosis





Younossi et al. ILC, Vienna 2019

The impact of the placebo response and importance of placebo control

Protocol defined vs. modified NASH resolution

NAS	n	Placebo, n (%)
Protocol-defined primary outcome		
Total	274	92 (17)
NAS ≥4 (moderate and severe)	234	76 (11)
NAS 3 (mild)	40	16 (50)
Modified definition of response		
Total	274	92 (12)
NAS ≥4 (moderate and severe)	234	76 (9)
NAS 3 (mild)	40	16 (25)

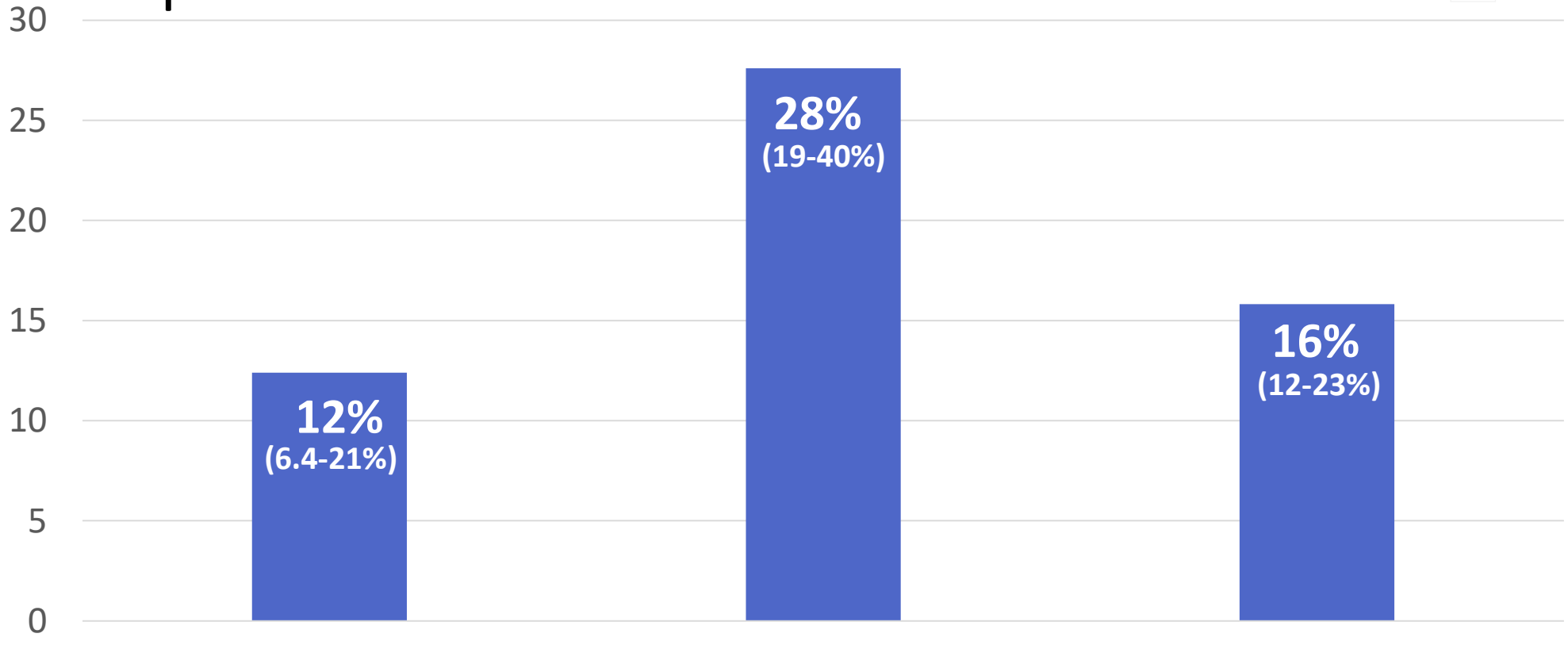
Response according to baseline fibrosis

Population	Selection, n	Placebo
All NAS ≥4	234[b]	76 (9)
	202[c]	63 (11)
NAS ≥4 with fibrosis (any stage)	204[b]	66 (11)
	176[c]	55 (13)
NAS ≥4 with moderate/advanced fibrosis (F2, F3)	118[b]	41 (7)
	99[c]	32 (9)

b - all patients; c- those with EOT biopsy

Ratziu, et al. *Gastroenterology.* 2016

Expected placebo response depends on the endpoint



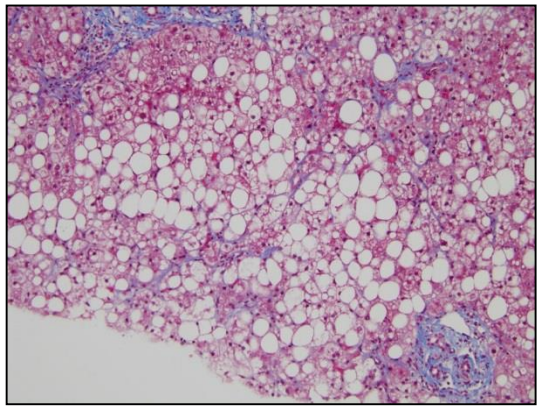
Factors influencing placebo response

- Disease activity at baseline ✓
- Endpoint ✓
- Weight loss ✓
- Surreptitious Vit E use (intentional or non-intentional) ✗
- Dietary macronutrients: e.g. Fructose, olive oil, coffee ✗
- Change in activity level, intensity of exercise ✗
- **Alcohol intake** ✗

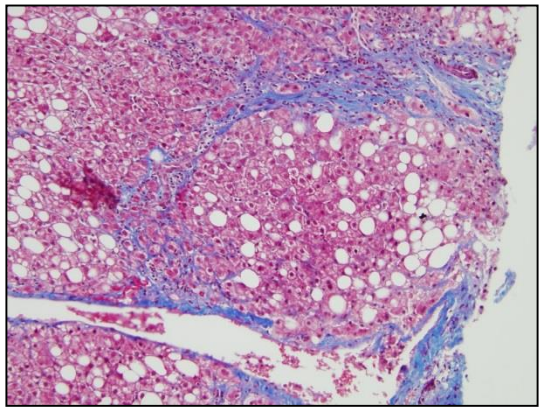
The pitfalls of current histologic endpoints

Currently accepted endpoints for non-cirrhotic NASH

- **Resolution of NASH**, *no worsening of fibrosis*



Stage 2-3



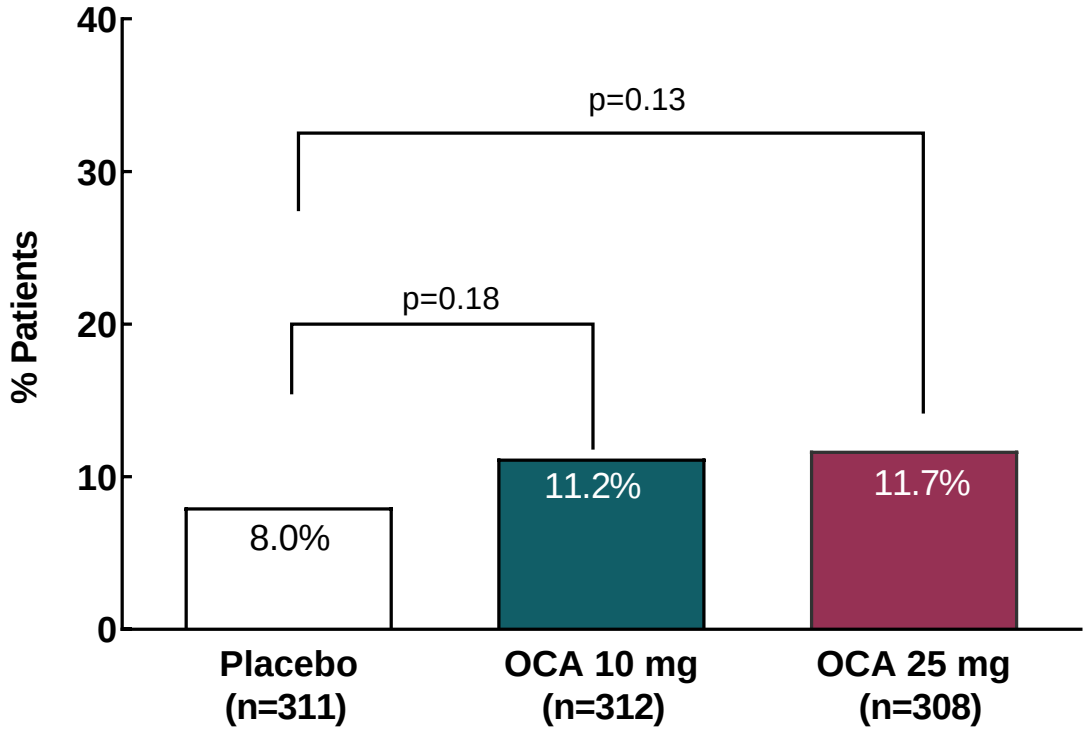
Stage 3-4

Resolution or improvement of NASH could reflect disease progression

- **Reduction in fibrosis,** *no worsening of NASH*

  - Fibrosis linked to hard clinical outcomes
  - Needs to not adversely impact metabolic or inflammatory activity

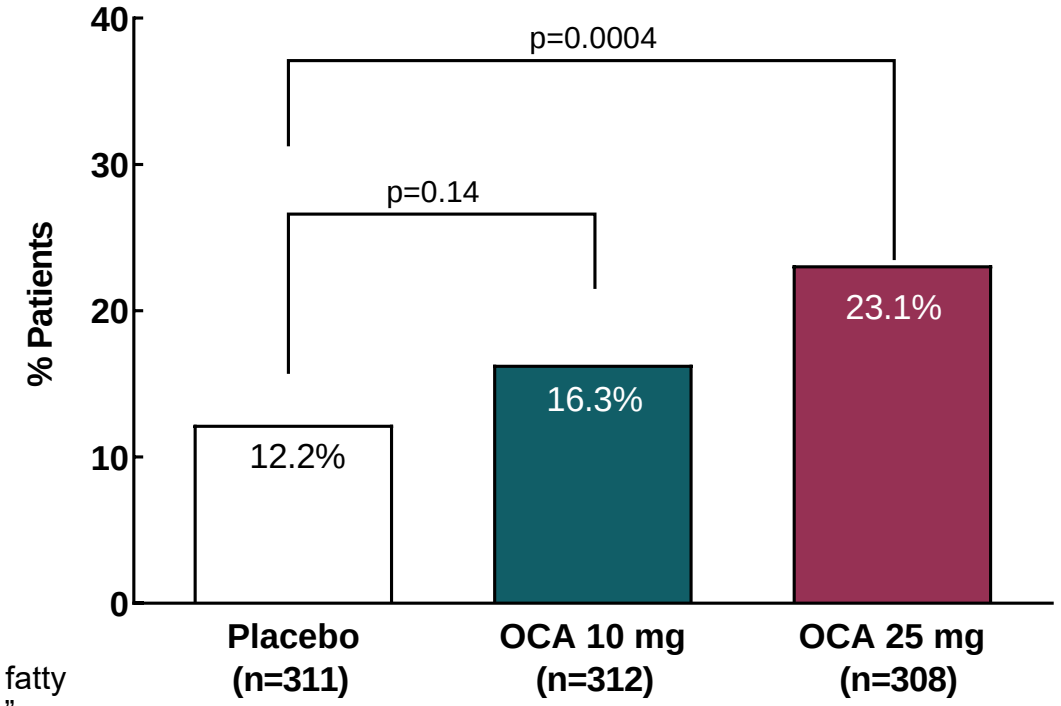
NASH Resolution With No Worsening of Fibrosis by criteria



Primary endpoint definition: (i) pathologist overall histopathologic assessment of "no fatty liver disease" or "fatty liver disease (simple or isolated steatosis) without steatohepatitis"; (ii) NAFLD Activity Score (NAS): hepatocellular ballooning = 0 and lobular inflammation = 0 or 1; and (iii) no increase in fibrosis stage from baseline

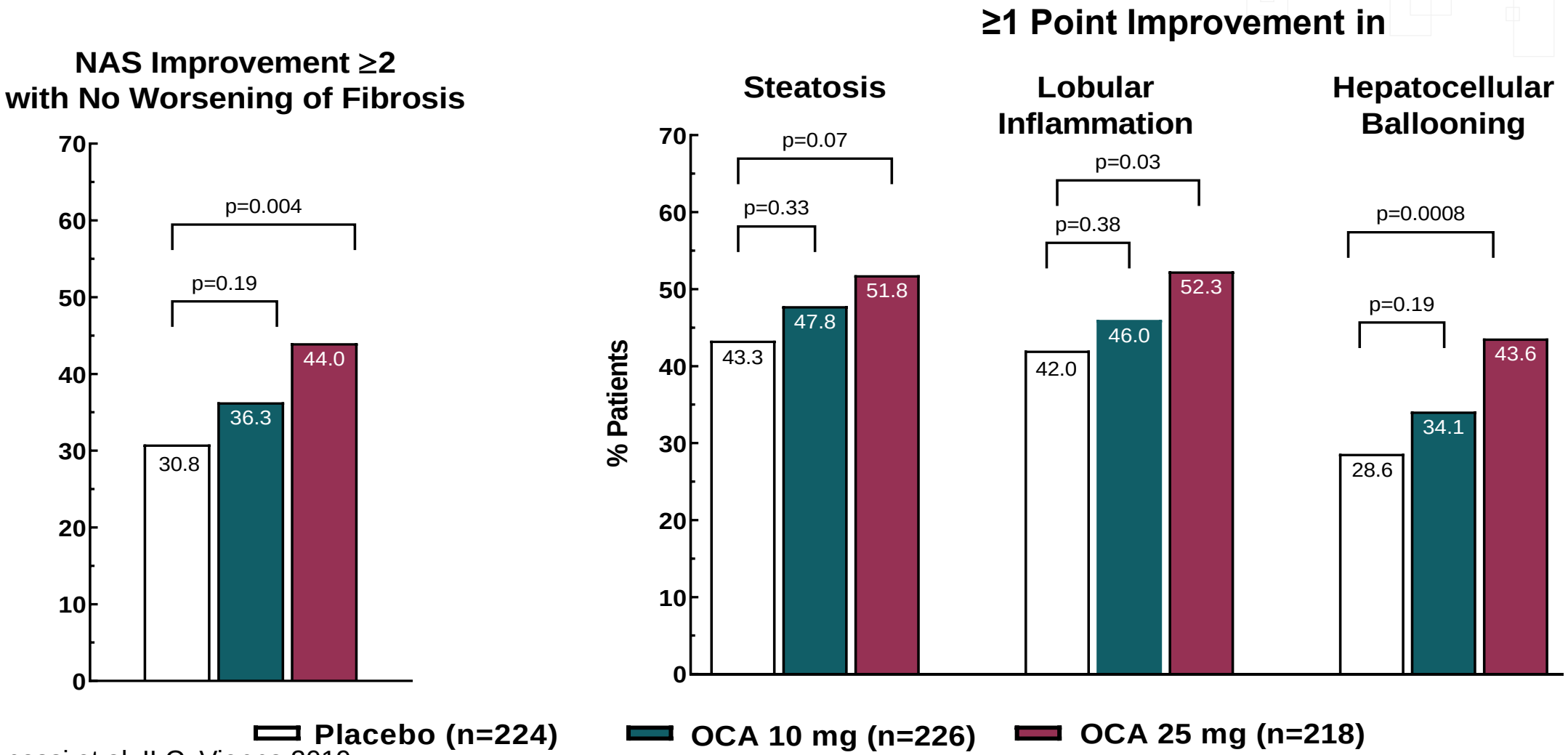
Younossi et al. ILC, Vienna 2019

Gestalt: Resolution of Definite NASH With No Worsening of Fibrosis



Endpoint defined as (i) resolution of definite NASH (i.e., absence of steatohepatitis) based on pathologist overall diagnostic assessment and (ii) no worsening of fibrosis stage from baseline.
P values are nominal.
ITT population (N=931).

Improvement by NAS ≥2 and individual components



Younossi et al. ILC, Vienna 2019

P values are nominal.
Per protocol population (N=668).

Inter- and Intra-rater Agreement on Major Categories

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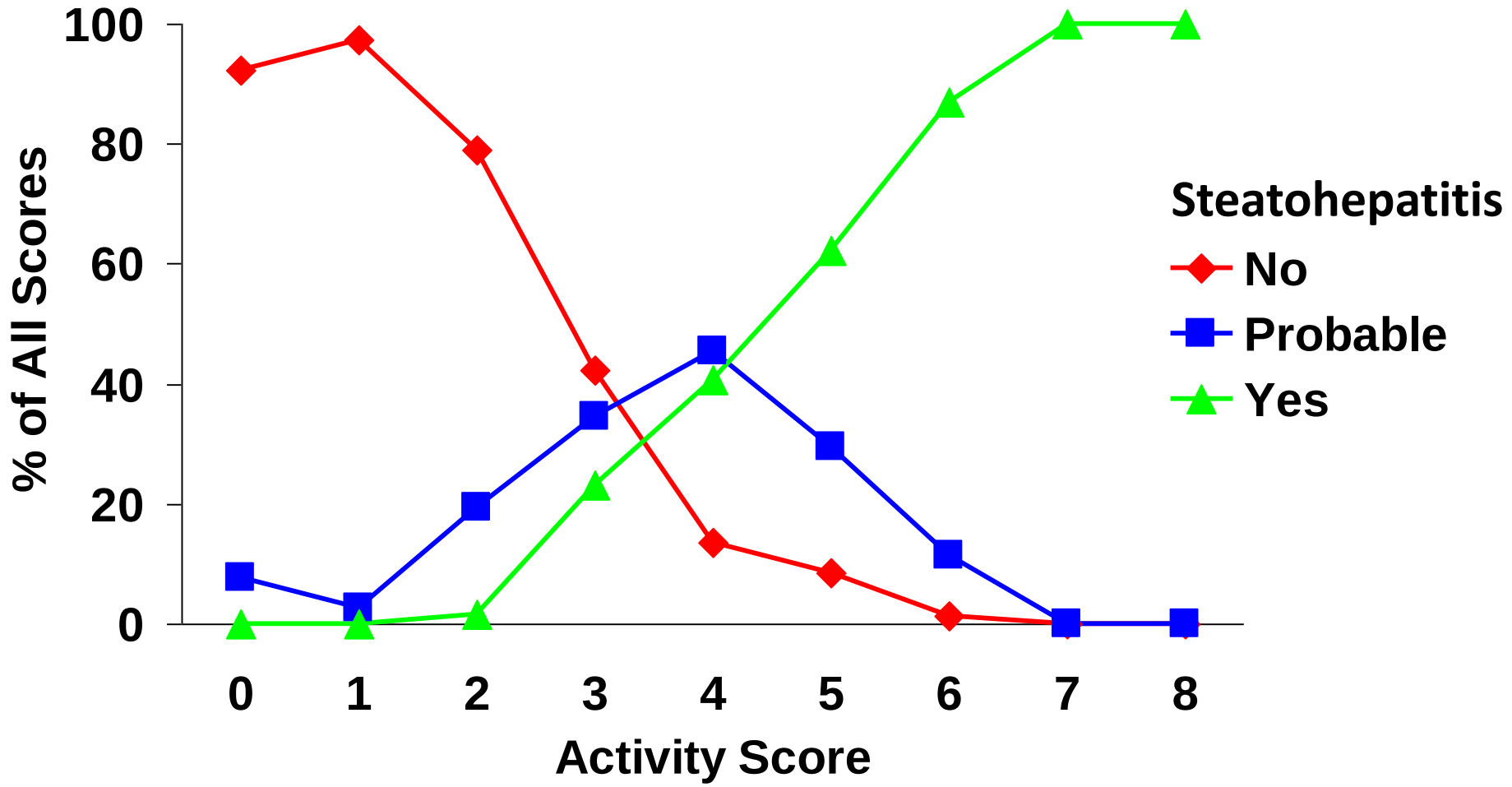
	Inter (adult)	Inter (ped)	Intra (adult)
Steatosis	0.79	0.64	0.83
Fibrosis	0.84	0.62	0.85
Lob. Inf.	0.45	0.28	0.60
Ballooning	0.56	0.22	0.66
Mallory's	0.58	0.69	0.64
Diagnosis	0.61	0.33	0.66

(All values are grouped, weighted Kappa values)

NAFLD Activity Score Discriminates Among Steatohepatitis Diagnoses In Adults



Is this NASH Donald Trump?

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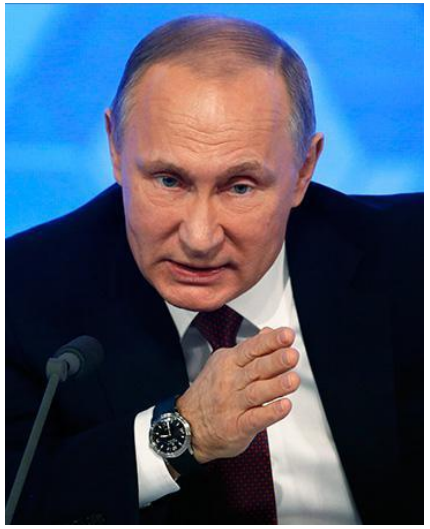
Criteria: Blond hair - likely dyed and modified, orange skin, small hands and CANNOT be diplomatic





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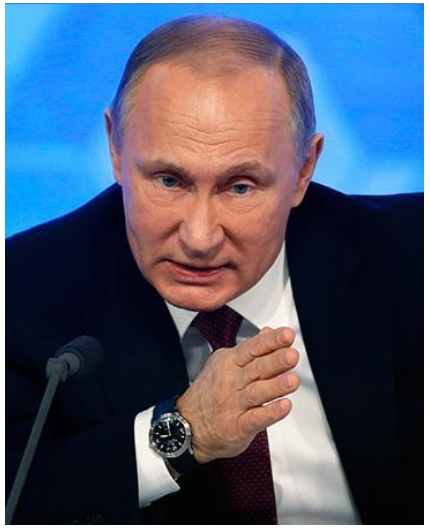

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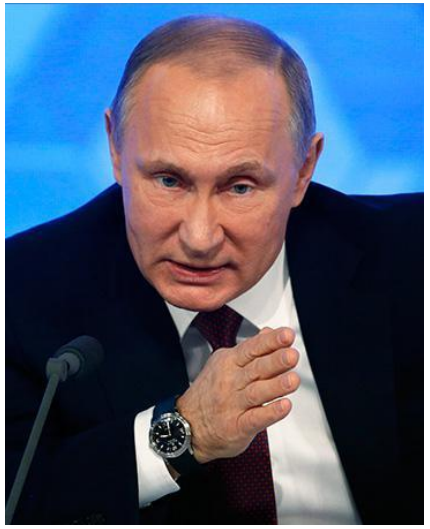

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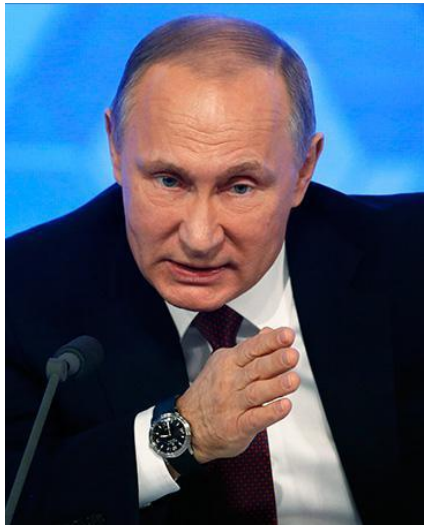


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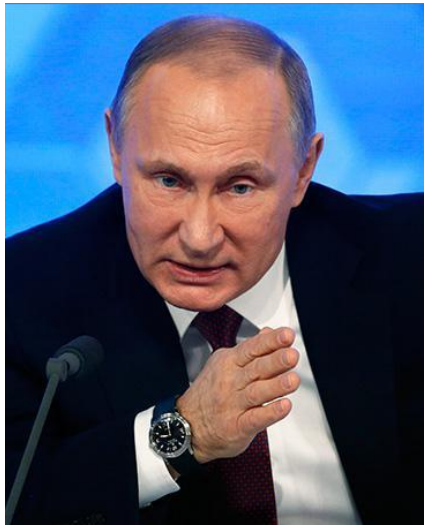

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Gestalt: You know him when you see him










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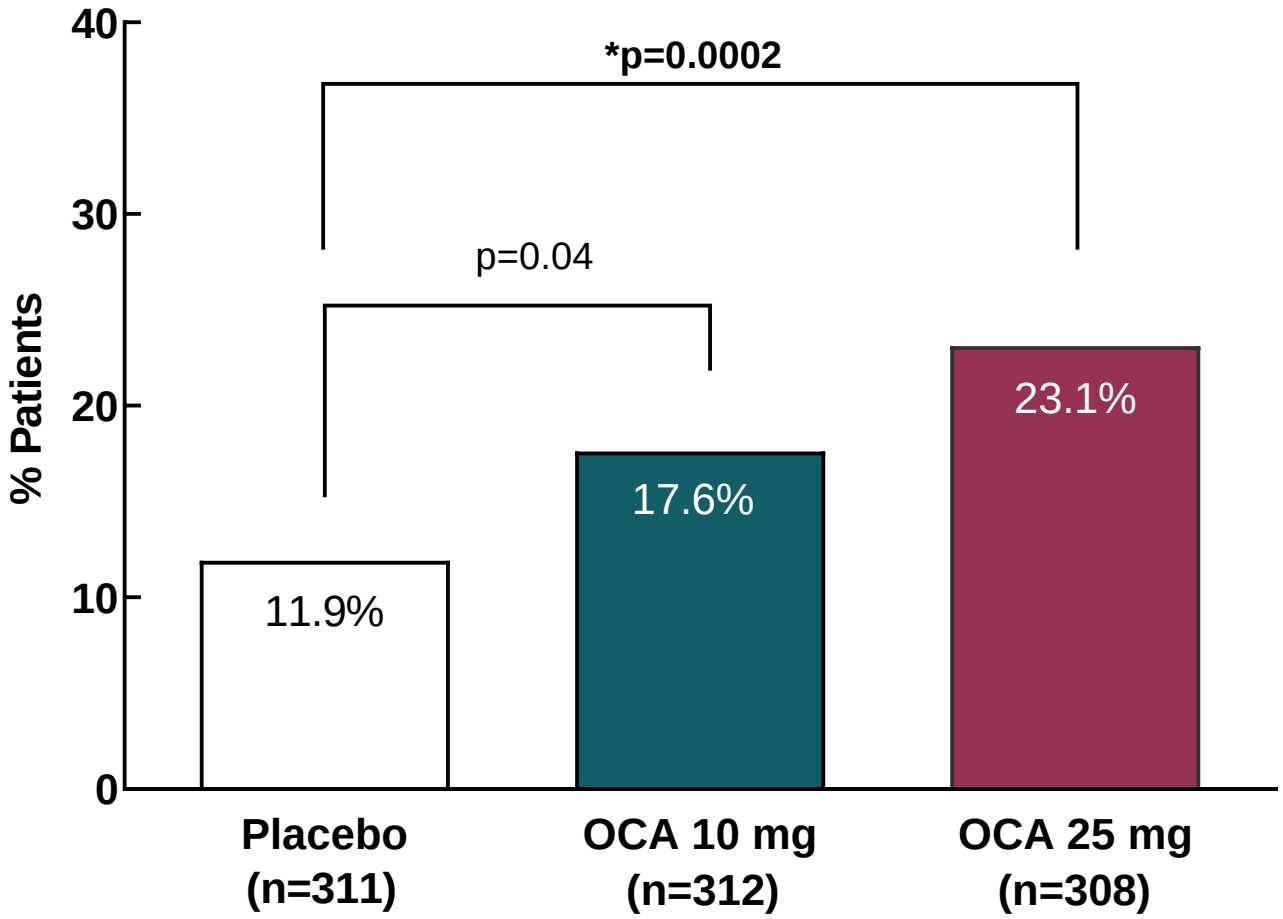
Fibrosis Improvement by ≥1 Stage with No Worsening of NASH (ITT, F2/3)



Primary endpoint definition:

- Improvement in fibrosis by ≥1 stage (NASH CRN)

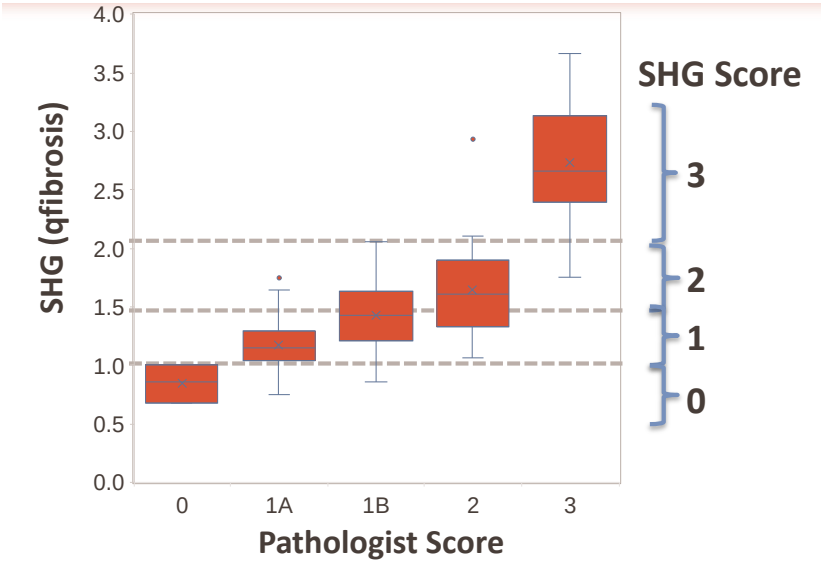
AND

- no worsening of lobular inflammation, hepatocellular ballooning **or steatosis**

Younossi et al. ILC, Vienna 2019

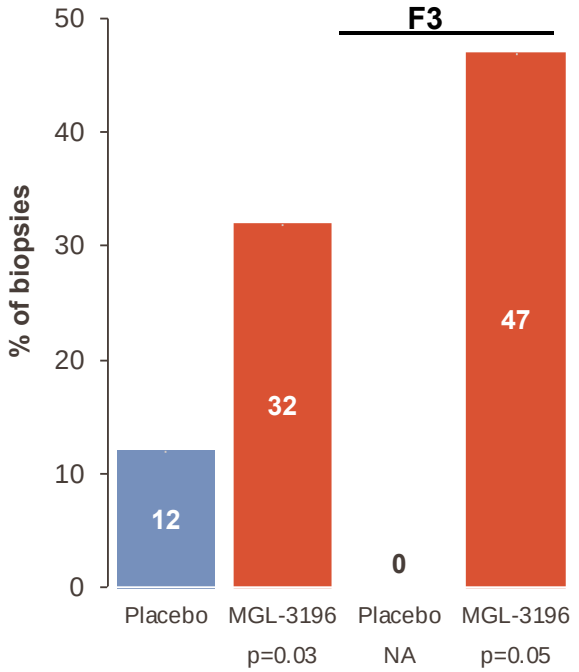
Week 36: MGL-3196 impact on Fibrosis

Using traditional staining, fibrosis was reduced by ≥ 1 point in 29% of MGL-3196 treated patients vs. 23% in placebo (F1-3, ≅ 50% F1))



Second Harmonic Generation (SHG) microscopy: Automated quantification of fibrosis on liver biopsy that correlated with pathologist read (baseline, r=0.76).

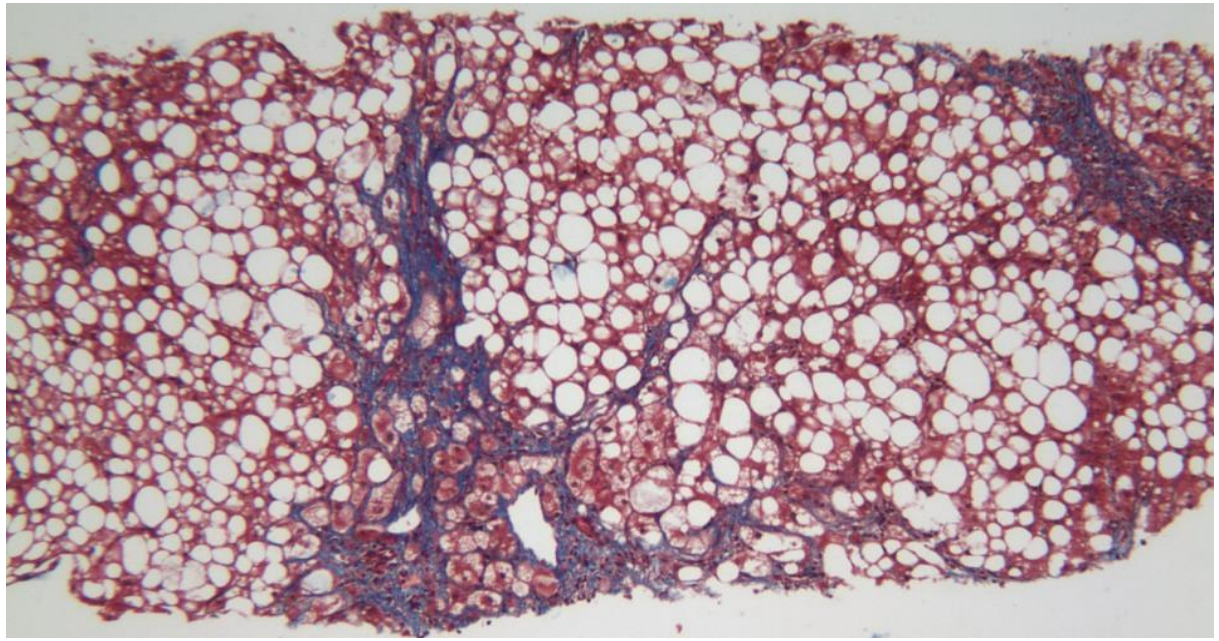
>=1 pt reduction in fibrosis on liver biopsy (SHG)



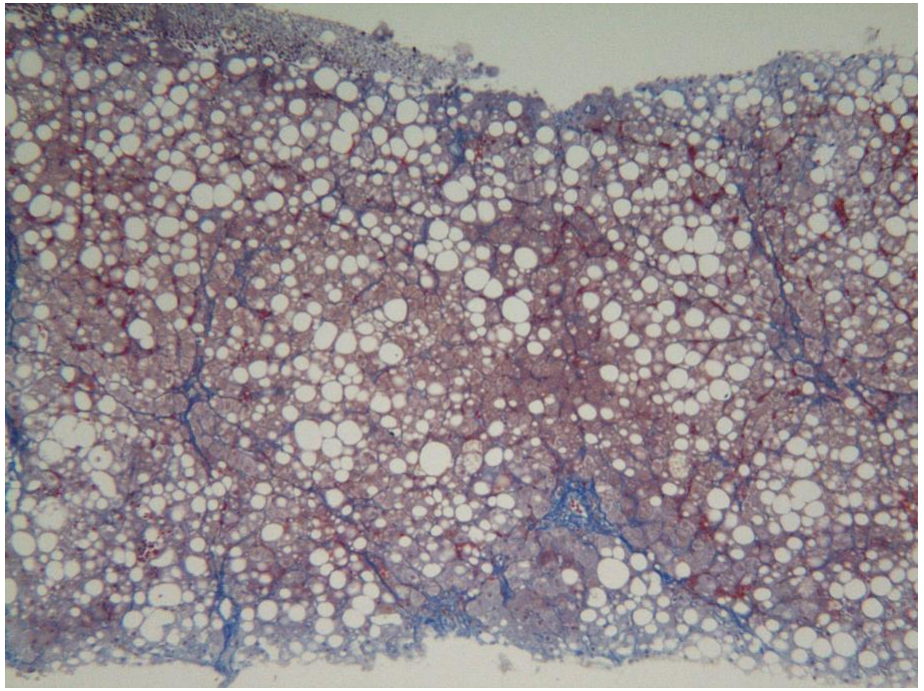
Those with F2/3 had more marked response

Variability in collagen burden within fibrosis stage

Baseline



Post-treatment



Both are technically stage 3 fibrosis

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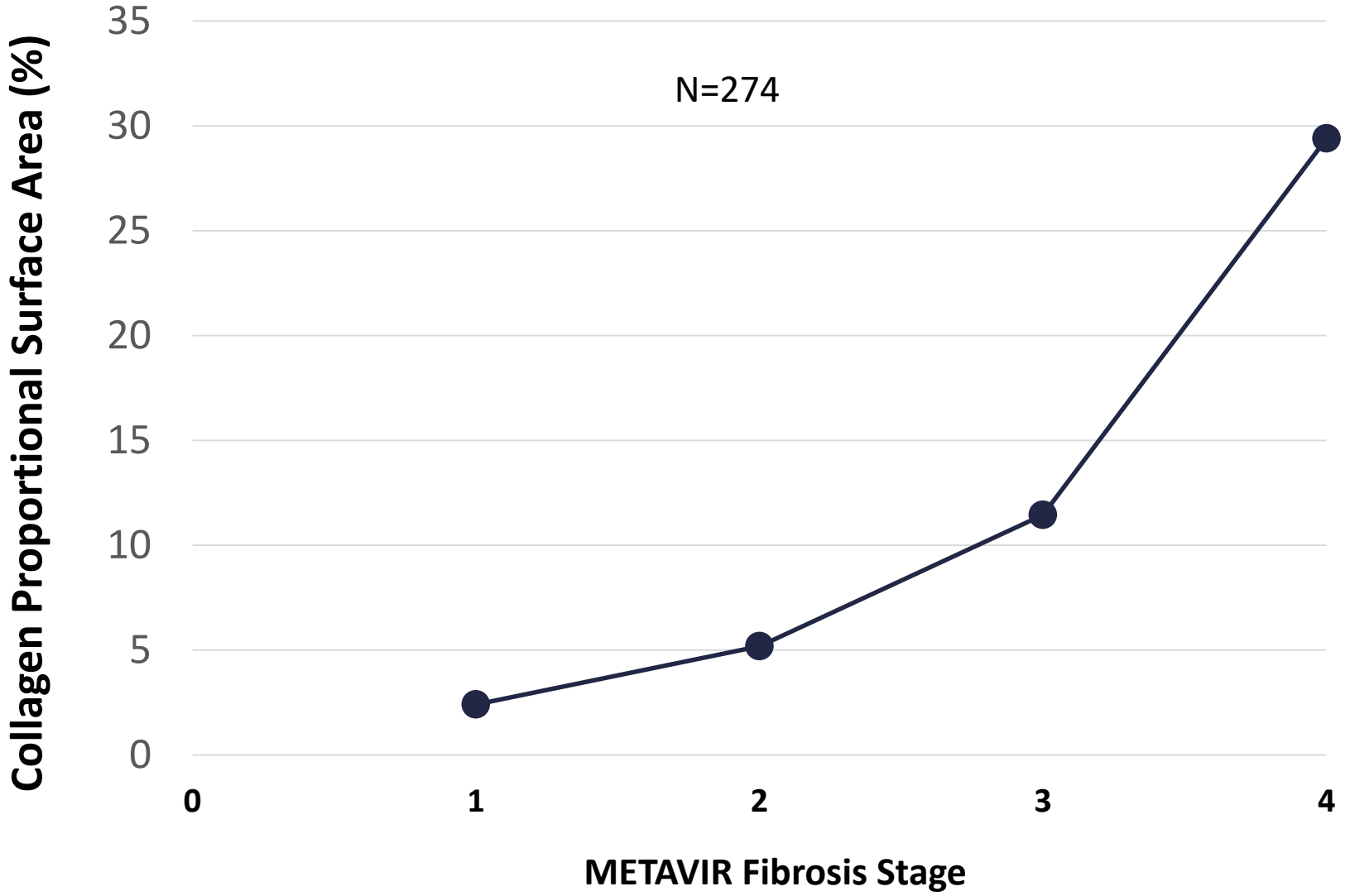
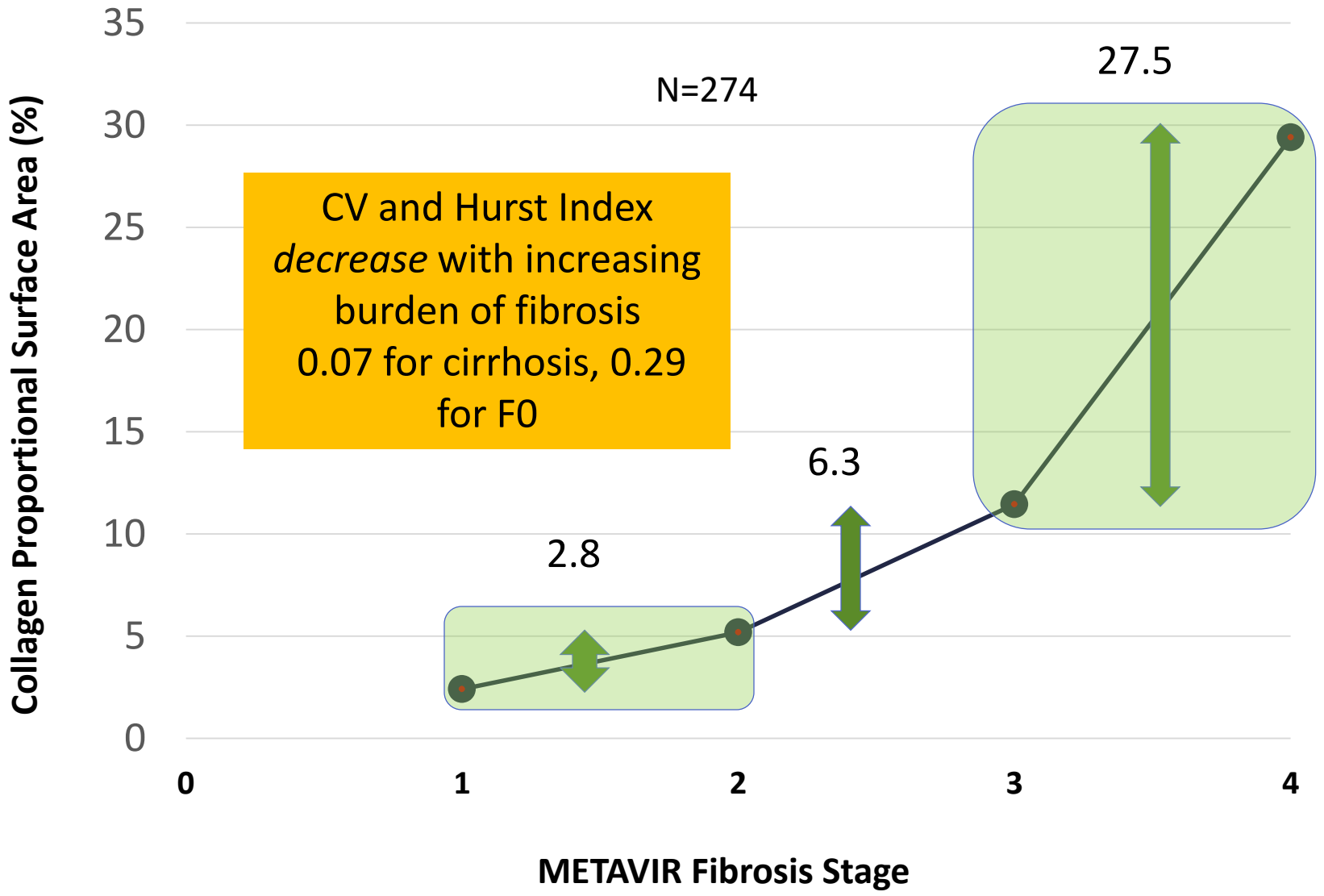
Histology courtesy of Elizabeth Brunt

Liver Collagen Burden is not Linear Across Fibrosis Stages



Chen et al., *Medicine* 2016 Aug; 95(35): e4736

Liver Collagen Burden is not Linear Across Fibrosis Stages



Chen et al., *Medicine* 2016 Aug; 95(35): e4736

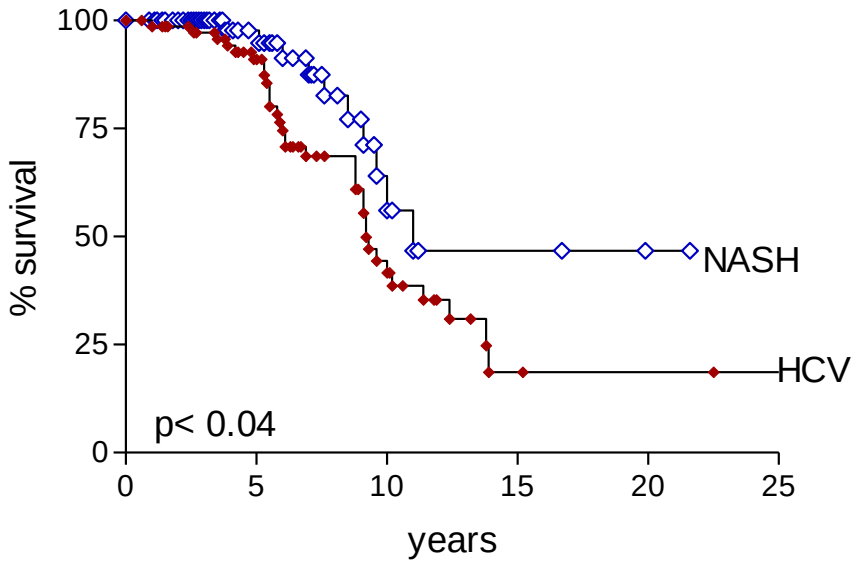
Limitations of current histologic endpoints

- Discrepancy between gestalt and quantitative assessment for NASH resolution
- Inter-observer variability (between local and central as well as between experts)
- Fibrosis stages may not accurately reflect the burden of fibrosis as a continuous measure

Studies evaluating efficacy in cirrhosis

Challenges in trials using endpoints to define clinically meaningful benefit

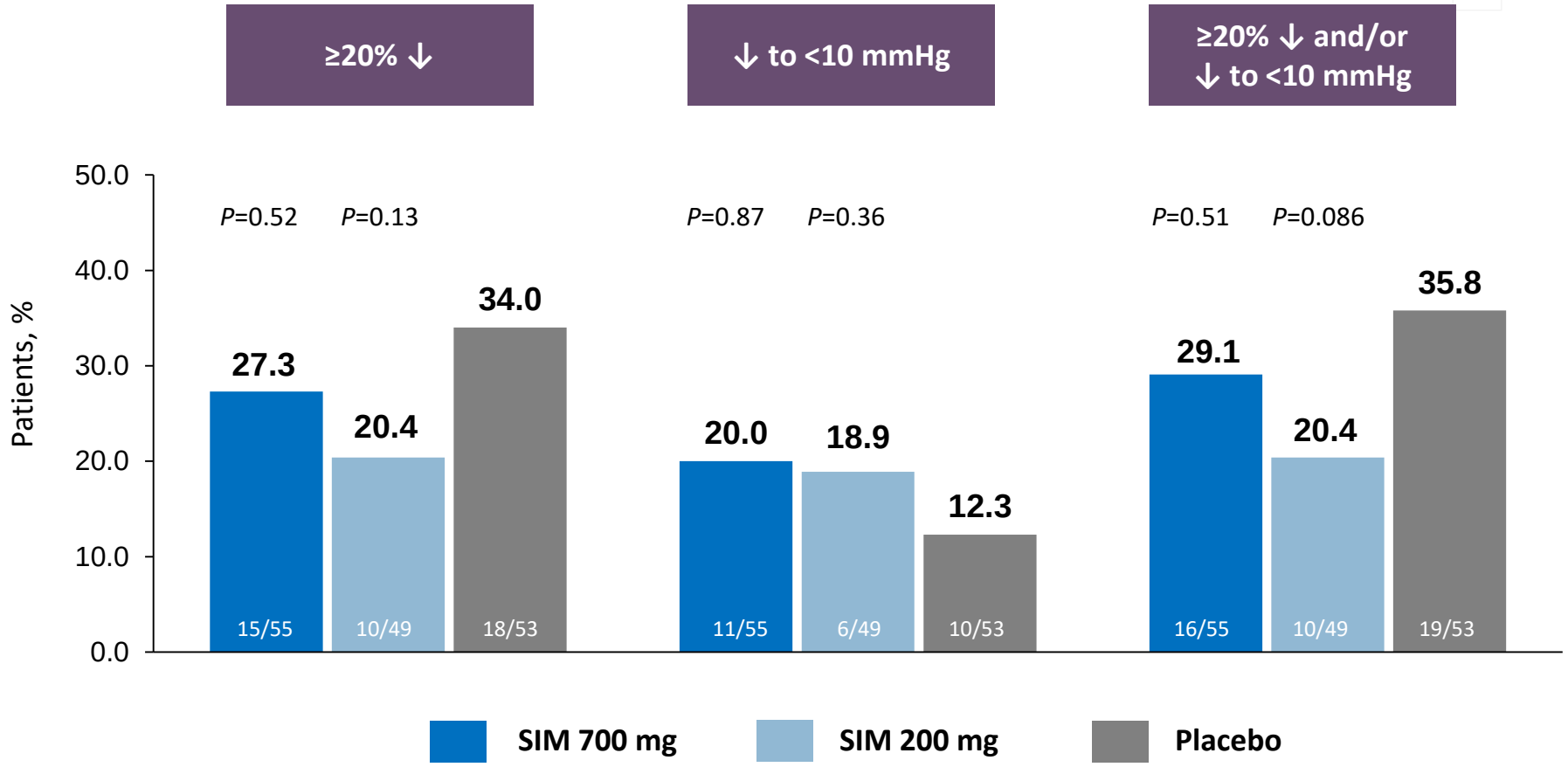
- Prolonged compensated phase
- More advanced patients (decompensated) may reach outcomes more quickly…but may be out of therapeutic efficacy window



Sanyal et al, Hepatology 2006, 43:682-689

SIM had no effect on portal pressure compared to placebo in patients with CSPHTN (HVPG ≥10mmHg)

Mean HVPG at entry was 12 mm, 68% had CSPH



Harrison, et al. *Hepatology.* 2019

Analyses restricted to cirrhotic subjects with HVPG ≥10 mmHg at baseline and Week 96 HVPG data. P-values for comparisons with placebo group adjusted for stratification factors.

Progression to cirrhosis

Bridging Fibrosis

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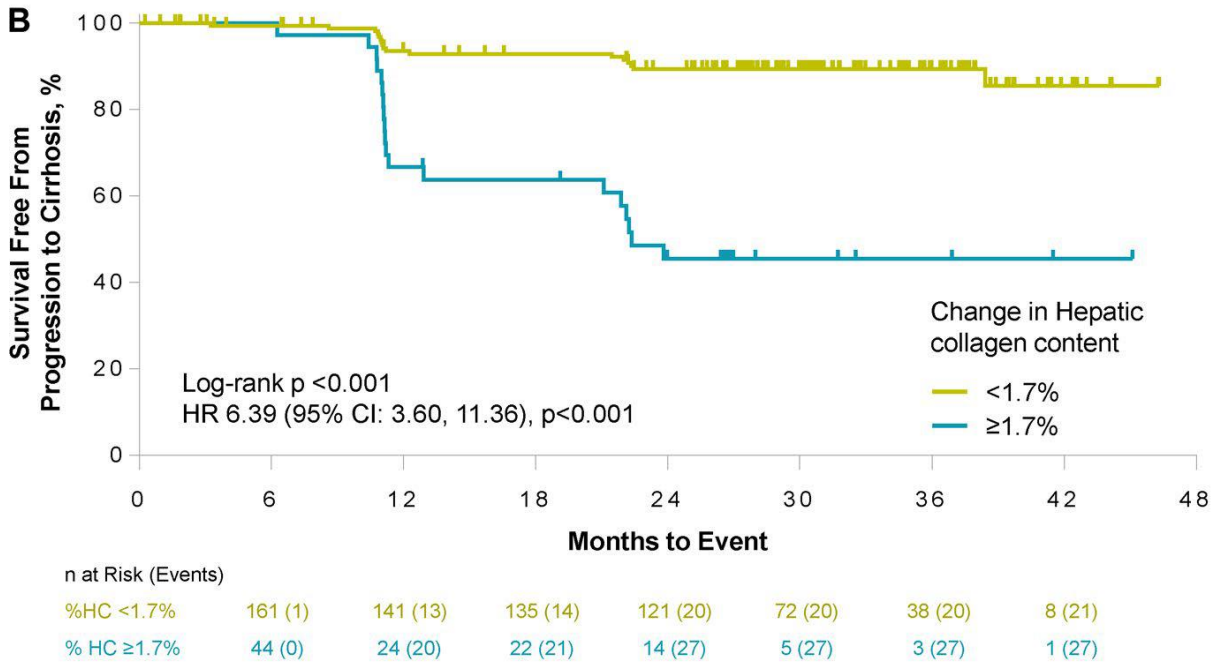
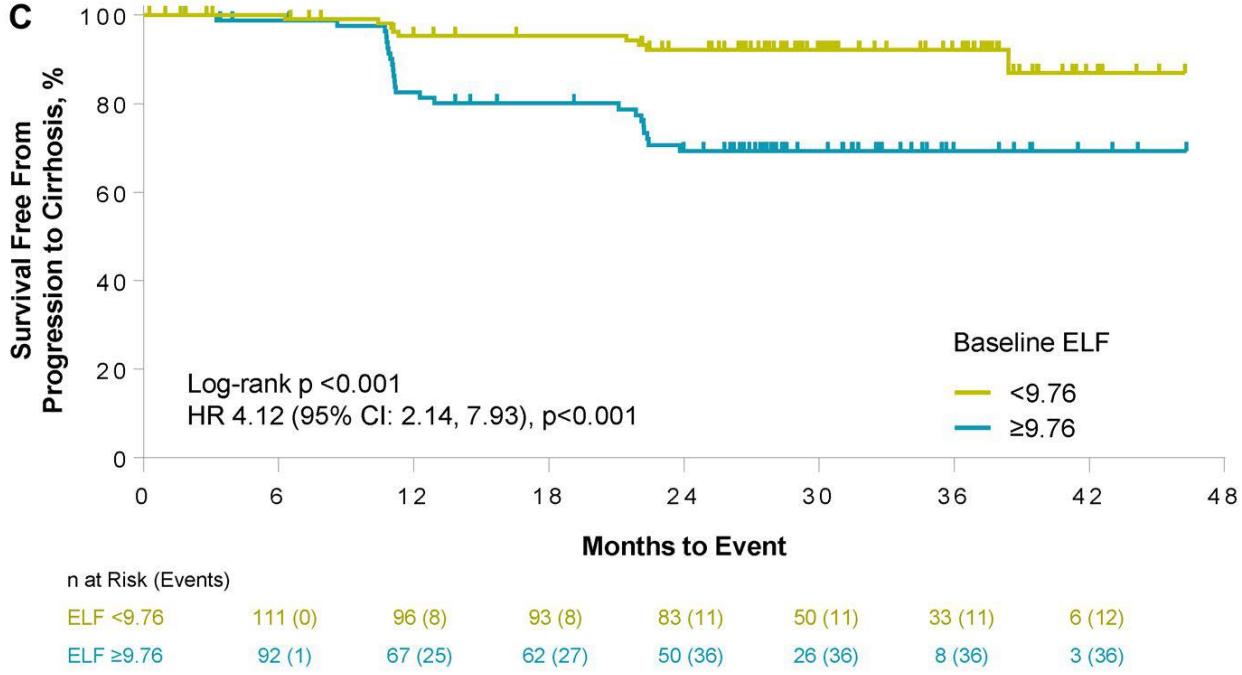
Change in hepatic collagen content



ELF

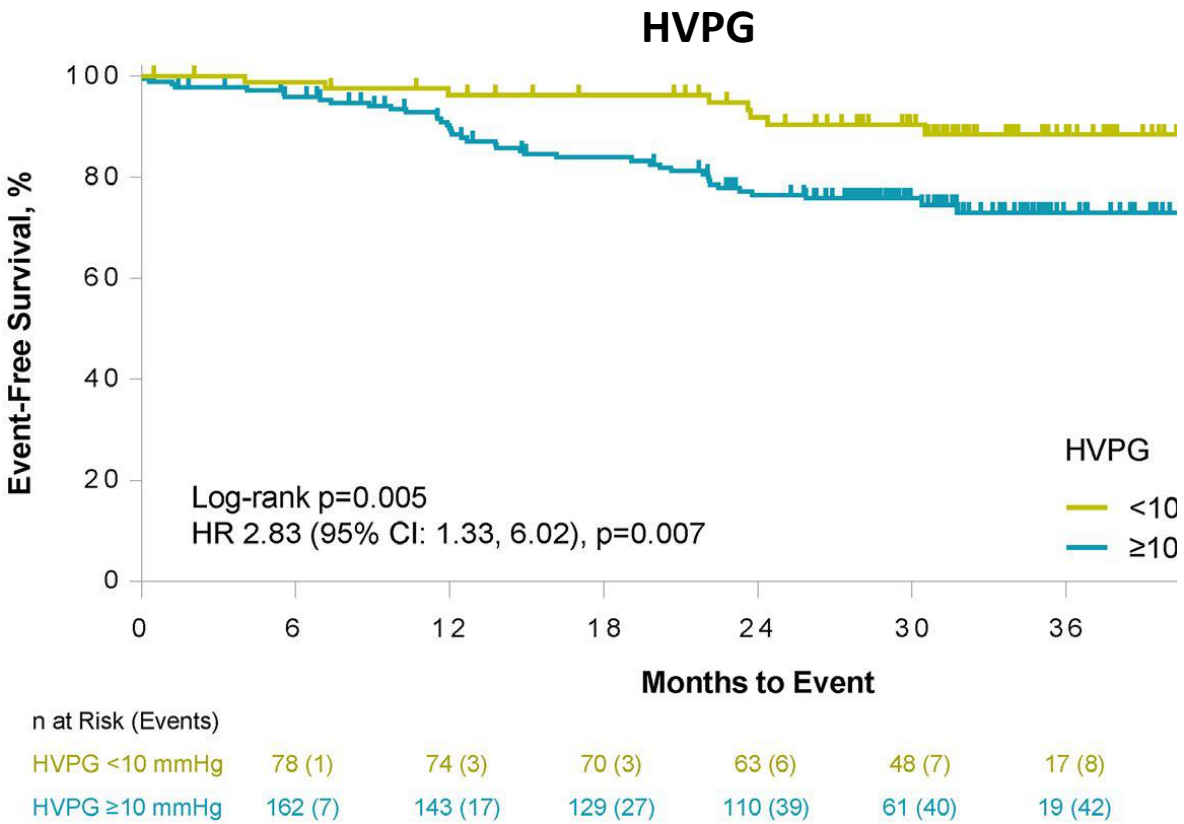


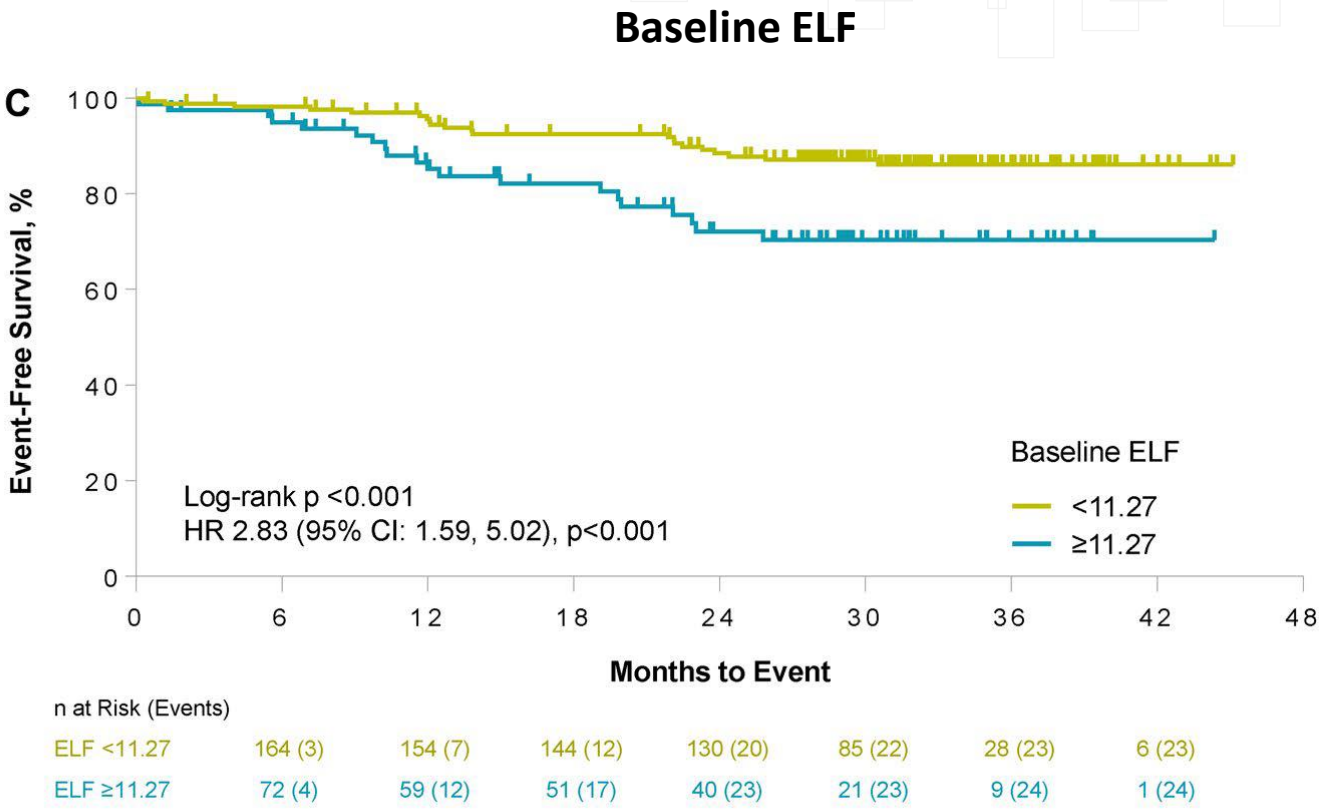
- **Median follow-up 24.9 months (range, 0.3–41.4)**

- **47 patients (21.5%) progressed to cirrhosis**
  - **89% (n=42) histologic progression**
  - **11% (n=5) clinical events**

Sanyal, et al. *Hepatology.* 2019

Liver related clinical events in patients with cirrhosis





- Median follow-up 24.9 months (range, 0.3–41.4)

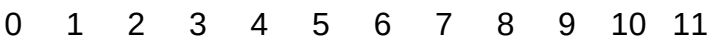
- Ascites (n=19)
- Encephalopathy (n=13)
- Variceal hemorrhage (n=6)
- Newly-diagnosed varices (n=4)
- ≥2-point increase in Child-Pugh score and/or MELD ≥15 (n=6)
- Death (n=1)

Sanyal, et al. *Hepatology.* 2019

Results: Impact of Fibrosis on Clinical Events

Cirrhosis

	Hazard Ratio *	95% CI	p-value
Ishak stage 5 vs 6 (baseline)	**1.25**	0.68, 2.29	0.48
No improvement vs improvement	**9.63**	1.33, 69.81	0.025
Hepatic collagen (baseline), per 5%	**1.39**	1.15, 1.69	<0.001
Change from baseline, per 5%	**1.20**	1.03, 1.39	0.017
ELF (baseline)	**2.37**	1.69, 3.31	<0.001
Change from baseline	**1.54**	1.10, 2.15	0.002



- **Increased risk of clinical events with:**
  - Higher baseline hepatic collagen content and ELF
  - Worsening of fibrosis (by Ishak stage, collagen content, ELF)

* Separate multivariate models run with baseline and change from baseline for each variable.

Subclassification of cirrhosis is important

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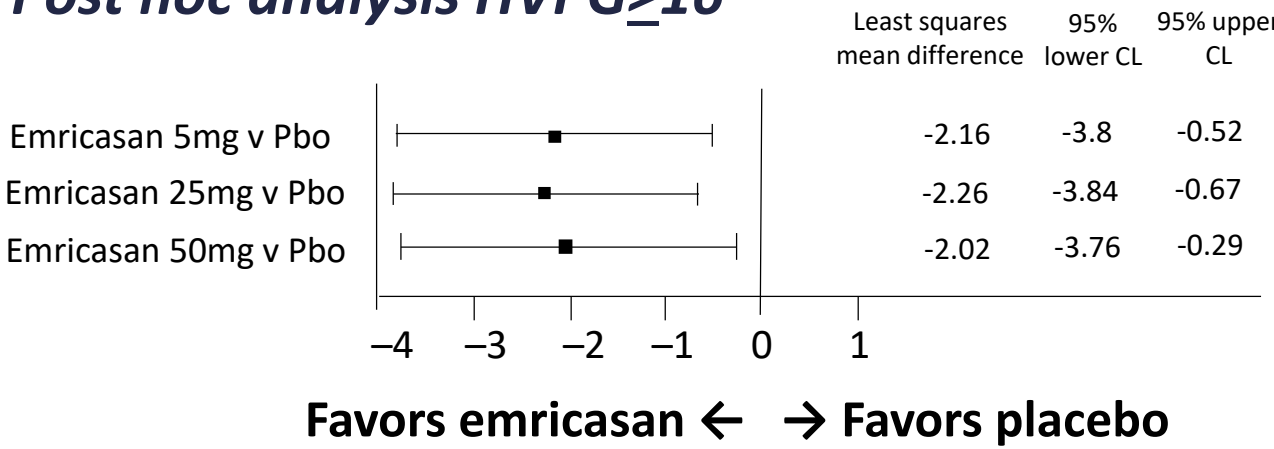
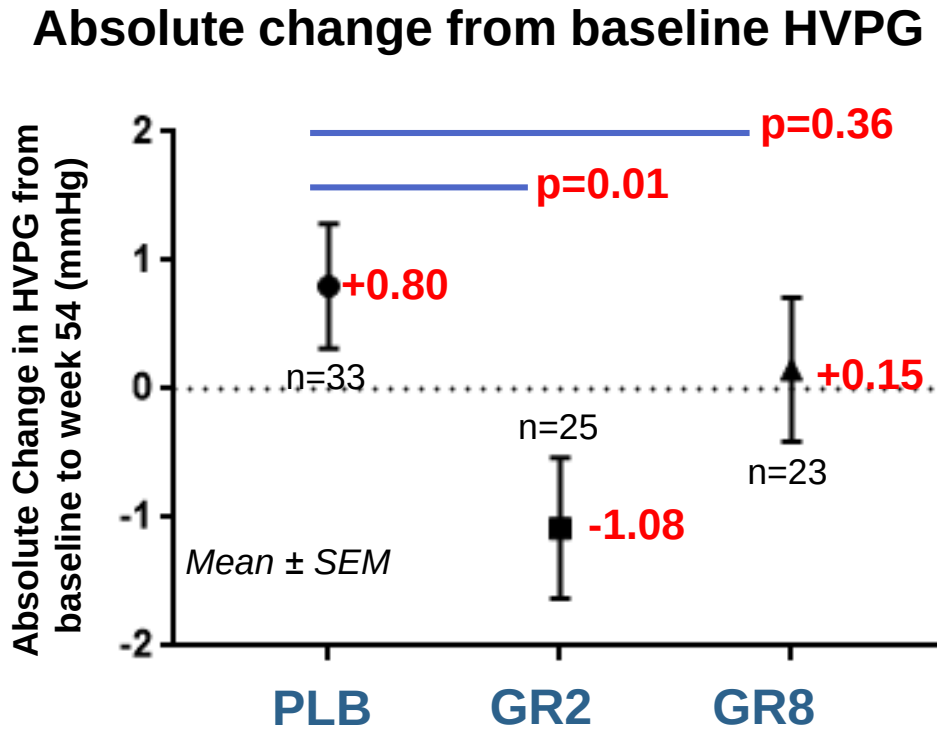
Emricasan: ITT no reduction in portal pressure vs Pbo

Galectin: ITT no reduction in portal pressure vs Pbo

Post hoc analysis HVPG≥16



Post hoc analysis cirrhosis no varices (post hoc)



Mean HVPG: 10.6mmHg vs 12.22mmHg

Garcia-Tsao G, et al. EASL 2019, Vienna, Austria. #LB-01
Chalasani et al 2018

New lessons learned from NASH trials

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Early phase trials	REGENERATE	MGL, others	SIMTUZUMAB	STELLAR 3/4, GAL, EMR, CVC
• Steatosis and ALT can predict histological response • Thus far, ALT has been more consistently predictive of histological improvement	• Success can be achieved in phase 3 trial of NASH • Histological endpoint of NASH resolution needs further refinement	• Better mechanisms to measure fibrosis improvement on a linear scale are needed	• Natural history of NASH in F3 and F4 patients • Increased collagen burden and ELF predictive	• More appraisal of evidence prior to phase 3. • Adaptation of stopping rules should be developed. • Cirrhosis populations

Thank you for your attention