Review of recent Clinical Trials in NASH

Paris NASH, September 2021

Mary Rinella, MD

Professor of Medicine

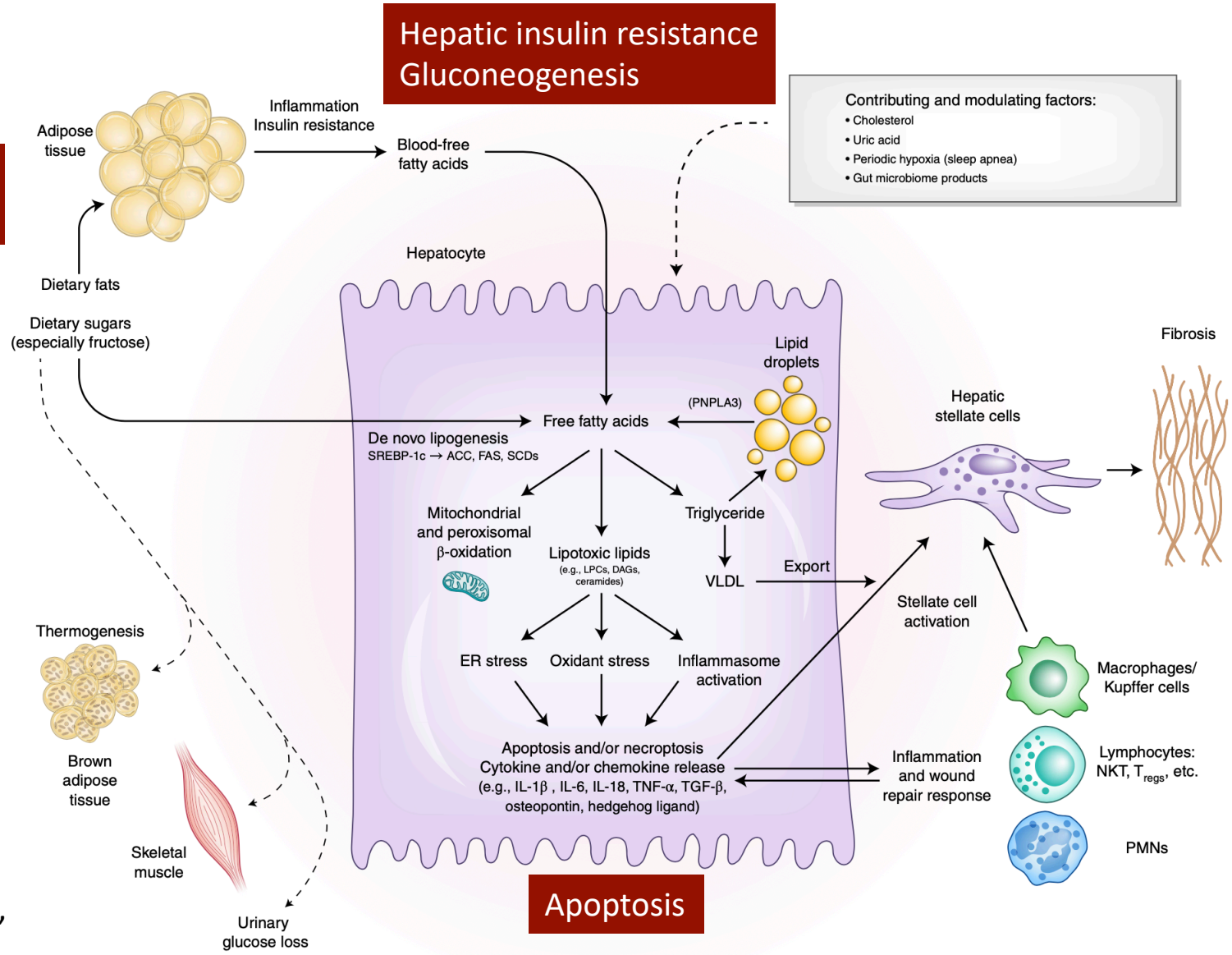
Disclosures

- **Consulting past 12 months:** Alnylam, Amgen, AMRA, BMS, Boehringer Ingelheim, Centara, Coherus, Enanta, Galecto, Intercept Pharmaceuticals, Madrigal, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Fractyl, Gelesis, Siemens, Thetis, Terns, Rivus, 3vBio (Sagimet), 89Bio and Novartis
- **All consulting contracts cancelled as of 2021**

Overview of NASH pathogenesis

Hepatic insulin resistance
Gluconeogenesis

Lipogenesis
Lipid transport



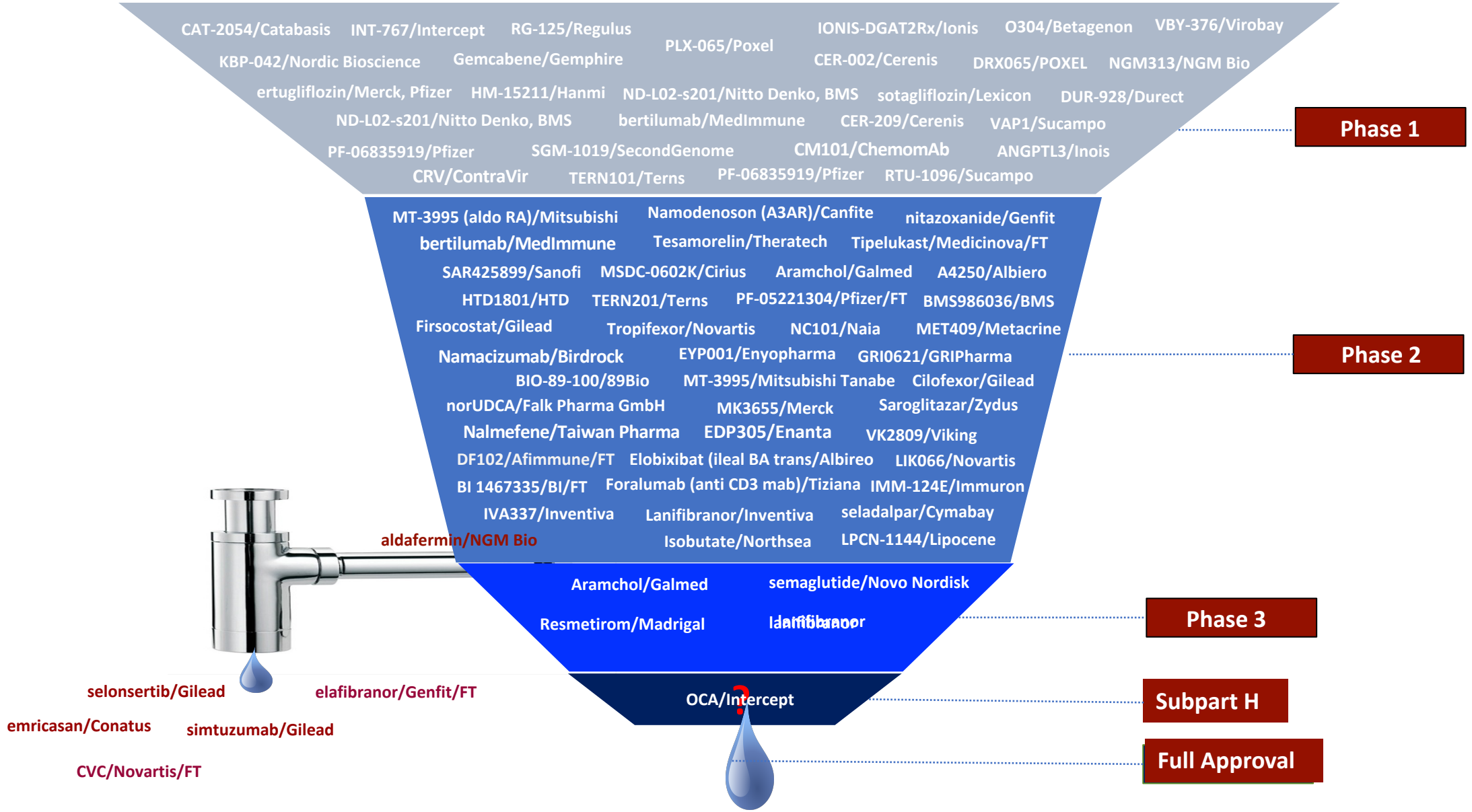
Extracellular matrix

Oxidative stress
Inflammation
Immune activation

Apoptosis

Friedman, Tetri, Rinella, Sanyal,
Nature Medicine 2018

Global Pipeline for NASH



NASH: Agents in Phase 3 2020

METABOLIC AGENTS

ANTI-FIBROTIC AGENTS

AGENT	MoA (TARGET)	TRIAL, PATIENTS AND ENDPOINT(S)
Obeticholic Acid (Ocaliva)	**Lipotoxicity/oxidative stress** (FXR agonist)	**REVERSE (n=540*, compensated cirrhosis) – Q3 2020**[2] (1) > Fibrosis improvement ≥1 stage without NASH worsening **REGENERATE (n=2065*, fibrosis stage 1–3) – PRO: FEB 2019, final Completion: OCT 2022**[3] (1 2) > Fibrosis improvement ≥1 stage without NASH worsening > NASH resolution without fibrosis worsening / All-cause mortality and liver-related events
Resmetirom (MGL-3196)	**Lipotoxicity** (THR-ß agonist)	**MAESTRO-NASH (n=2000*, fibrosis stage 2–3) – PRO: JUN 2021, final Completion: MAR 2024**[4] (3 3) > NASH resolution without worsening of fibrosis
Aramchol	**Fatty acid synthesis** (SCD1 inhibitor)	**ARMOR (NASH and fibrosis) – PRO: JUN 2022, final Completion: DEC 2024**[5] (4 4) > Histological endpoint at 52 weeks > Composite of progression to cirrhosis, liver-related clinical outcomes and all-cause mortality
Elafibranor	Lipotoxicity/oxidative stress (PPARα/δ agonist)	**RESOLVE-IT (n=2000*, fibrosis stage 1–3)** • NASH resolution without worsening of fibrosis • Long-term composite of all-cause mortality, cirrhosis and liver-related events
Selonsertib	Apoptosis/necrosis (ASK1 inhibitor)	**STELLAR-3 (n=808, fibrosis stage 3)** • Fibrosis improvement ≥1 stage without NASH worsening • Event-free survival
Belapectin (GR-MD-02) (P2/3 adaptive)	**Fibrosis** (Galectin-3 inhibitor)	**NASH-RX (n=500*, compensated NASH cirrhosis) – Q4 2022**[3] (2) > NASH resolution without worsening of fibrosis
Cenicriviroc	**Inflammation/fibrosis** (CCR2/5 antagonist)	**AURORA (n=2000*, fibrosis stage 2–3) – PRO: OCT 2021, final Completion: 2028**[4] (4 6) > Fibrosis improvement ≥1 stage without NASH worsening > Composite of progression to cirrhosis, liver-related clinical outcomes and all-cause mortality

1 1 2 3 1 4 2 3 4 6

PRIMARY and FINAL READOUT

2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028

*. **1**. ClinicalTrials.gov. NCT02704403; **2**. ClinicalTrials.gov. NCT03439254; **3**. ClinicalTrials.gov. NCT02548351;. **4**. NCT03900429; **5**. https://www.prnewswire.com/il/news-releases/galmed-pharmaceuticals-announces-successful-completion-of-end-of-phase-2-meeting-with-fda-and-plan-for-start-of-phase-3-300827912.html (accessed Sept 2019).*

Adapted from S. Harrison

NASH: Agents in Phase 3 2021

METABOLIC AGENTS

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Semaglutide	**GLP-1 RA**	**N=1200, SQ OW** > Part 1: Histological endpoint at 72 weeks, Part 2: Clinical events > Part liver-related clinical outcomes and all-cause mortality	Enrolling
Lanifibranor	**Pan-PPAR**	**N=1200, 800mg, 1200mg** > Part 1: Histological endpoint at 72 weeks, Part 2: Clinical events > Part liver-related clinical outcomes and all-cause mortality	Enrolling
Belapectin (GR-MD-02) (P2/3 adaptive)	**Fibrosis** (Galectin-3 inhibitor)	**NASH-RX (n=500*, compensated NASH cirrhosis) – Q4 2022**[3] > NASH resolution without worsening of fibrosis	Enrolling (2)



. ***1***. *ClinicalTrials.gov. NCT02704403;* ***2***. *ClinicalTrials.gov. NCT03439254;* ***3***. *ClinicalTrials.gov. NCT02548351;*. ***4***. *NCT03900429;* ***5***. *https://www.prnewswire.com/il/news-releases/galmed-pharmaceuticals-announces-successful-completion-of-end-of-phase-2-meeting-with-fda-and-plan-for-start-of-phase-3-300827912.html (accessed Sept 2019).*

Adapted from S. Harrison

REGENERATE 18-month interim analysis: Fibrosis improvement by ≥1 Stage with no worsening of NASH (ITT, F2/3)

2480 patients
Randomization 1:1:1

Primary endpoint definition:

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

AND

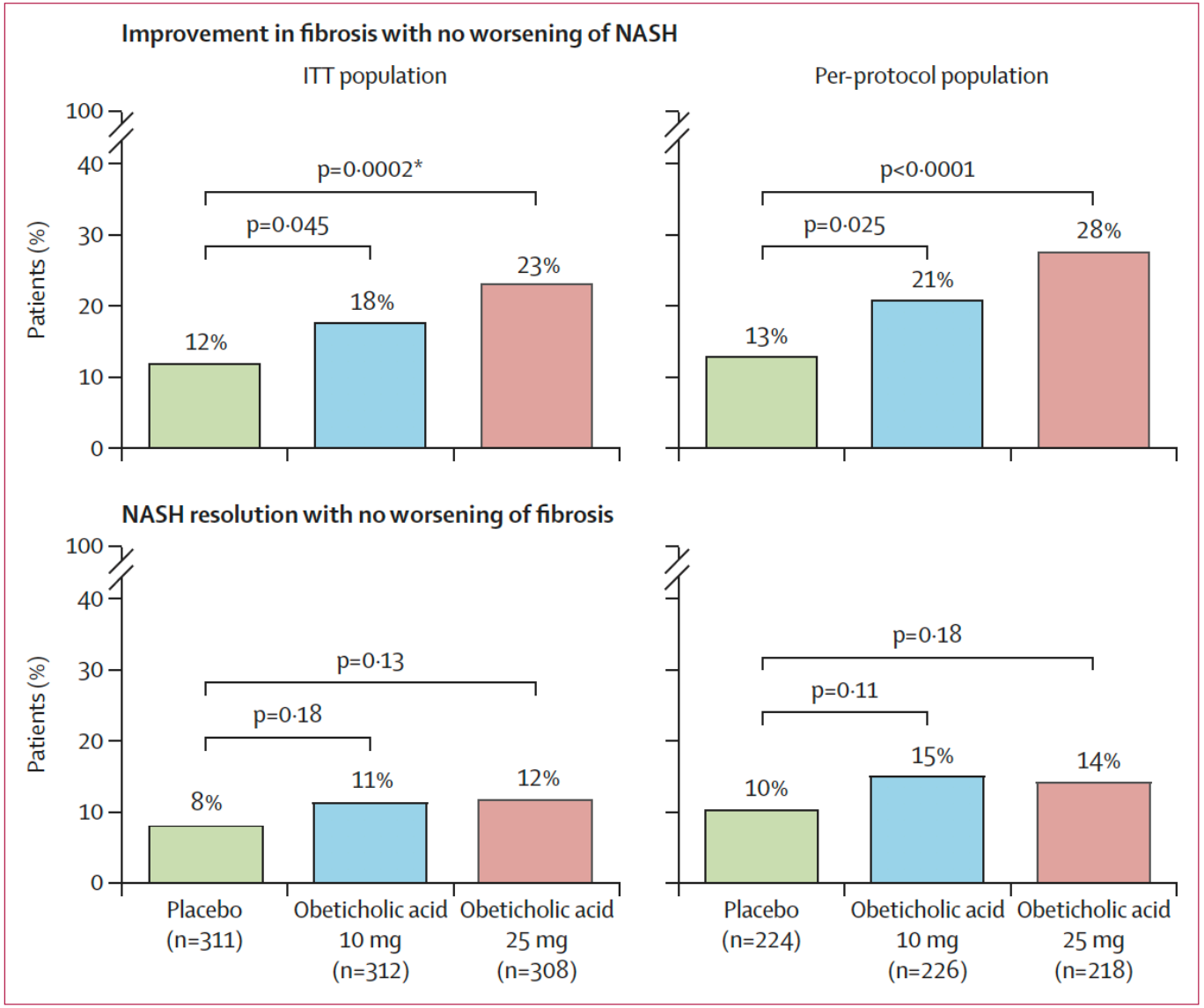
- no worsening of lobular inflammation, hepatocellular ballooning **or steatosis**

OR

- Resolution of NASH

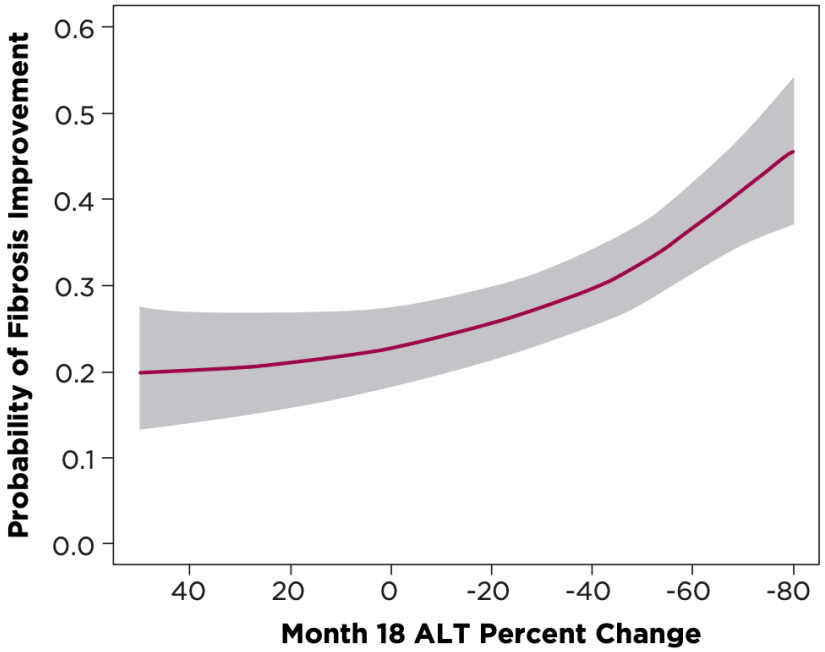
AND

- No worsening of fibrosis

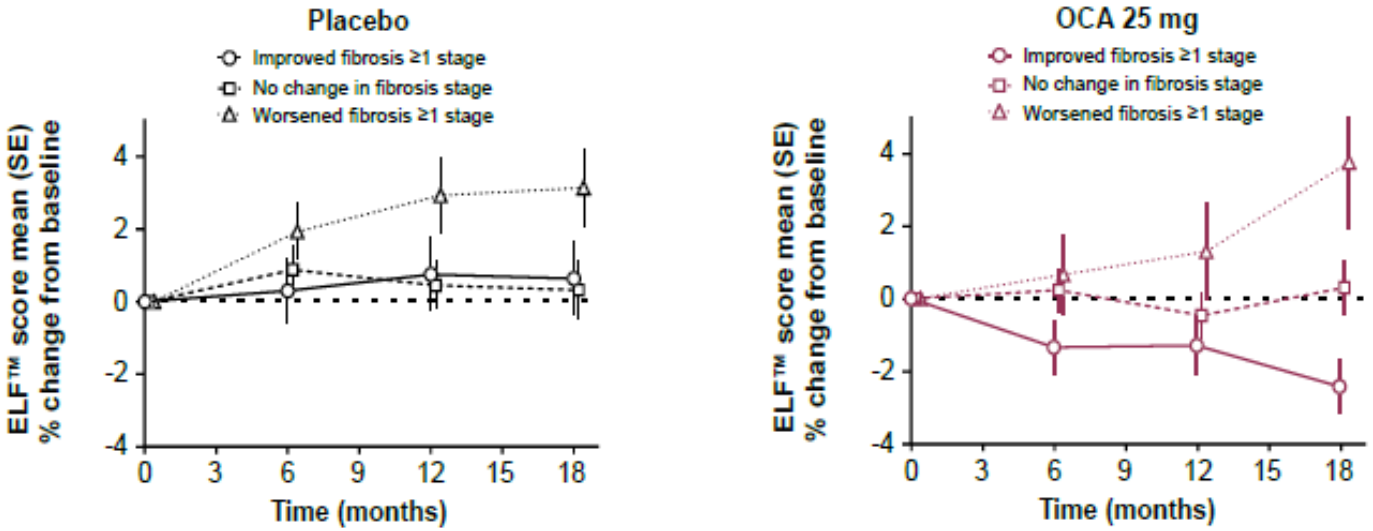


Younossi et al. *The Lancet*, 2019

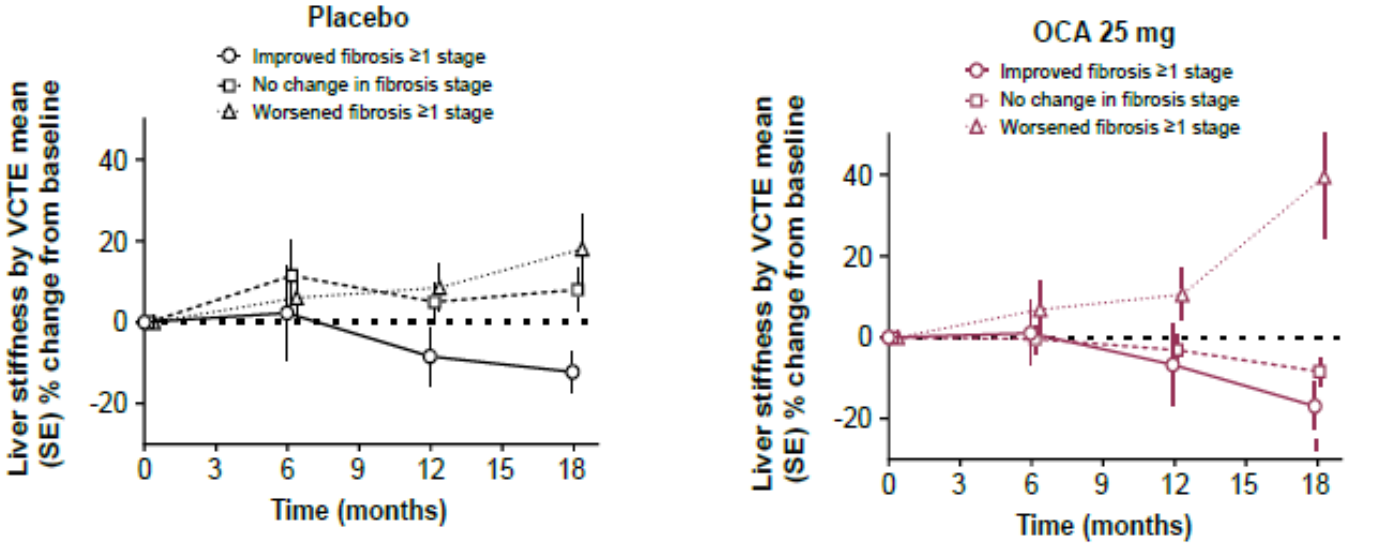
REGENERATE trial: Correlation of NITs with histological response



Histological response assessed by ELF

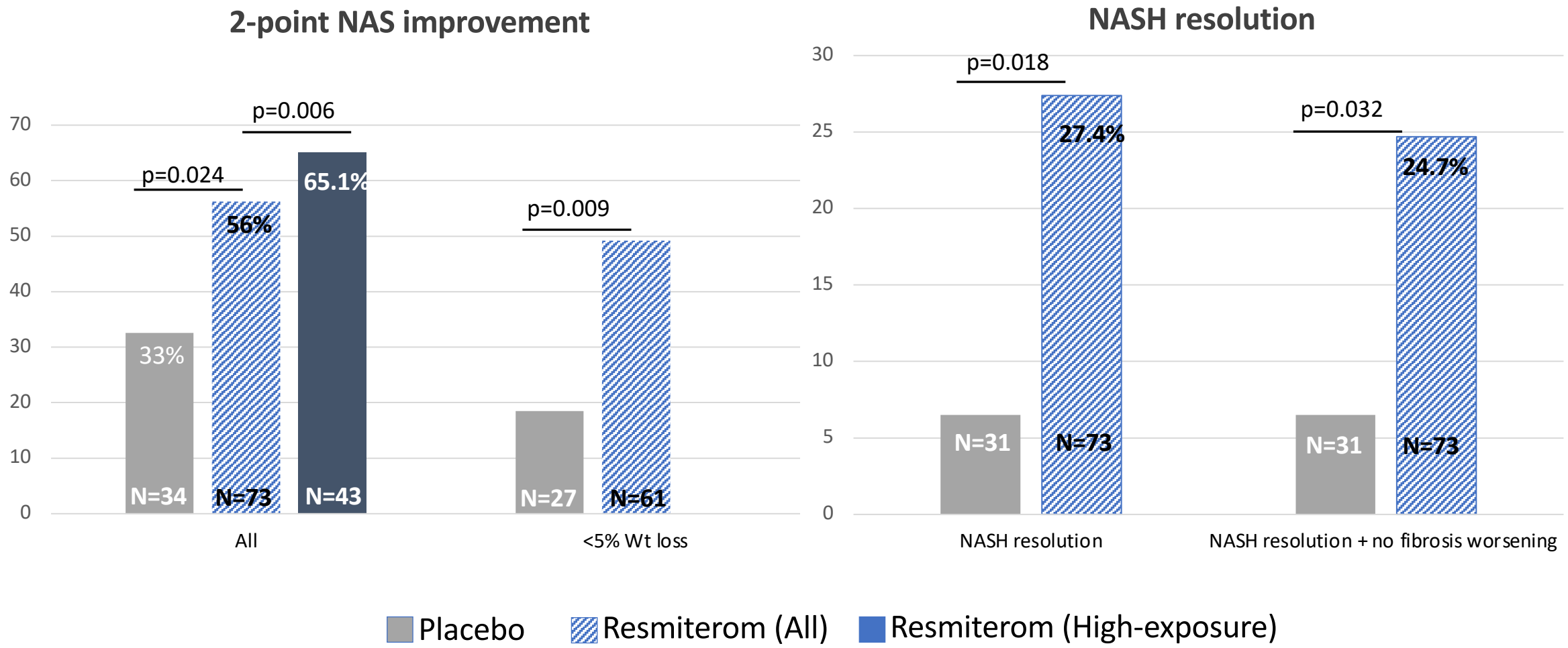


Histological response assessed by transient elastography



Rinella ME, et al. *submitted*

MGL-NASH Ph 2b Histological Endpoints



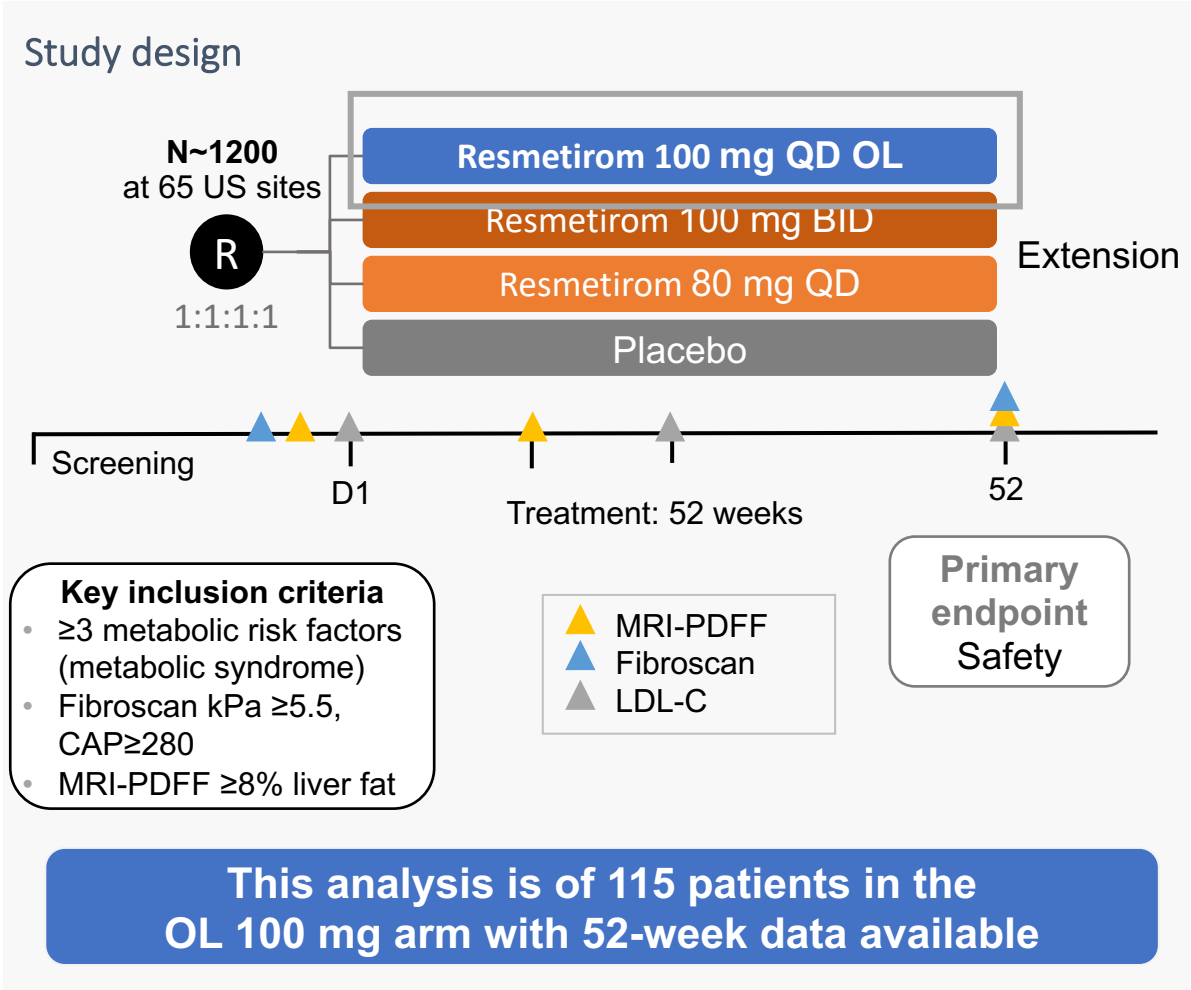
Harrison et al. Lancet 2019

MAESTRO-NAFLD-1: Reduction in fibrosis and steatohepatitis imaging and biomarkers in Phase 3, 52-week resmetirom NASH trial

- Resmetirom is a liver-directed, orally active, selective THR-β agonist

Clinical trial	Preclinical	Phase 1	Phase 2	Phase 3	Description
Phase 2 MGL-3196-05	Completed				• **MRI-PDFF, liver biopsy: endpoints achieved** • 36 wks with 36-wk OLE
Phase 3 MAESTRO-NASH	Recruiting				• **Treatment of NASH F2-F3** • Serial liver biopsy • 52-wk Phase 3; 54-month outcomes
Phase 3 MAESTRO-NAFLD-1	Ongoing				• **Treatment of NASH** • **Safety, lipids and NASH biomarker and imaging study** • 52-wk • Enrolment of DB arms completed • **OL 100 mg arm; includes NASH cirrhotics**

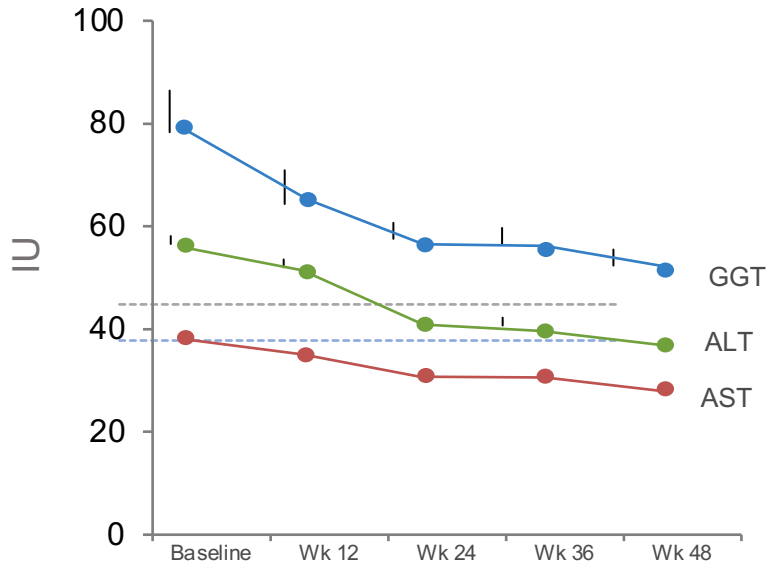
Primary and key secondary endpoints of MAESTRO-NAFLD-1 include: safety, relative percent reduction of MRI-PDFF (week 16), LDL cholesterol (LDL-C) (week 24), Apolipoprotein B and triglycerides, PRO-C3 (week 52), and safety.



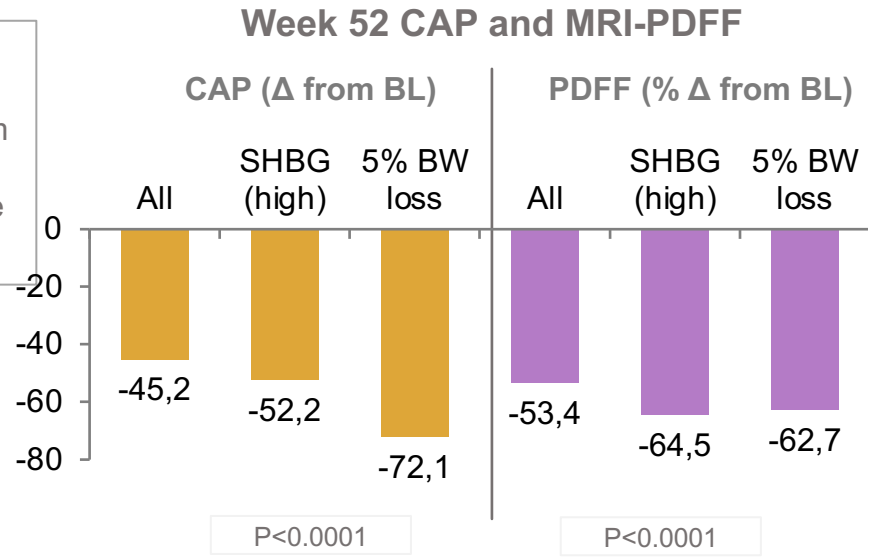
Harrison S, et al. EASL 2021. #GS-2563

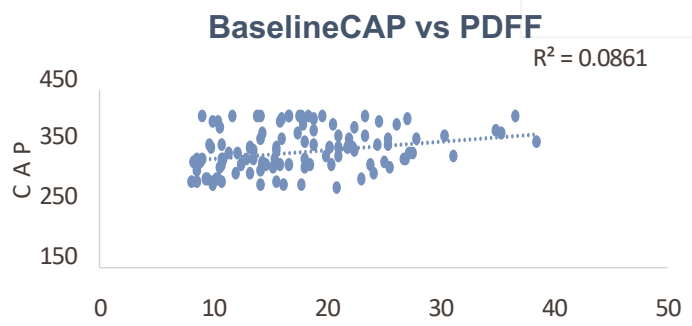
MAESTRO-NAFLD-1: Reduction in biomarkers in Phase 3, 52-week resmetirom NASH trial

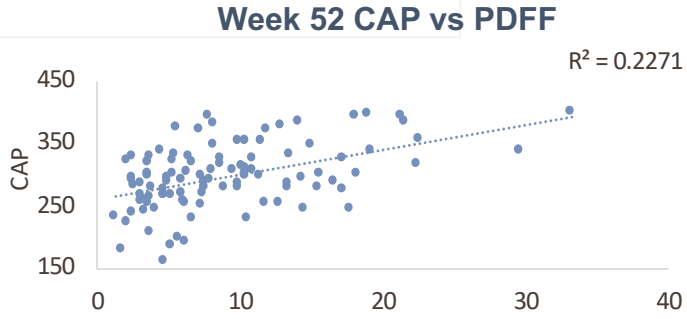
Week 48	Δ from BL	% Δ from BL	P-value
ALT	–20.36	–33.04	<0.0001
AST	–10.19	–21.50	0.0003
GGT	–28.52	–19.83	0.015



SHBG (high), majority of patients at target resmetirom liver exposure based on % change in SHBG



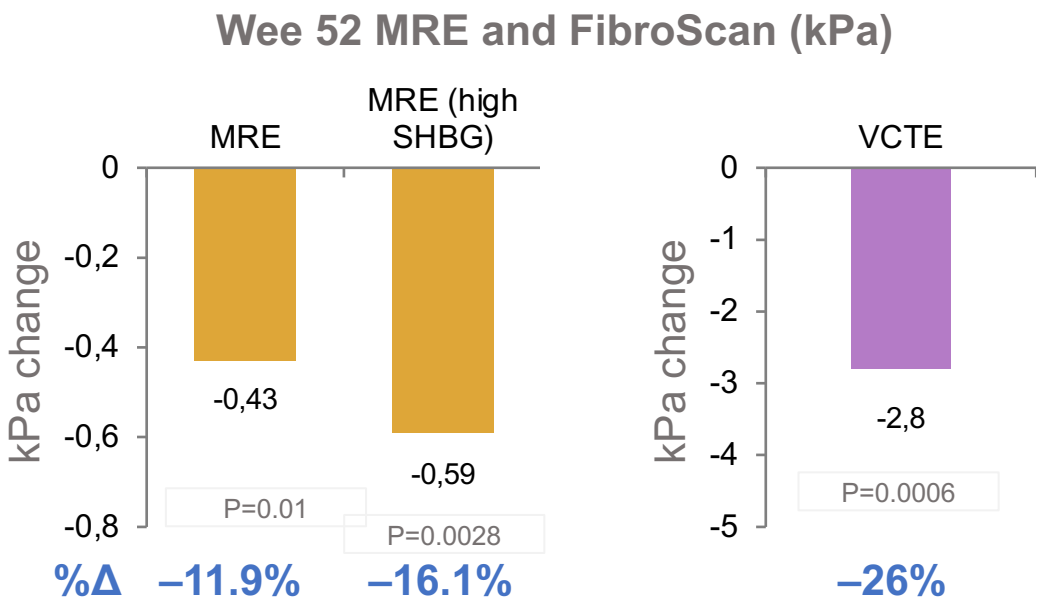




Note: Poor correlation between CAP and PDFF

Harrison S, et al. EASL 2021. #GS-2563

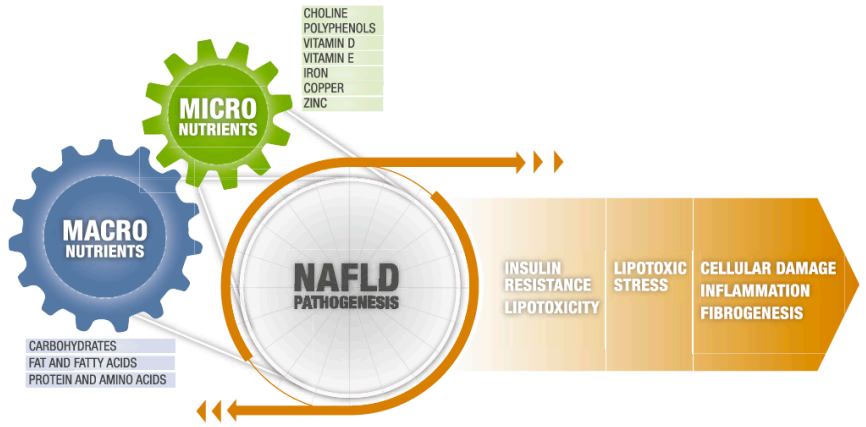
MAESTRO-NAFLD-1: Reduction in fibrosis and steatohepatitis imaging and biomarkers in Phase 3, 52-week resmetirom NASH trial



- Approximately 50% of patients had a 15% reduction in MRE (kPa) and/or 25% reduction in FibroScan (VCTE) kPa

- Well tolerated
- NIT-selected NAFLD cases exhibited reductions from BL in PDFF, MRE, ELF, CK18 – with a beneficial lipid profile
- BUT relatively small cohort and no placebo group
- Disconnect between CAP and PDFF brings into question value of FAST, etc. as ‘Pharmacodynamic/Response’ biomarker

Therapy to counter substrate overload in NASH



Nutritional therapies have lacked Sustainability and attainability (≤15% at one year)



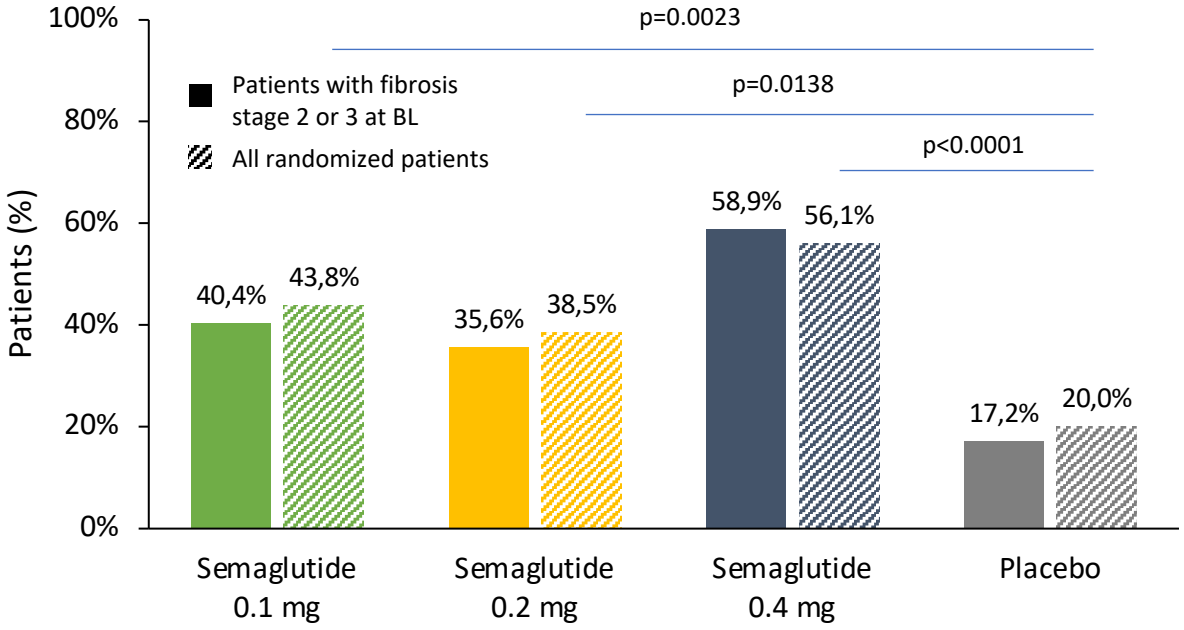
GLP1 RAs

Decreased glucagon concentrations
Improved insulin sensitivity
Decreased A1C
Slowed gastric emptying
Increased satiety
Decreased free fatty acid concentrations
Decreased body weight

Efficacy and Safety of Semaglutide SC QD vs PBO in patients with NASH

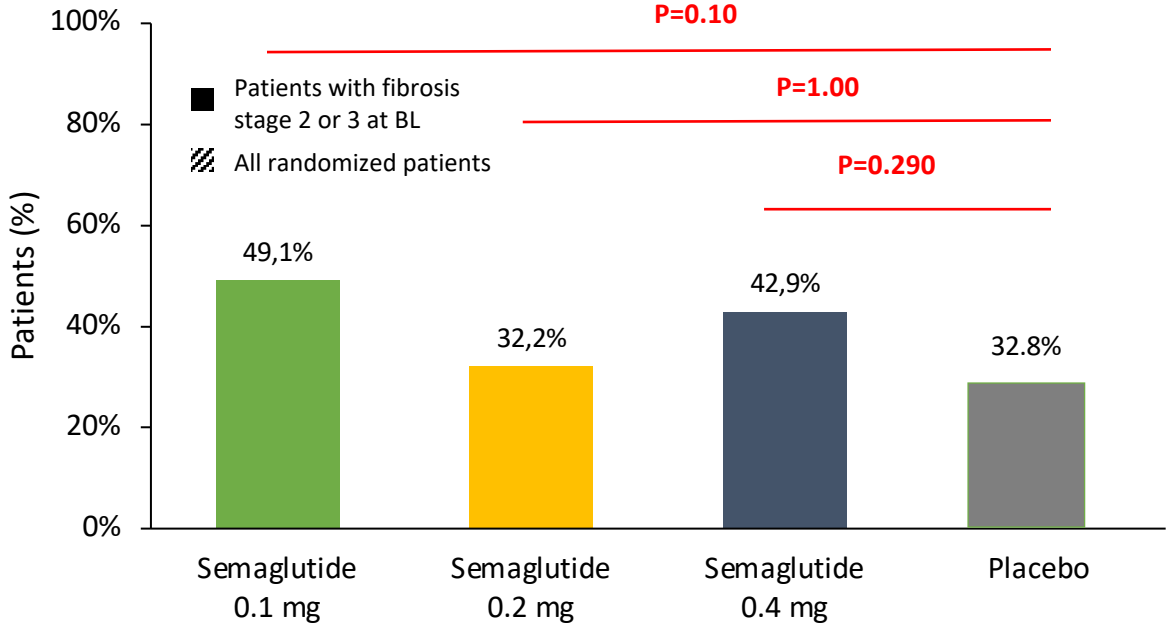
Resolution of **steatohepatitis** and no worsening in liver fibrosis

Patients with fibrosis Stage 2 or 3 at BL and all randomized patients



Improvement in liver **fibrosis** and no worsening in steatohepatitis

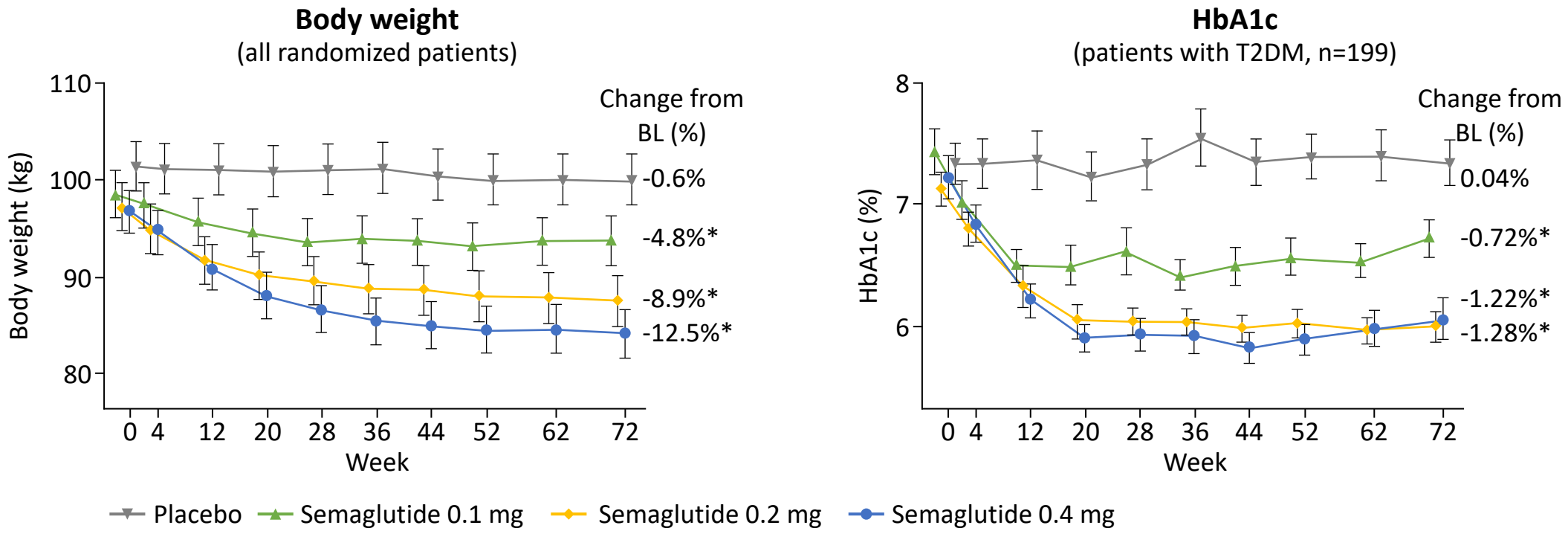
Patients with fibrosis Stage 2 or 3 at BL and all randomized patients



N=320

Newsome PN, et al. *NEJM* 2021 ;384(12):1113-1124.

Impact of semaglutide versus placebo on body weight and HbA1c



- SEMA 0.4 mg resulted in increased HDL-C and decreased free fatty acids, triglycerides, and VLDL-C versus placebo

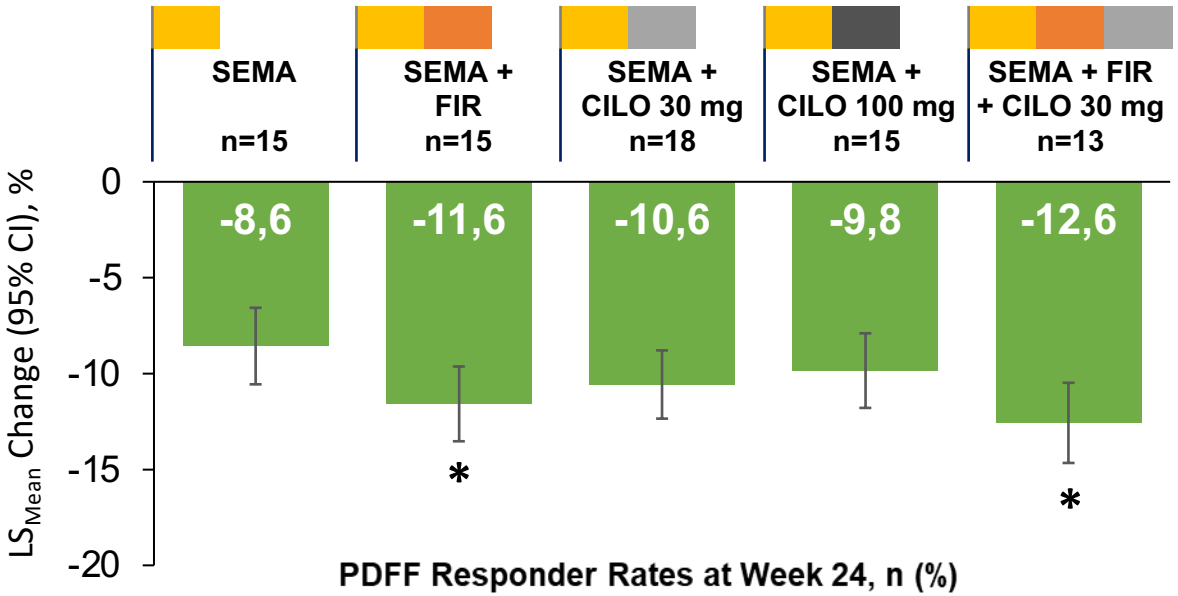
Data are observed means with standard error of the mean.
*p<0.05 for estimated treatment difference versus placebo.

- Safety profile: Major AEs were nausea, constipation, and vomiting, no drug discontinuation due to AEs

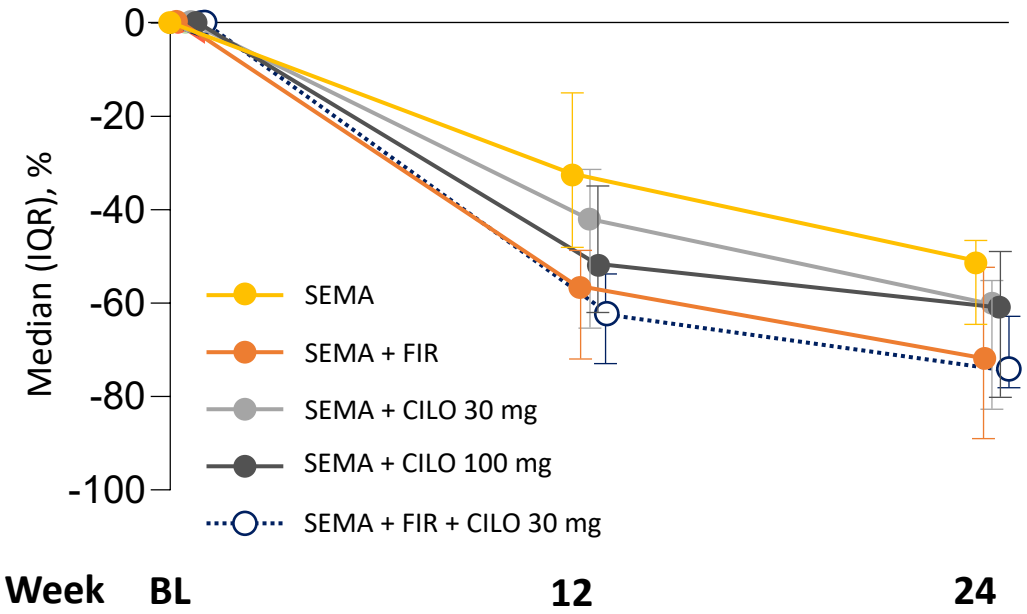
Newsome PN, et al. NEJM 2020

Safety and efficacy of combination therapies including semaglutide (QW), cilofexor, and firsocostat in patients with NASH

Absolute change in MRI-PDFF at Week 24



Relative change from baseline



PDFF Responder Rates at Week 24, n (%)

≥30% ↓	12 (80)	14 (93)	17 (94)	13 (87)	12 (92)
≥50% ↓	6 (40)	10 (67)	14 (78)	8 (53)	11 (85)
≥70% ↓	1 (7)	4 (27)	6 (33)	5 (33)	4 (31)

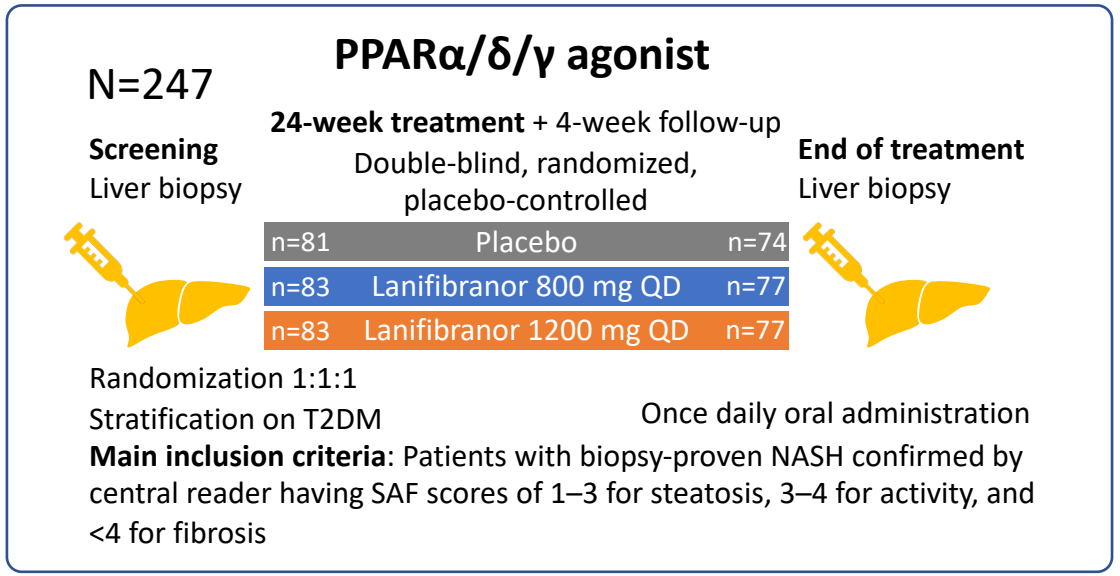
Data collected beyond 30 days after last dose of any study drug excluded from analysis. Changes in PDFF based on ANCOVA models adjusted for BL and diabetes status.
*p<0.05 vs SEMA alone.

- Greatest reductions in PDFF in FIR groups
  - Similar findings observed with CAP

- There were similar relative reductions in body weight across groups

Alkhouri N, et al. AASLD TLMdX2020. #LO2

NATIVE Phase 2b trial: Impact of lanifibranor on NASH resolution and fibrosis regression after 24 weeks



Compound	$PPAR_\alpha$ EC50 (nM)	$PPAR_\delta$ EC50 (nM)	$PPAR_\gamma$ EC50 (nM)
Lanifibranor[1]	**1630**	**850**	**230**
Fenofibrate	2400	-	-
Pioglitazone	-	-	263
Rosiglitazone	-	-	13
Elafibranor[2]	10	100	-
Seladelpar[3]	-	2	-

1. Inventiva Company data; 2. Hanf R et al. Diabetes and Vascular Dis Res. 2014; 3. Cymabay company presentation.

Francque SM, et al. AASLD TLMdX2020. #12

Primary endpoint:

- **Decrease from baseline to Week 24 of ≥2 points of inflammation and ballooning (as measured by SAF-Activity score) and no worsening of fibrosis**

Secondary endpoints:

- Resolution of NASH and no worsening of fibrosis
- Improvement of fibrosis by ≥1 stage and no worsening of NASH
- Decrease from baseline to Week 24 of ≥2 points of the NAS CRN score and no worsening of fibrosis
- Resolution of NASH and improvement of fibrosis by ≥1 stage
- Change in parameters of glycemic control (fasting glucose, insulin, HOMA index, HbA1c, …)
- Change in liver enzymes (ALT, AST, GGT, ALP, total bilirubin)
- Change in main plasma lipid parameters (TC, HDL-C, calculated LDL-C, TG, …)

Other outcome measures:

- Change in inflammatory markers (fibrinogen, hs-CRP, alpha2 macroglobulin, haptoglobin, …)
- Change in fibrosis markers (TIMP-1, TIMP-2, HA, PIIINP, NFS, FIB-4 score, ELF score, Pro-C3, …)

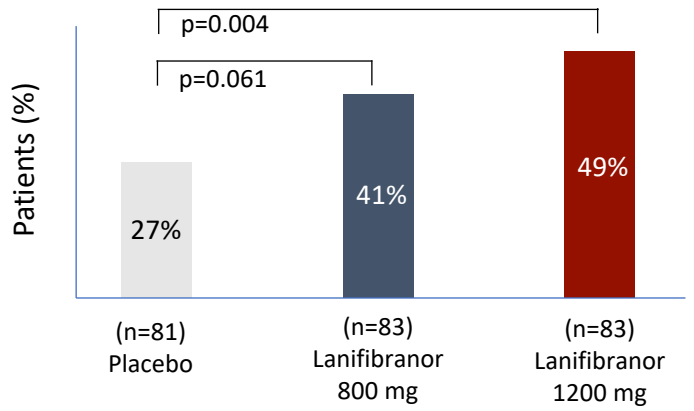
Data are mean ± SD or n (%).

By using SAF Activity ≥3 as inclusion criterion rather than NAS ≥4, NATIVE selected a higher percentage of patients with severely active steatohepatitis associated with advanced fibrosis (although no *a priori* minimum fibrosis criterion was set).

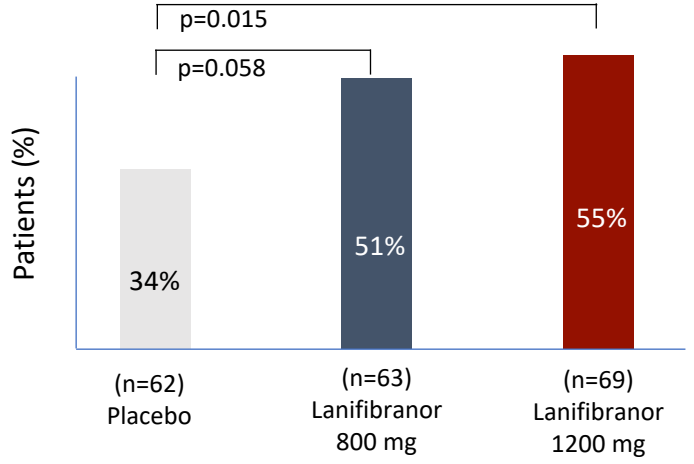
Impact of lanifibranor on histology endpoints

≥2-point improvement in SAF-Activity (inflammation and ballooning) with no worsening of fibrosis

FAS (N=247)[a]

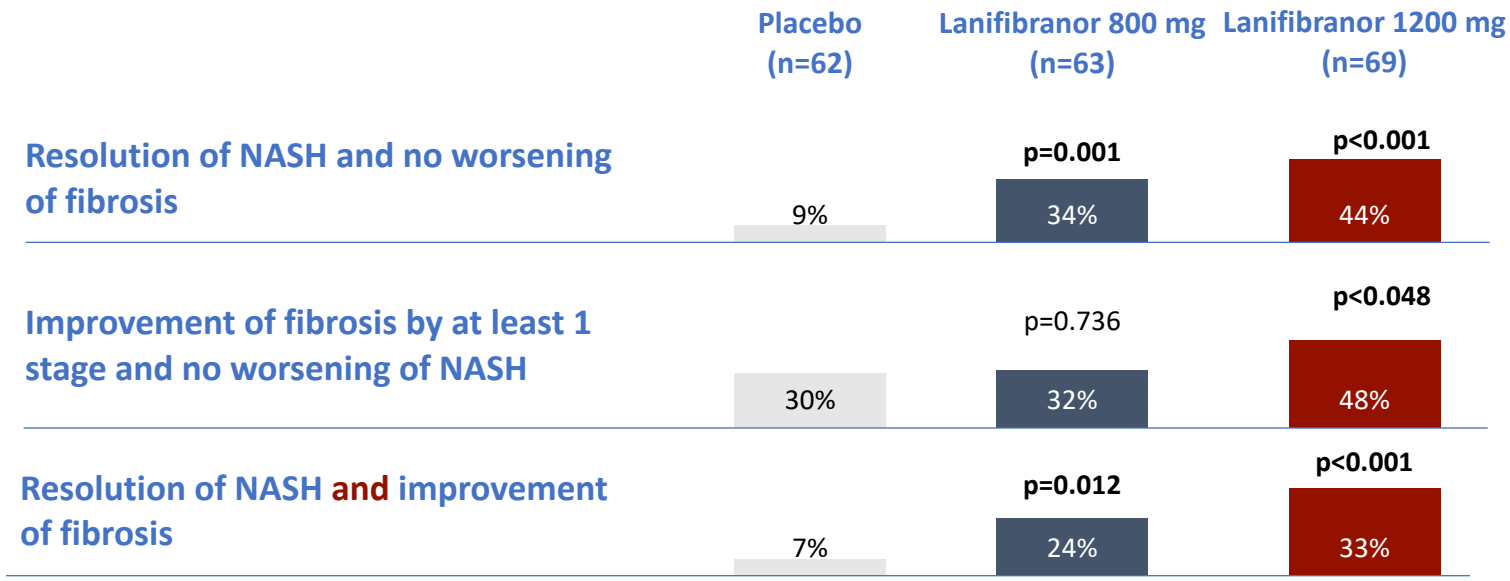


PP (n=194)



Francque SM, et al. AASLD TLMdX2020. #12

FAS – F2/F3 patients



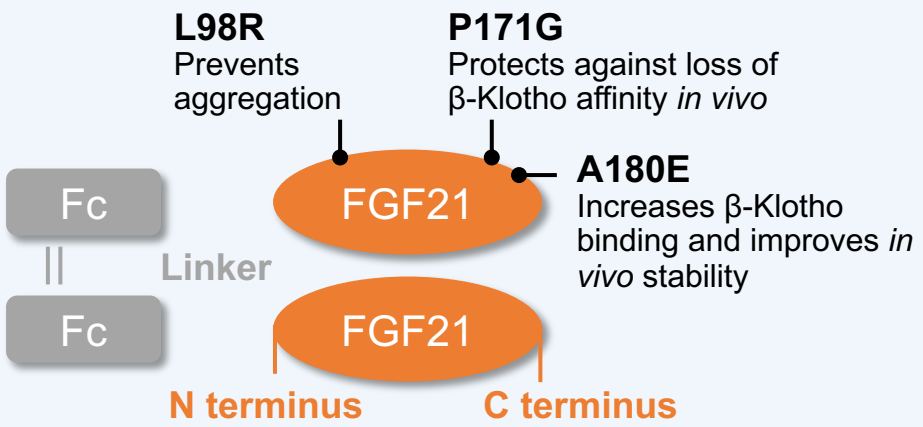
- Statistically significant decrease of ALT, AST, and GGT HDL-C at Week 4
- Statistically significant decrease in triglycerides at Week 14
- No change in LDL-C
- Statistically significant decrease of HbA1c

[a]Missing biopsies are considered non-responders.

- Lanifibranor 1200 mg/day achieved primary endpoint and key secondary endpoints
- Beneficial metabolic profile
- Well tolerated
- Currently in Ph3

Efruxifermin

Efruxifermin is a long-acting FGF21 analog based on a fusion polypeptide of human IgG1 Fc with FGF21

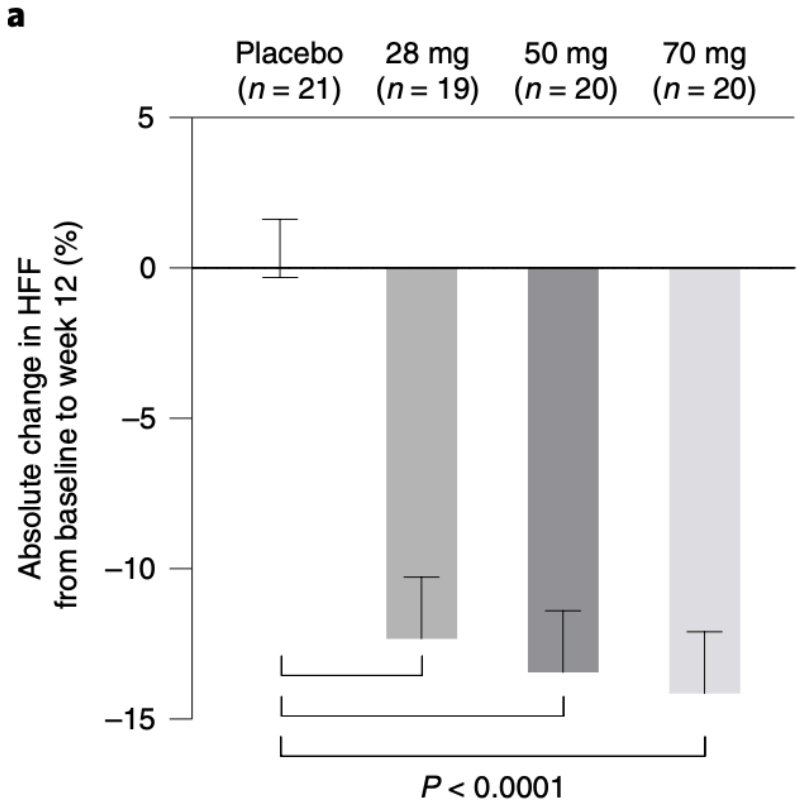




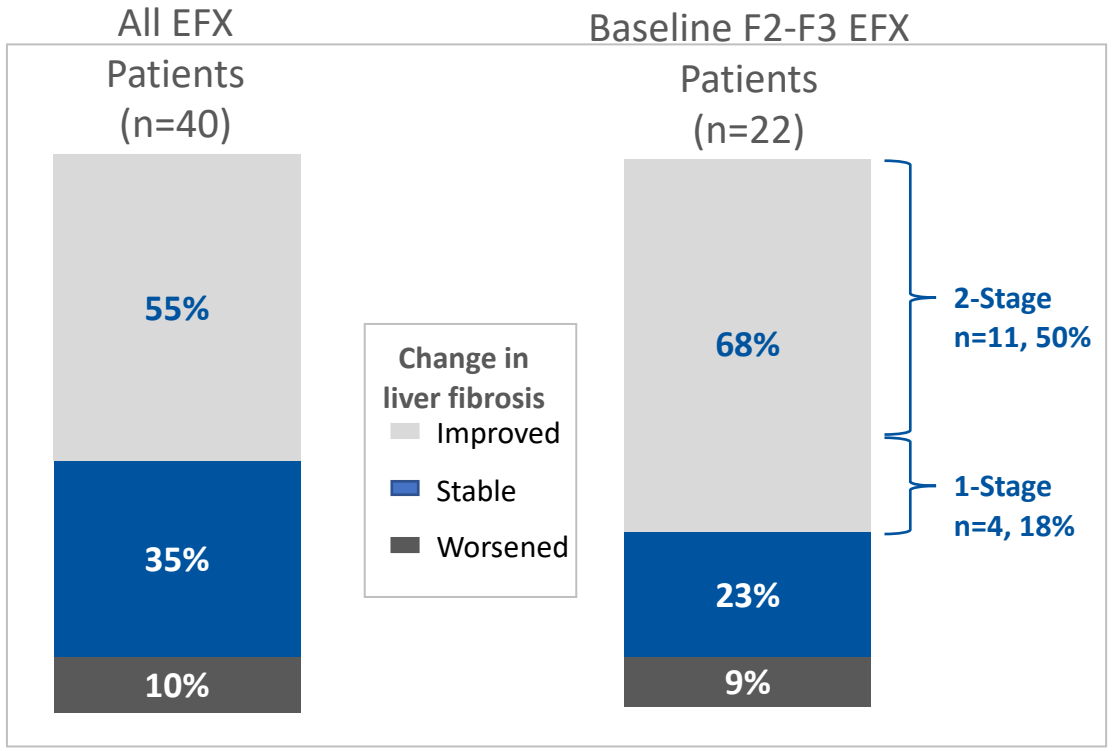
Akero

Effruxifermin Ph2a: F1-3, NAS ≥4, HFF ≥10%, TE >7kPa for 16 weeks

Primary: PDFF drop at 12 weeks

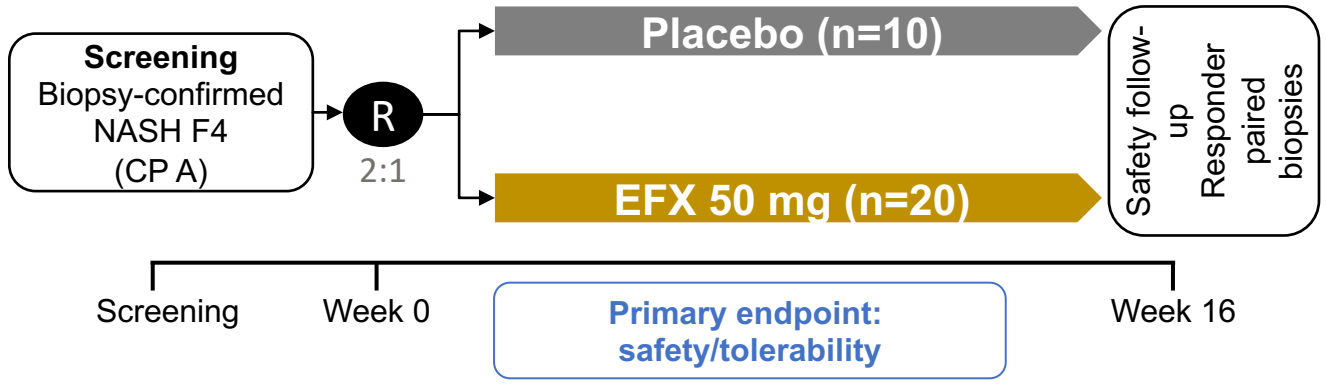


Fibrosis Improvement

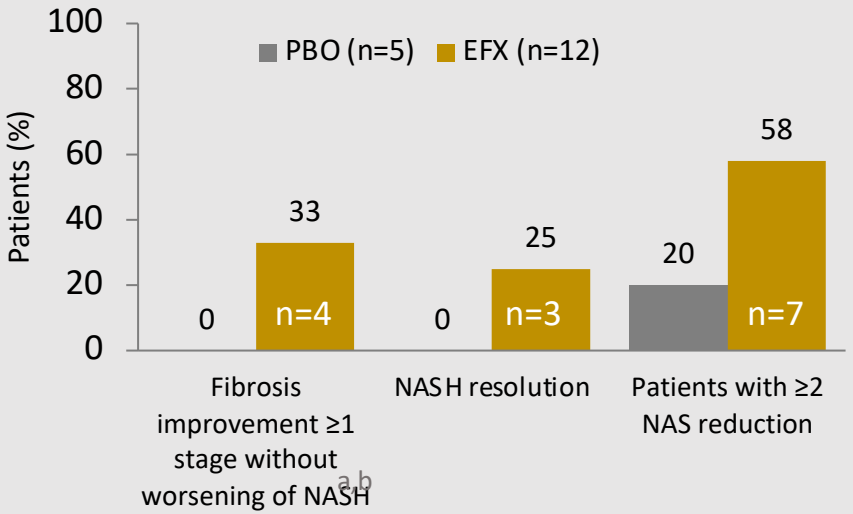


Harrison S, et al. *Nature Medicine* 2021

EFX in F4 cohort



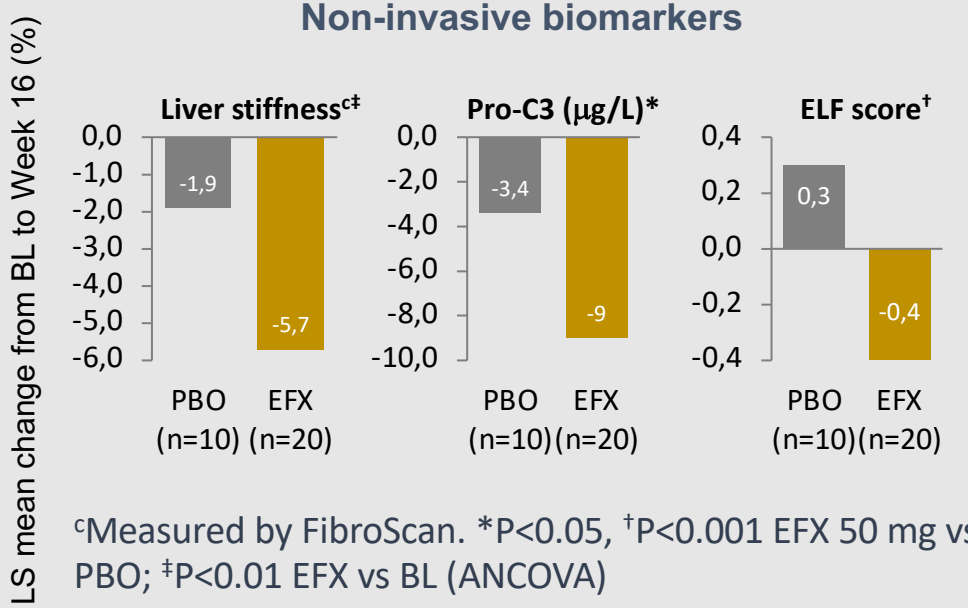
Histologic outcomes



[a,b]

[a]No increase in NAS for ballooning, inflammation or steatosis;[b]Study not powered to assess statistical significance of changes in histologic endpoints

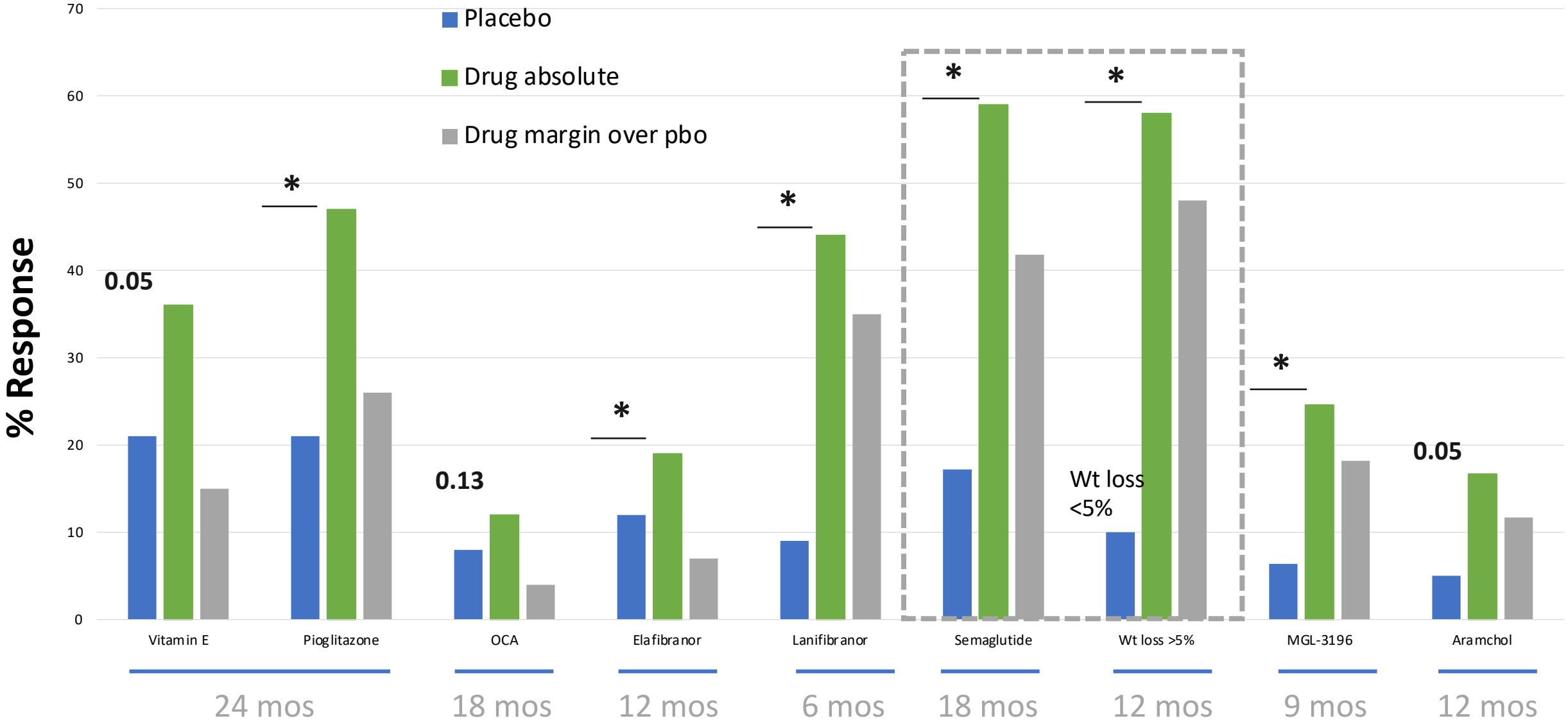
Non-invasive biomarkers



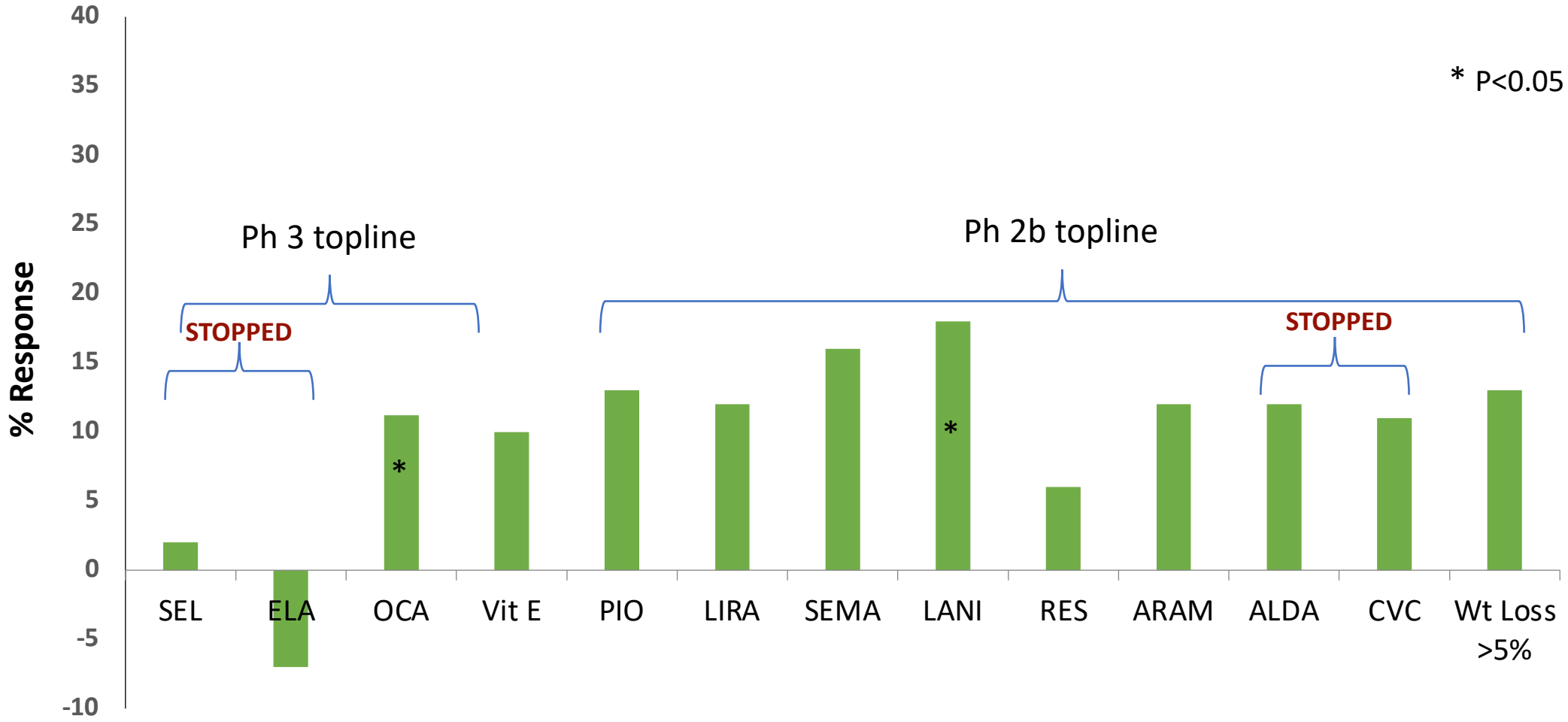
[c]Measured by FibroScan. *P<0.05, [†]P<0.001 EFX 50 mg vs PBO; [‡]P<0.01 EFX vs BL (ANCOVA)

Harrison S, et al. EASL 2021. #LBO-2800

NASH Resolution



Fibrosis Improvement ≥1 Stage – Margin over Placebo



Harrison et al. STELLAR3/4; Sanyal et al NEJM 2010; Vilar-Gomez et al. Gastro 2015;149:367–78;Newsome et al NEJM 2020; AASLD #104; AASLD #LB4; Lawitz et al. EASL 2018 ; AASLD #14; Sanyal et al. *Lancet*, accepted; Petit et al. *Clin Endocrinol Metab*, February 2017; AASLD #736; AASLD #LB23; AAASLD #LB5; Loomba et al. *Hepatology* 2018

SHG = second harmonic generation digital image analysis; NGM bio press release

Combination Strategies

ADVANTAGES

- Enhanced efficacy
- Improved Therapeutic Index

DISADVANTAGES

- Cost
- Complexity
  - Dosing
  - Aes
  - Handling
  - Manufacturing
  - Intellectual property

Jamaican 4x100m Relay World Record

Seoul, Sept 4th 2011



All:

- World class sprinters in their own right
- Got along well with each other
- Had complementary strengths
- Similar endurance
- Same home

What does the future hold for NASH therapeutics?

- Promising therapeutic options are emerging
- Identification of NASH phenotypes →More precision driven care
- Combination approaches
- Further validation of non-invasives and less reliance on histology to assess therapeutic efficacy





Thank you for your attention

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