inventiva

KOL Webcast Event From EASL 2021

June 29, 2021

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Today's speakers

Frédéric Cren, MA/MBA, Chairman, CEO and cofounder

Pierre Broqua, Ph.D., CSO and cofounder

Michael Cooreman, MD, CMO

Prof. Naim Alkhouri, MD

VP of Academic Affairs Chief of Transplant Hepatology, Director of the Fatty Liver Program Arizona Liver Health

Prof. Sven Francque, MD

Head of the Department of Gastroenterology and Hepatology of the Antwerp University Hospital, Co-Principal Investigator of NATIVE trial

Update on the NASH field

Prof. Naim Alkhouri, MD

Director of the Fatty Liver Program VP of Academic Affairs

Chief of Transplant Hepatology

Arizona Liver Health (ALH)

ARIZONA LIVER HEALTH™

NITs to Predict Response to Treatment

FDA Efficacy Endpoints for Phase 3 Trials: Liver Histologic Improvement

NASH Resolution

- Resolution of steatohepatitis on overall histopathologic reading

and

- No worsening of liver fibrosis

Fibrosis Improvement

- Improvement ≥ 1 fibrosis stage

and

- No worsening of steatohepatitis

OR BOTH

1. US FDA. Draft Guidance. Noncirrhotic NASH With Liver Fibrosis. December 2018.

Biomarkers to Assess Treatment Response

Liver Fat Fraction (MRI-PDFF)

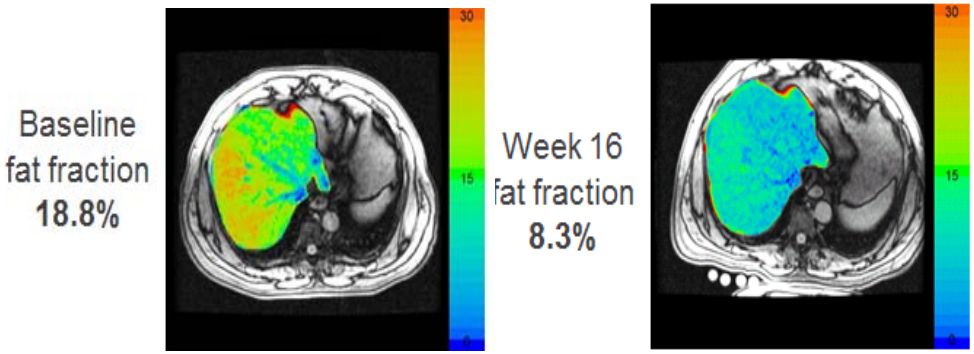
- ≥ 5% absolute/ ≥ 30% relative reduction associated with improvement in NAS

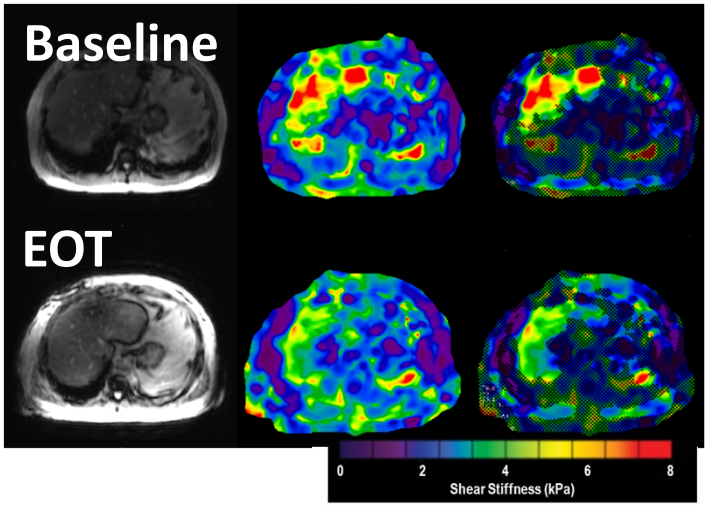
ALT/ AST

- ≥ 17 U/L reduction predicts histologic response

?MRE/ cT1/ LSM?

- MRE: ≥ 15% relative reduction from BL?
- cT1: > 88 ms reduction from BL or change in category?
- LSM decrease by 20- 25% from BL?

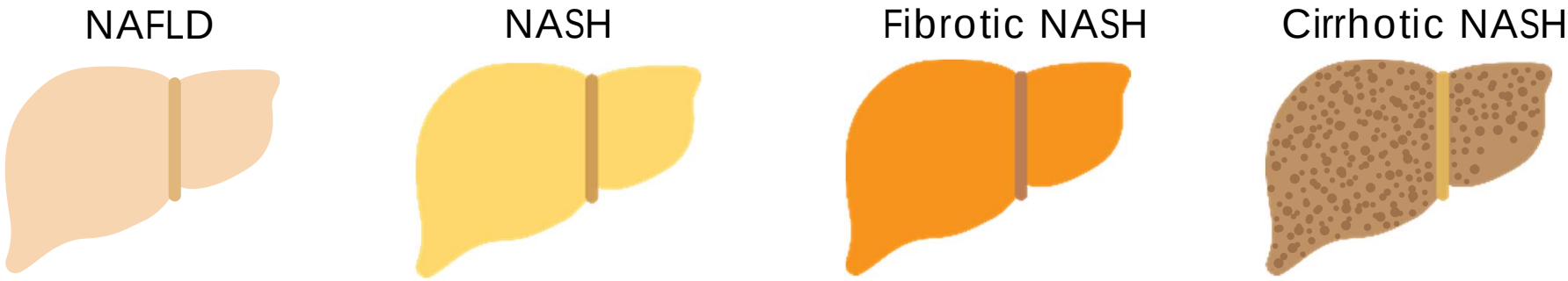




Loomba. Gastroenterology. 2019;156:88.
Patel. Therap Adv Gastro 2016;9:692.

Future Treatments for NASH

NASH Clinical Trial Overview
The $40B Race to Treatment

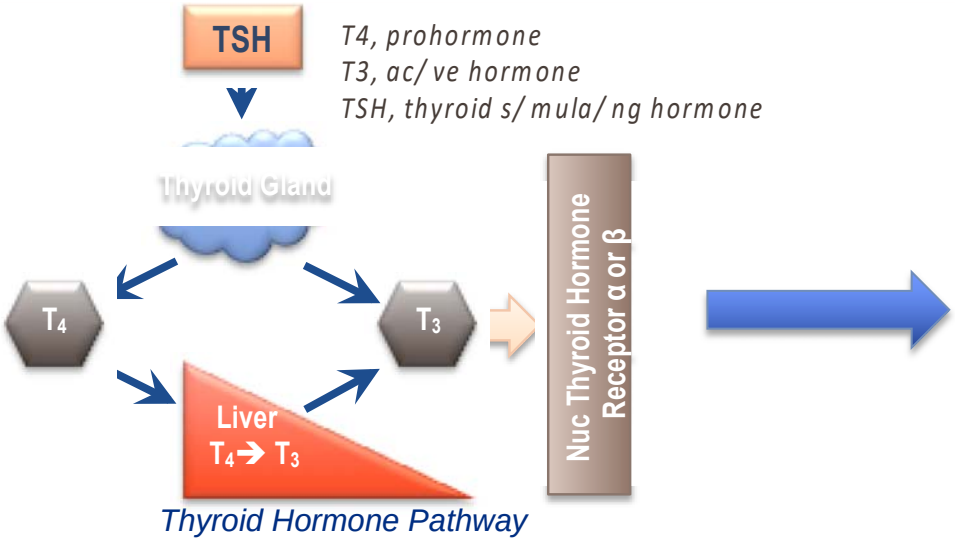


Insulin resistance and/or lipid metabolism	Lipotoxicity and oxidative stress	Inflammation and immune activation	Cell death (apoptosis and necrosis)	Fibrogenesis and collagen turnover
PPARγ: Pioglitazone	PPARα/γ: Saroglitazar	CCR2/5: Cenicriviroc (inflammatory target but affects fibrosis)		Galectin: GR-MD-02
GLP-1: Liraglutide, semaglutide	Pan-PPAR: Lanifibranor	AOC3: BI-1467335		
SGLT: Empagliflozin, licogliflozin, canagliflozin	FGF19: NGM282	P2X7R: SGM-1019		
DPP-4 Sitagliptin	FGF21: Pegbelferim	TLR-4: JKB-121/122		
ACC: GS-0976, PF-05221304	FXR: OCA, cilofexor, tropifexor, nidufexor			
SCD1: Aramchol	MPC: MSDC-0602K			
	TGR-5: INT-767/777			
	THR-β: MGL-3196, VK2809			

Several therapeutic agents in phase 3:
- **Semaglutide (GLP-1)**
- **Lanifibranor (pan-PPAR agonist)**
- **Resmetirom (THR-beta agonist)**
- **Obeticholic acid (FXR agonist)**

Metabolic Targets

Resmetirom (MGL-3196): selective thyroid hormone receptor-beta agonist



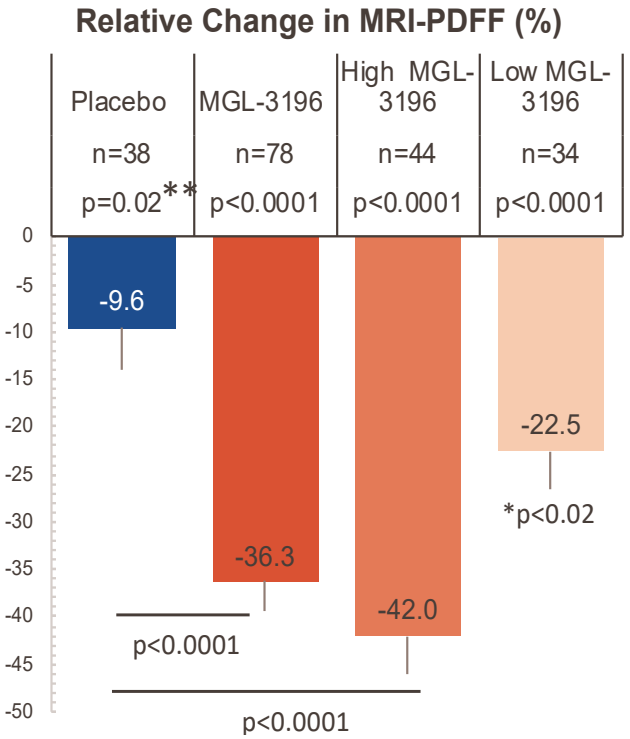
In humans THR-β agonism:

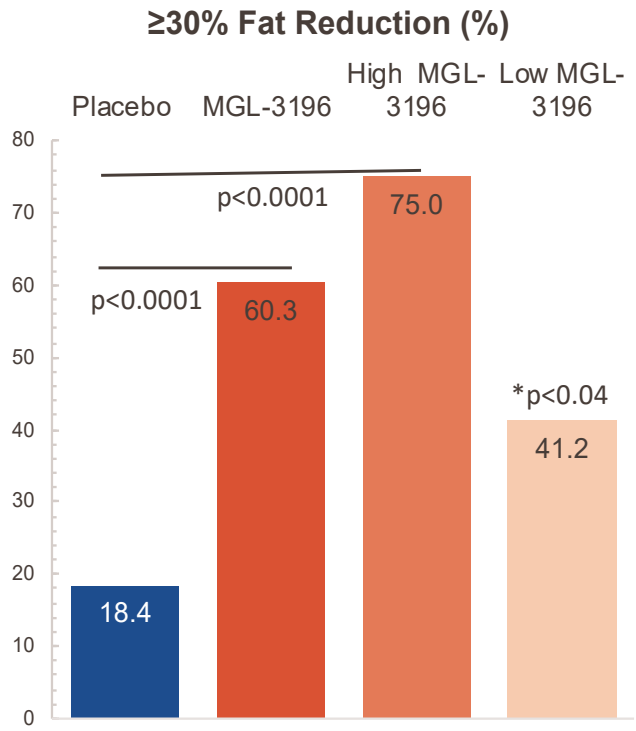
- Lowers LDL-cholesterol
- Lowers triglycerides
- Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

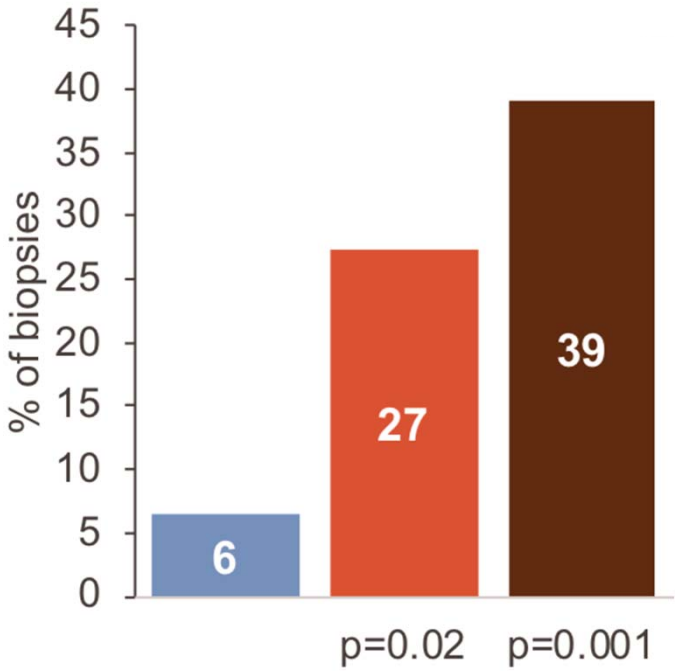
Resmetirom significantly decreases hepatic fat in NASH patients at week 12 MRI-PDFF, and was associated with NASH resolution at week 36 biopsy

Fat Reduction at week 12 MRI-PDFF



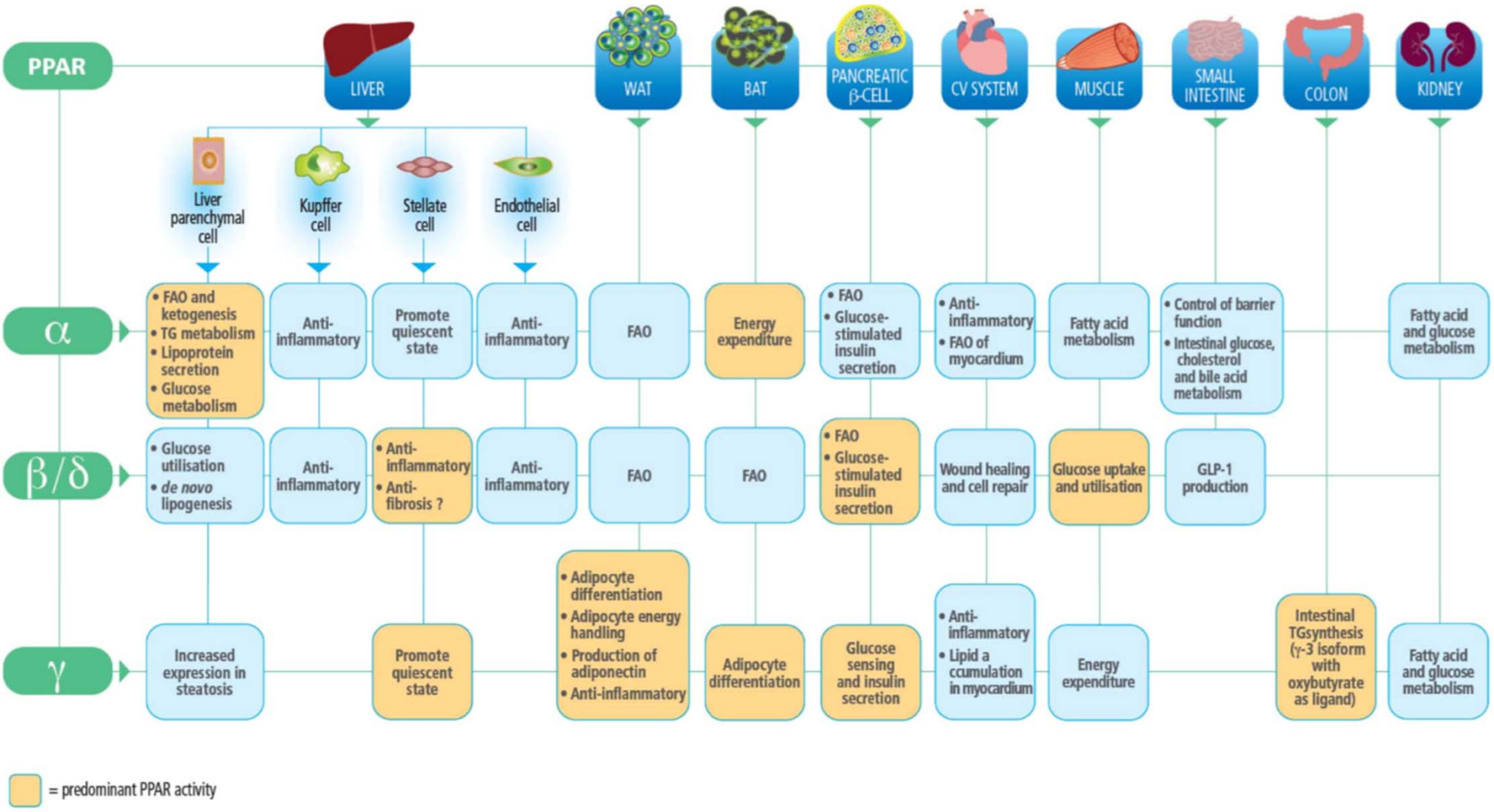


NASH Resolution at week 36 biopsy



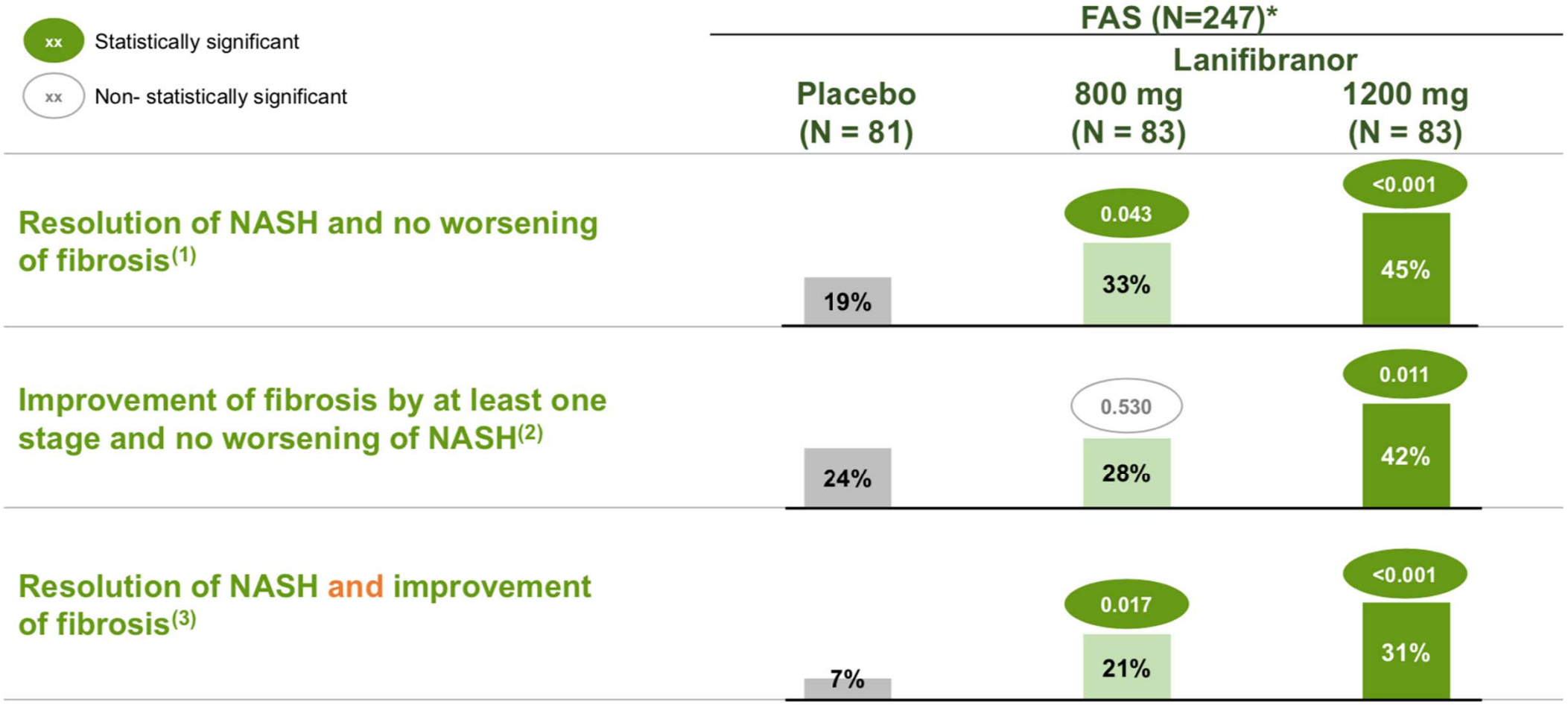
Harrison SA, et al. *J Hepatol.* 2019;70(suppl):e791-e792. Abstract SAT-347.

Lanifibranor: A pan-PPAR agonist



Francque et al. Nature Rev Gastroenterol Hepatol 2020

Lanifibranor: Significant improvements in both resolution of NASH and regression of fibrosis

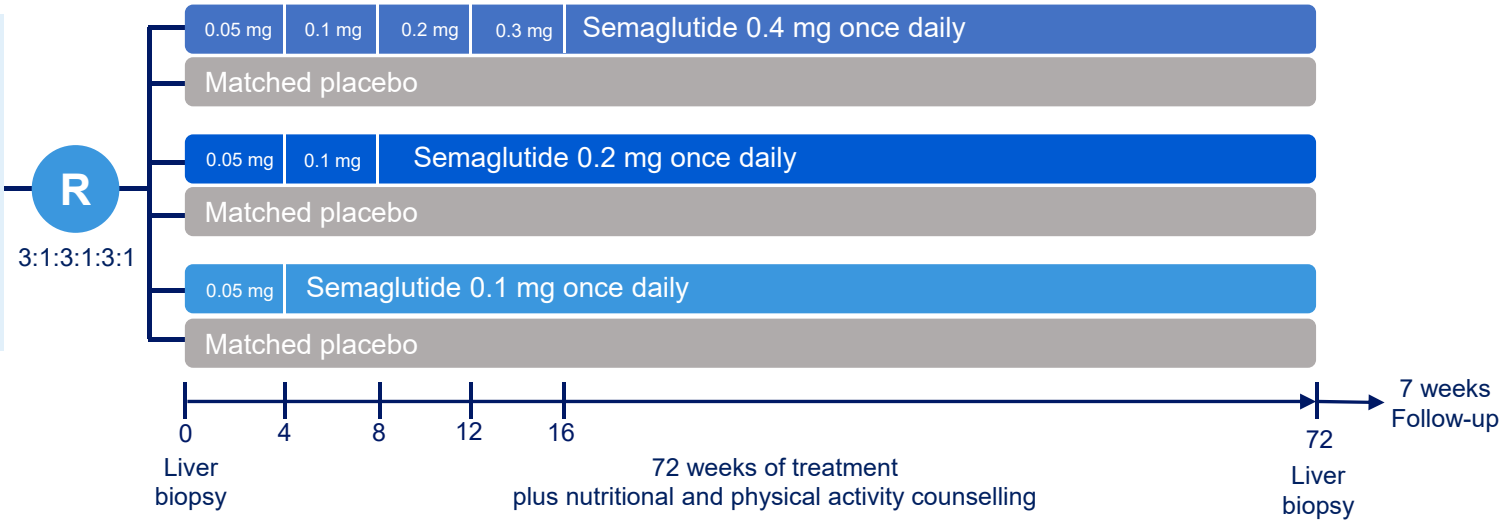


Semaglutide: Efficacy and safety of once-daily SQ

Trial objective: To compare the effect of three different doses of semaglutide subcutaneous (s.c.) once daily versus placebo on histological resolution of NASH

Eligible patients

Biopsy confirmed NASH
NAS ≥ 4
Fibrosis stage 1, 2 or 3
BMI > 25 kg/m^2
HbA_{1c} ≤ 10%



Primary endpoint:

Resolution of steatohepatitis and no worsening in liver fibrosis in patients with baseline fibrosis stage 2 or 3

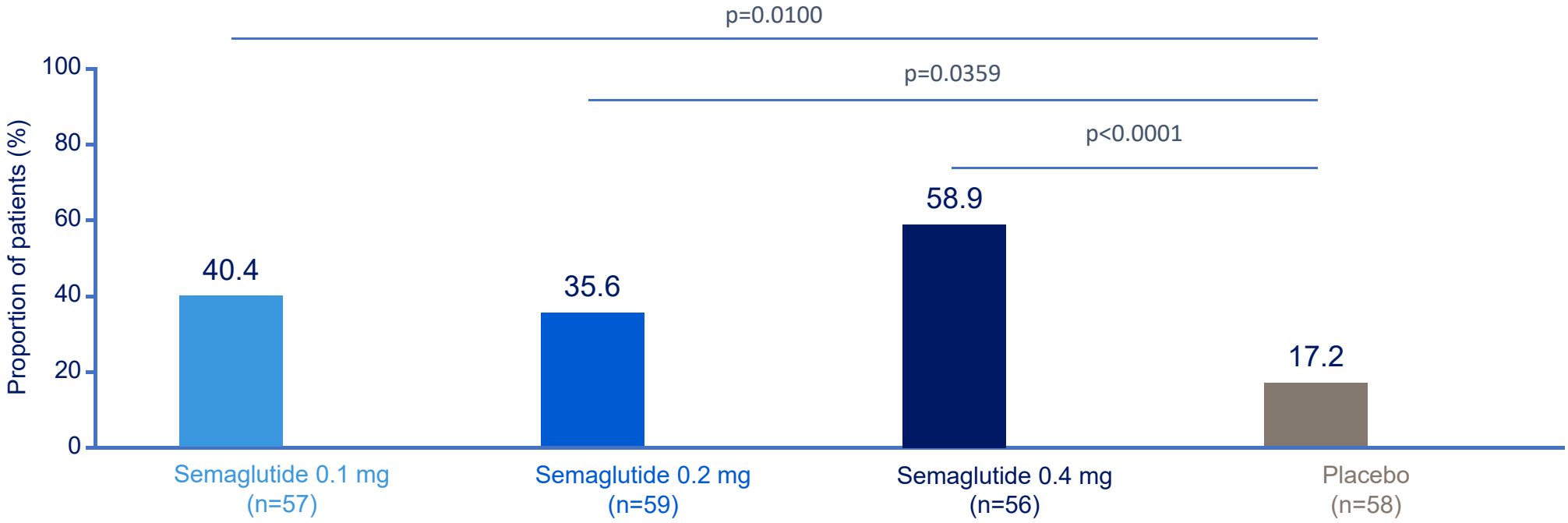
Confirmatory secondary endpoint:

Improvement in liver fibrosis and no worsening in steatohepatitis with baseline fibrosis stage 2 or 3

BMI, body mass index; HbA_{1c}, glycated hemoglobin; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis.

Resolution of steatohepatitis and no worsening in liver fibrosis

Patients with fibrosis stage 2 or 3 at baseline



Data based on in-trial period. Two-sided p-values from a Cochran-Mantel-Haenszel test. Patients with missing data handled as non-responders. p<0.05 signifies statistical significance.

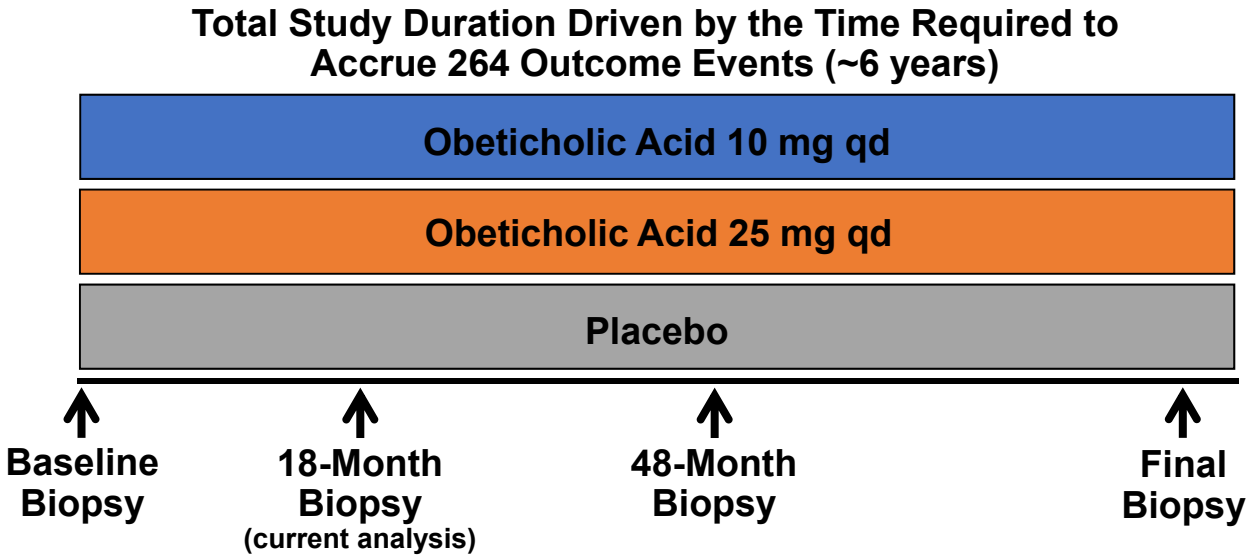
Gut-Liver Axis/ Bile Acids/ FGFs

REGENERATE Study Design: OCA in Non-Cirrhotic NASH

Phase 3 (target ~2400 patients)

-Biopsy confirmed NASH
-Fibrosis stage 2 or 3 (NASH CRN)
-NAFLD activity score ≥4
-Interim analysis: Month 18

-Additional outcomes: Histological progression to cirrhosis, ascites/ SBP, variceal bleed, hepatic encephalopathy, HCC, liver transplant or eligibility for liver transplant, and death.

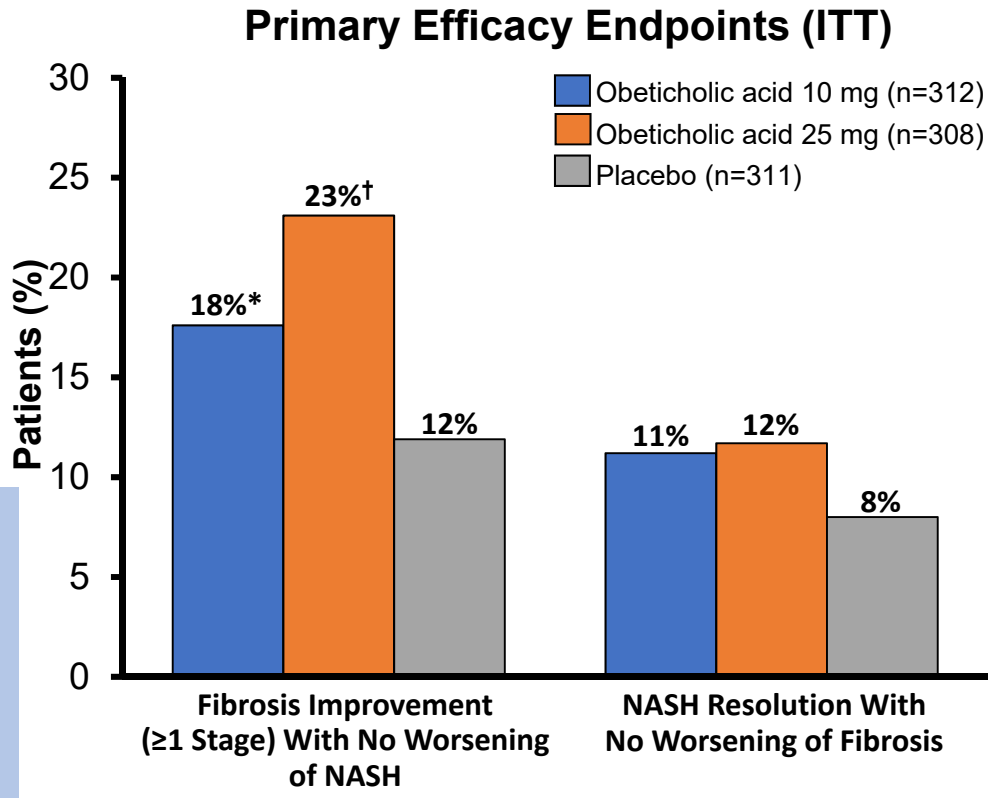


Younossi Z, et al. *J Hepatol.* 2019;70(suppl):e5. Abstract GS-06.

REGENERATE Study: Interim Efficacy Analysis at 18 Months

- **Fibrosis improvement** (≥1 stage) and no worsening of NASH in patients (obeticholic acid versus placebo)
  - 10 mg: 18% versus 12% (*P*<0.05)
  - 25 mg: 23% versus 12% (*P*=0.0002) versus placebo

- **Pruritus: 50% in the OCA 25 mg arm**
- **Worsening lipid profile: Increase in LDL and decrease in HDL**
- **Cholecystitis**



Drug (route of administration)	Lanifibranor (Oral)	Resmetirom (Oral)	Semaglutide (Injectable)	Efruxifermin (Injectable)	Aldafermin (Injectable)	Pioglitazone (Oral)
Hepatic efficacy endpoints						
NASH Resolution						
Fibrosis Improvement		—	—			
MRI-PDFF	No Data		No Data			No Data
ALT						
Effects on MetS						
Weight	Weight gain				Neutral	Weight gain
Dyslipidemia					Increase in LDL	
Insulin Resistance		—			Neutral	
Major AEs	Weight gain, ? Bone loss	? Bone loss, ? Thyroid effects	GI AEs, pancreatitis, retinopathy	GI AEs, tremors, ? Bone loss	GI AEs, ? Malignancies	Weight gain, Bone loss, ?Bladder Ca

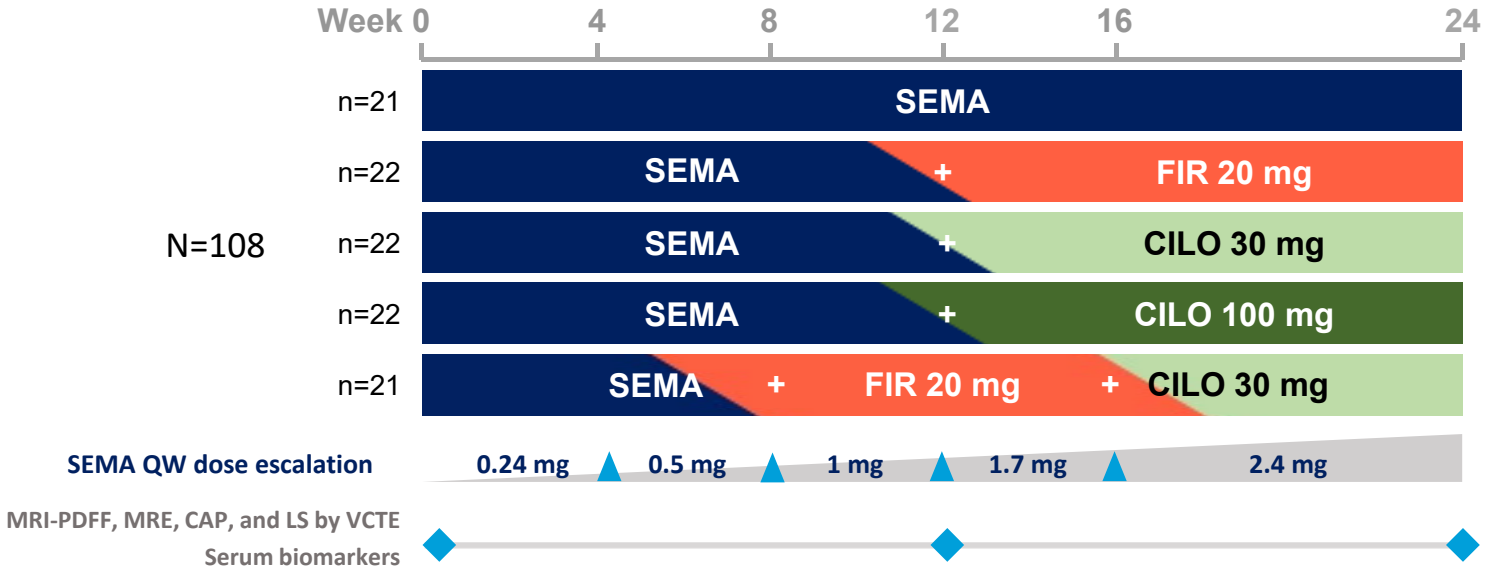
Safety and Efficacy of Combination Therapies Including Semaglutide, Cilofexor, and Firsocostat in Patients with NASH

Naim Alkhouri,[1] Robert Herring,[2] Heidi Kabler,[3] Zeid Kayali,[4] Tarek Hassanein,[5] Anita Kohli,[1] Ryan Huss,[6] Yanni Zhu,[6] Jun Xu, [6] Lars Holm Damgaard,[7] Kristine Buchholtz,[7] Mette Skalshøi Kjær,[7] Clare Balendran,[7] Robert P. Myers,[6] Rohit Loomba,[8] Mazen Noureddin[9]

1. Arizona Liver Health, Chandler, AZ; 2. Quality Medical Research, Nashville, TN; 3. Jubilee Clinical Research, Las Vegas, NV; 4. Inland Empire Liver Foundation, Rialto, CA; 5. Southern California Research Center, Coronado, CA; 6. Gilead Sciences, Inc., Foster City, CA; 7. Novo Nordisk A/S, Bagsværd, Denmark; 8. University of California at San Diego, La Jolla, CA; 9. Cedars-Sinai Medical Center, Los Angeles, CA

The Liver Meeting, 13–16 November 2020: Abstr LO2

Study Design

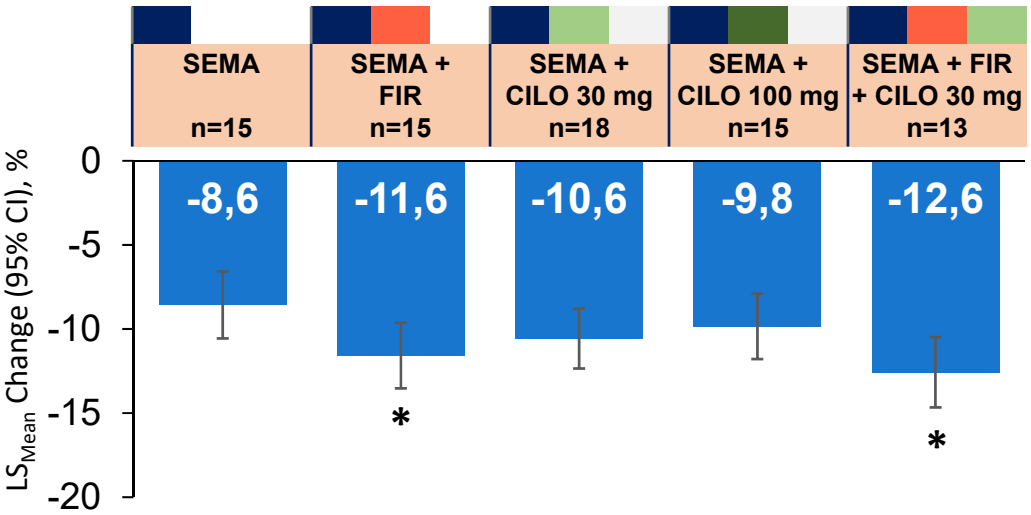


- Key inclusion criteria
  - Histologically confirmed NASH with NASH CRN F2–F3 fibrosis (or equivalent), **or**
  - Clinical diagnosis of NAFLD, MRI-PDFF ≥10%, LS by VCTE ≥7.0 kPa, and FibroTest <0.75
- Randomization stratified by diabetes mellitus (1:1:1:1:1); open label

CAP, Controlled Attenuation Parameter; CILO, cilofexor; CRN, Clinical Research Network; FIR, firsocostat; LS, liver stiffness; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; QW, once weekly; SEMA, semaglutide; VCTE, vibration-controlled transient elastography.

MRI-PDFF: Greater Improvements with Combinations

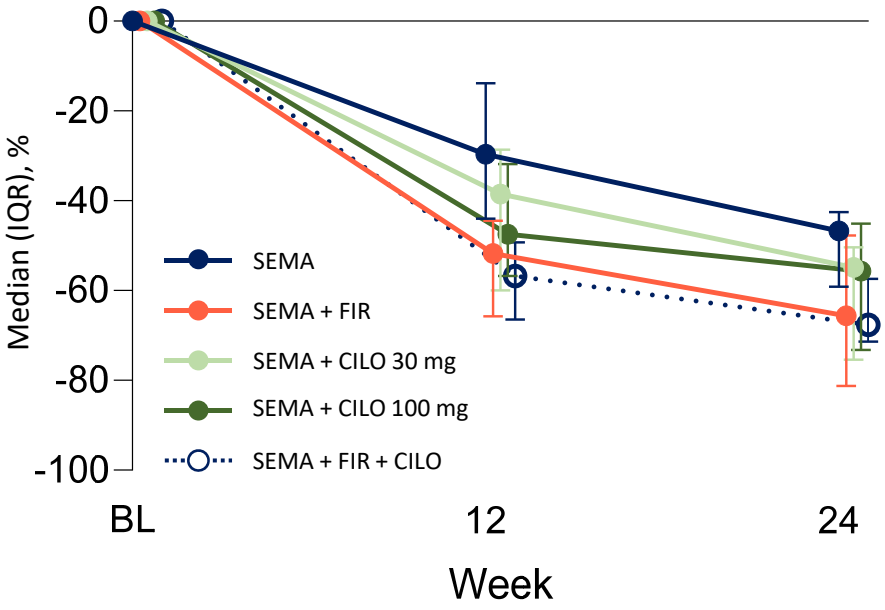
Absolute Change at Week 24



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)

Relative Change from Baseline

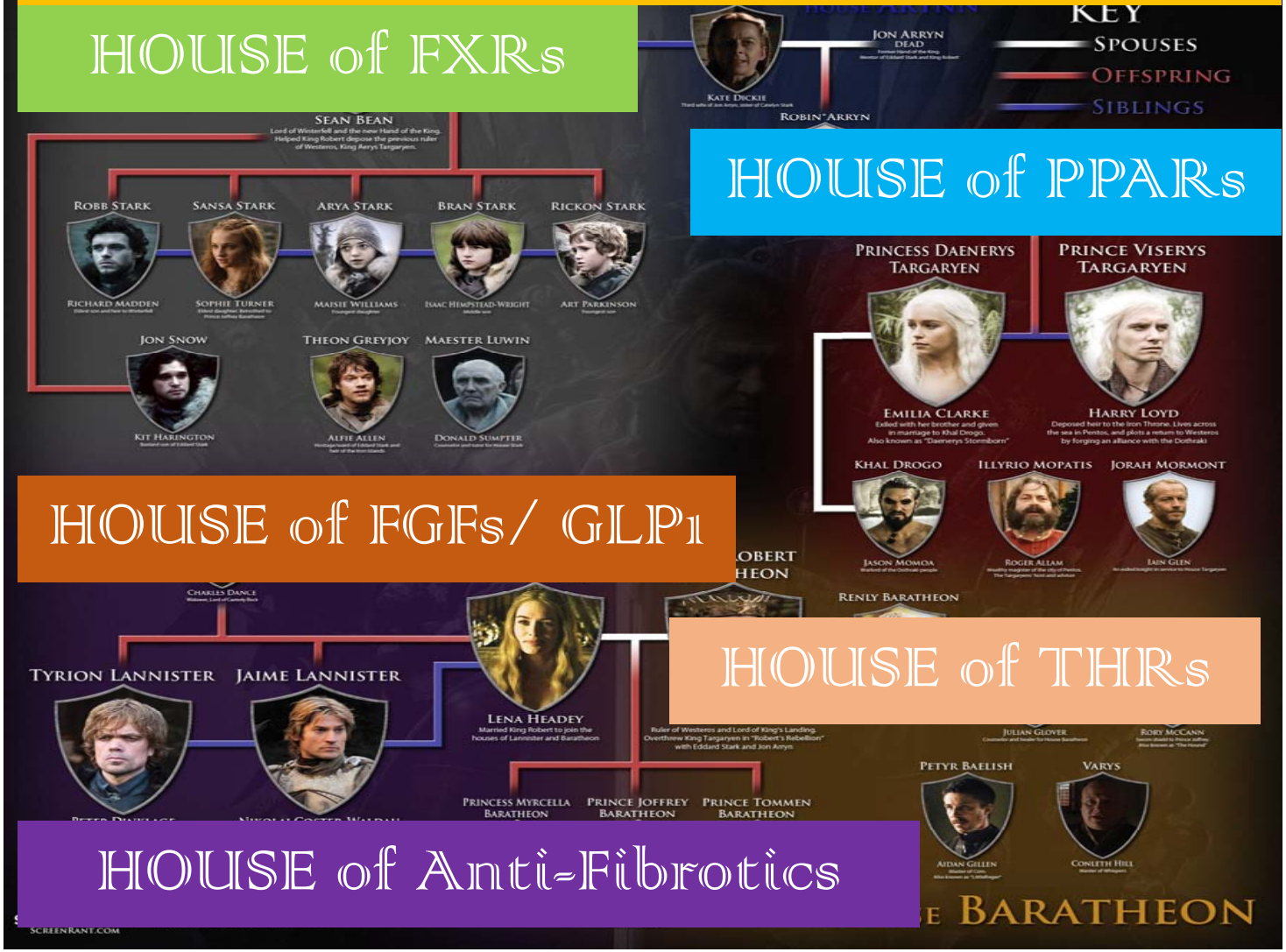


- Greatest reductions in PDFF in FIR groups
  - Similar findings observed with CAP

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. ANCOVA, analysis of covariance; BL, baseline; CAP, Controlled Attenuation Parameter; CI, confidence interval; CILO, cilofexor; FIR, firsocostat; IQR, interquartile range; LSmean, least squares mean; MRI, magnetic resonance imaging; PDFF, proton density fat fraction; SEMA, semaglutide.

NASH DRUGS GOT

HOUSE of FXRs



HOUSE of PPARs

HOUSE of FGFs/ GLP1

HOUSE of THRs

HOUSE of Anti-Fibrotics

Take Home Message

- NITs are rapidly replacing liver biopsy to determine disease severity and response to treatment.

- Promising results from several clinical trials including combination therapy.

- @AlkhouriNaim

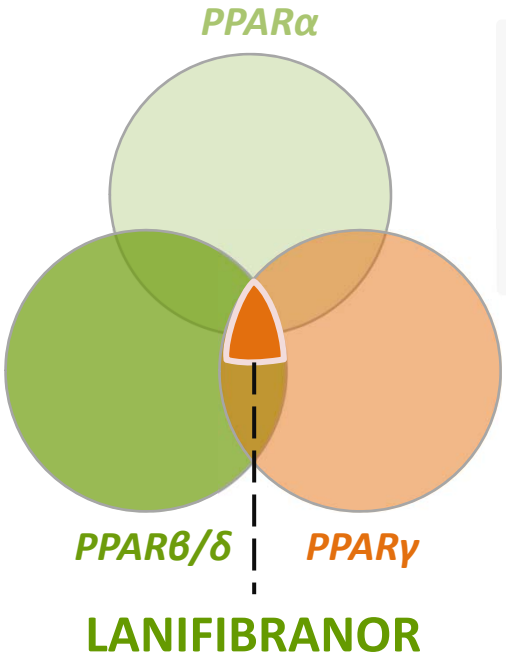
- @azliver

Review of lanifibranor EASL 2021 abstracts

Prof. Sven Francque, MD

Head of the Department of Gastroenterology and Hepatology of the Antwerp University Hospital, Co-Principal Investigator of NATIVE trial

Lanifibranor: activating the 3 PPAR isotypes could lead to an optimal treatment of NASH



METABOLISM

PPARα *PPARδ* *PPARγ*

- ↑ Insulin sensitivity
- ↑ HDLc
- ↓ Triglycerides

STEATOSIS

PPARγ

- ↓ FA uptake
- ↑ FA catabolism
- ↓ Lipogenesis

INFLAMMATION AND BALLOONING

PPARα *PPARδ* *PPARγ*

- ↓ NFkB-dependent gene activation
- ↓ Inflammasome
- ↓ Ballooning

FIBROSIS

PPARδ *PPARγ*

- ↓ Stellate cell proliferation and activation
- ↓ Collagen and fibronectin production

VASCULAR

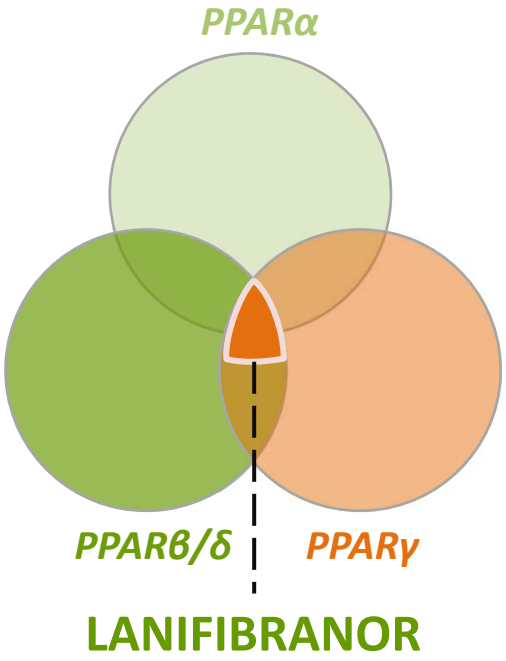
PPARα *PPARγ*

- ↓ Portal pressure
- ↓ LSEC capillarization
- ↓ Intrahepatic vascular resistance

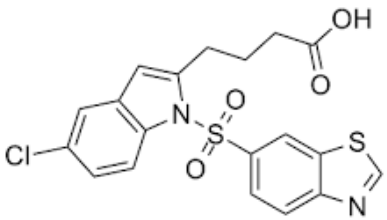
Francque *et al.* Nat Rev Gastroenterol Hepatol 2021

Lanifibranor: a pan-PPAR agonist entering phase 3 in NASH

Moderate and balanced pan-PPAR agonist activity



- Small molecule that activates all three PPAR isotypes in humans
- Differentiated chemical structure: not a fibrate or a TZD
- Once daily oral administration
- Beneficial effect on NASH resolution and fibrosis regression in Phase 2b after 24 weeks of therapy*
- **BREAKTHROUGH THERAPY** and **FAST TRACK** designations in NASH granted by the FDA

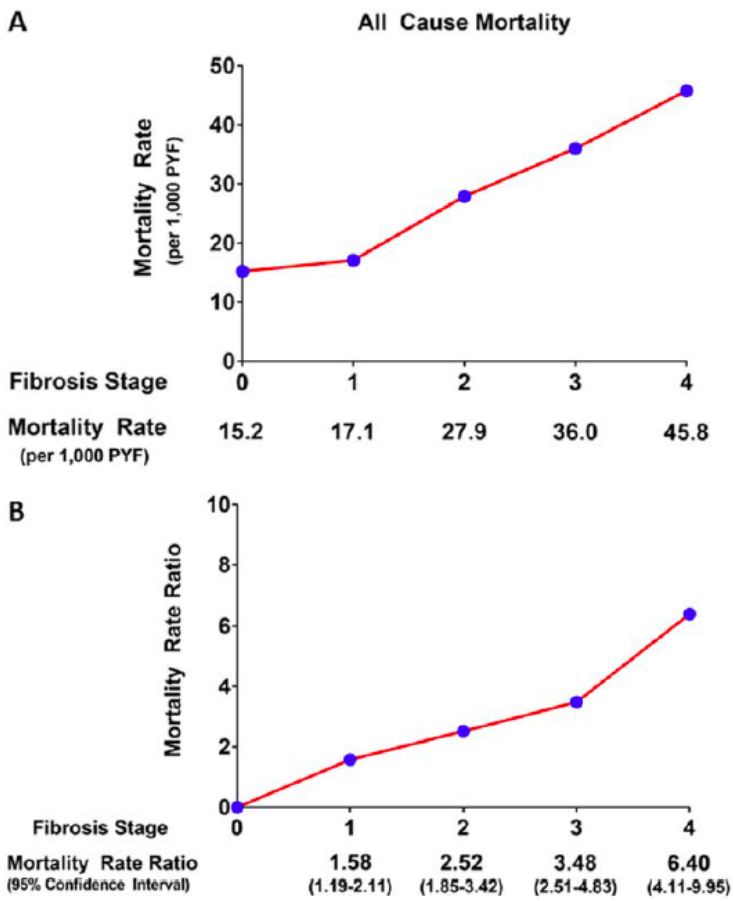


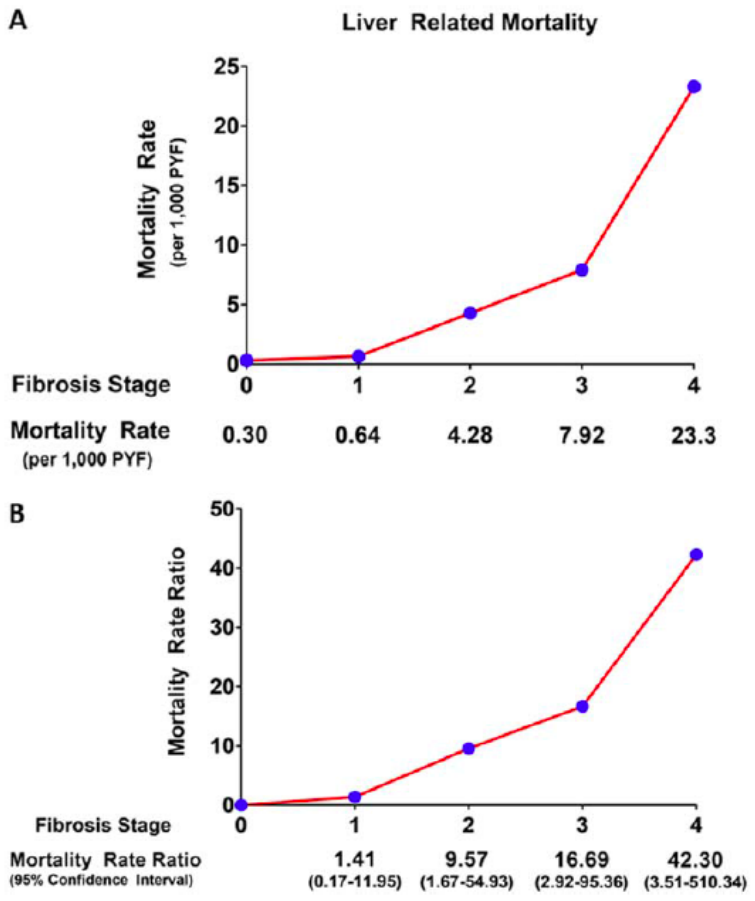
*Francque *et al*. AASLD 2020

Favourable tolerability profile

- Phase I trials with more than **200** healthy volunteers and Phase IIa trial with **47** TD2M patients
- Approximately **250** patients treated for 24 or 48 weeks in Inventiva's completed Phase IIb clinical trials
- FDA confirmation that the **non-clinical toxicology package is complete and acceptable for NDA filing**

Liver fibrosis is the most important predictor of mortality in NAFLD





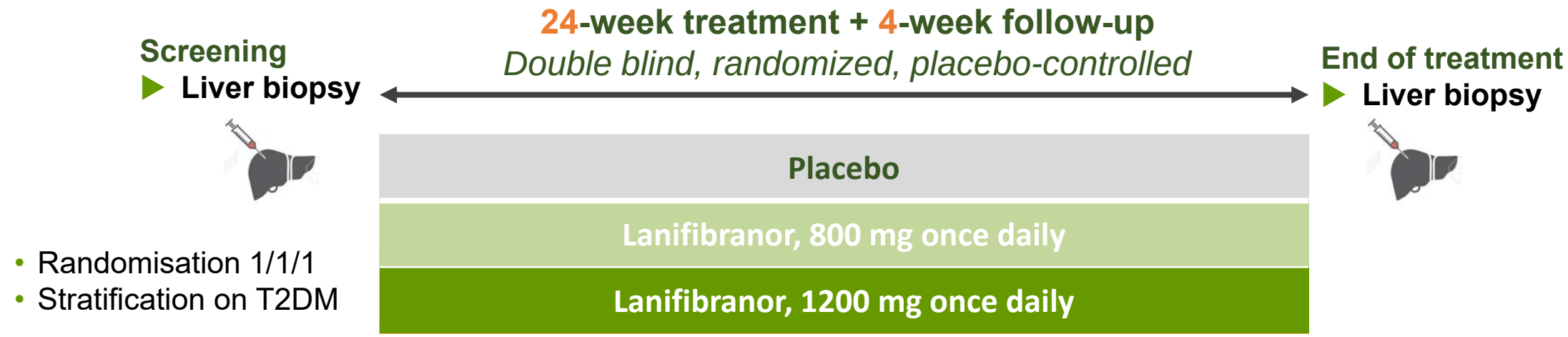
Dulai *et al*. Hepatology 2017

Lanifibranor therapy improves markers of lipid metabolism, insulin resistance, liver injury and fibrosis in patients with NASH and F2 and F3 fibrosis stages: a subgroup analysis of the phase 2b NATIVE study

Sven Francque, Michael P. Cooreman, Martine Baudin,
Philippe Huot-Marchand, Lucile Dzen, Jean-Louis Junien,
Pierre Broqua, Manal F. Abdelmalek

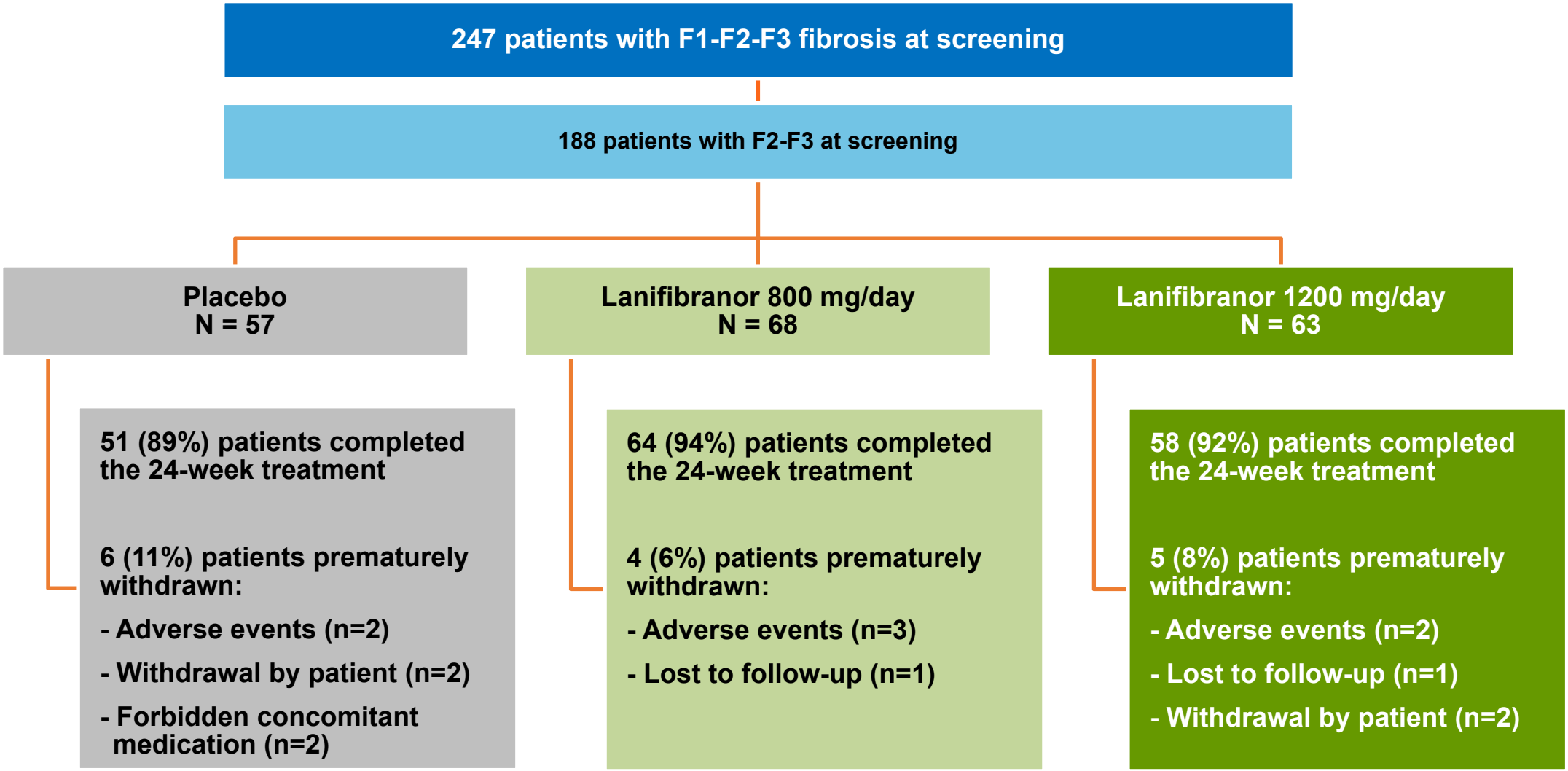
Phase 2b trial design

Clinicaltrials.gov identifier: NCT03008070



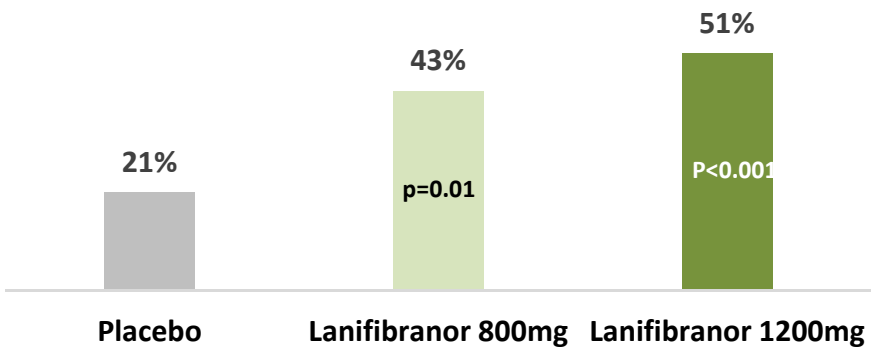
- **Main inclusion criteria**: patients with biopsy-proven NASH confirmed by central reader having Steatosis-Activity-Fibrosis (SAF) scores of 1-3 for **S**teatosis, 3-4 for **A**ctivity, and <4 for **F**ibrosis

Patient disposition in F2-F3

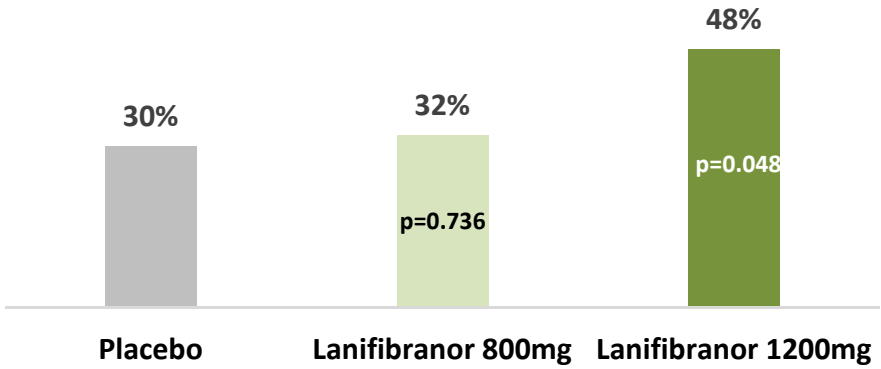


Effect of lanifibranor therapy on histological endpoints, in F2-F3

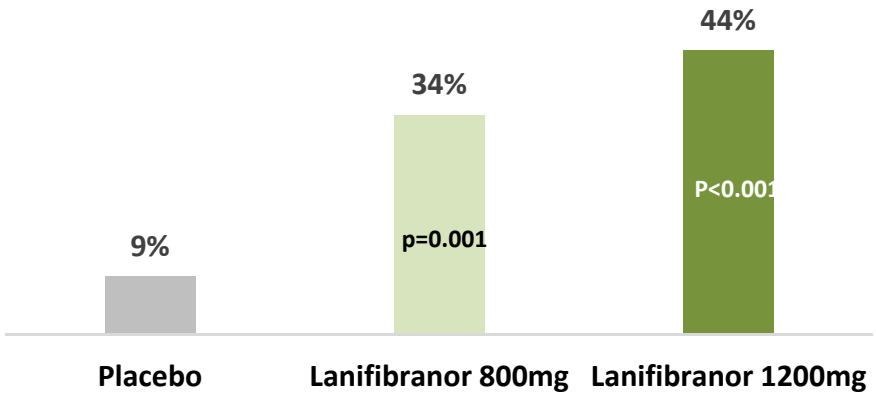
Reduction of 2 points of SAF Activity Score and no worsening of fibrosis



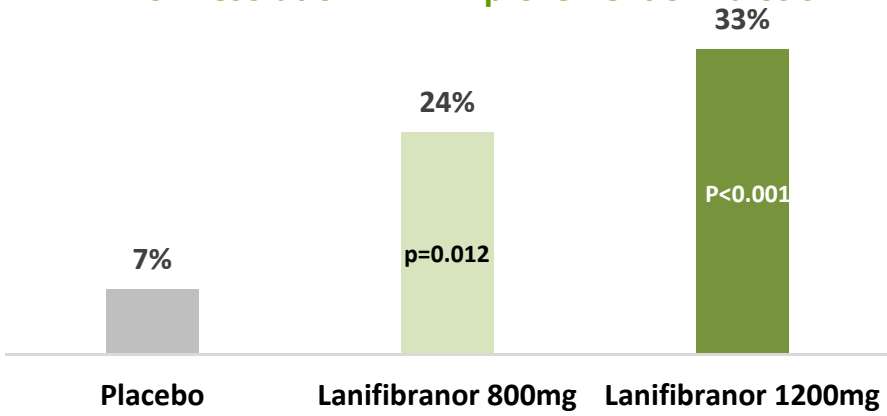
Fibrosis improvement w/o worsening of NASH



NASH resolution w/o worsening of fibrosis

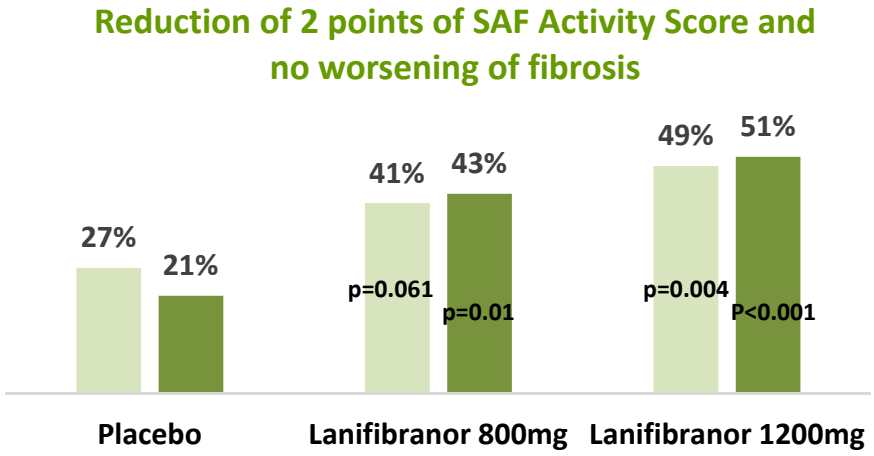


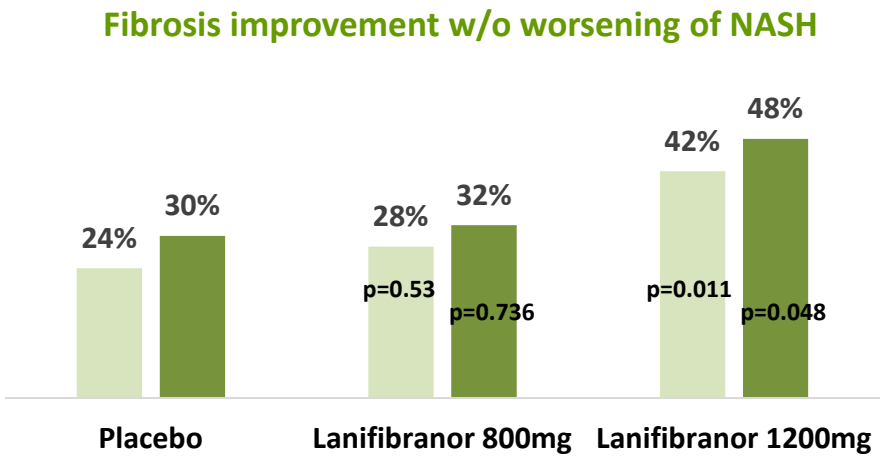
NASH resolution AND Improvement of fibrosis

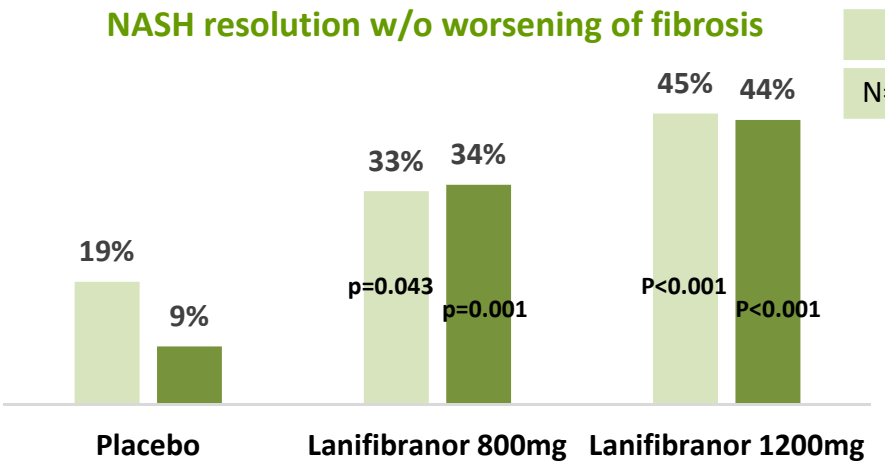


▶ **Effect is higher in the F2-F3 subpopulation**

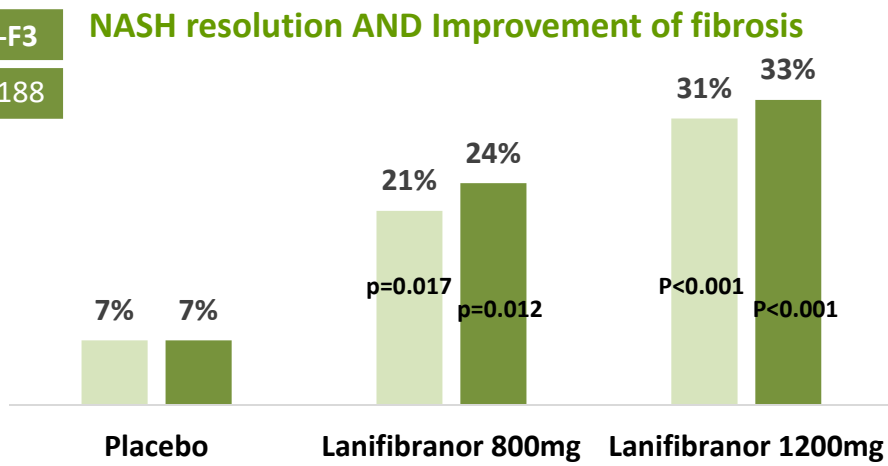
Effect of lanifibranor therapy on histological endpoints, in the overall population and the subgroup of F2-F3







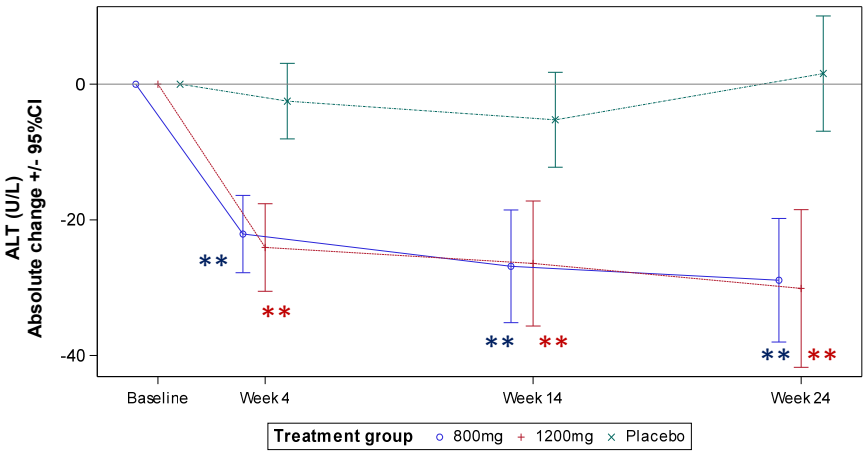
All	F2-F3
N=247	N=188



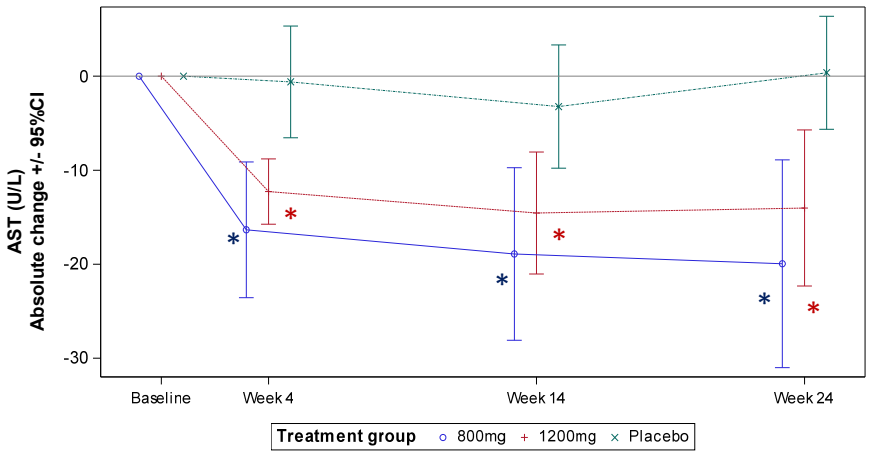
▶ **Effect is higher in the F2-F3 subpopulation**

Effect of lanifibranor therapy on liver enzymes in F2-F3

Absolute change from baseline in ALT

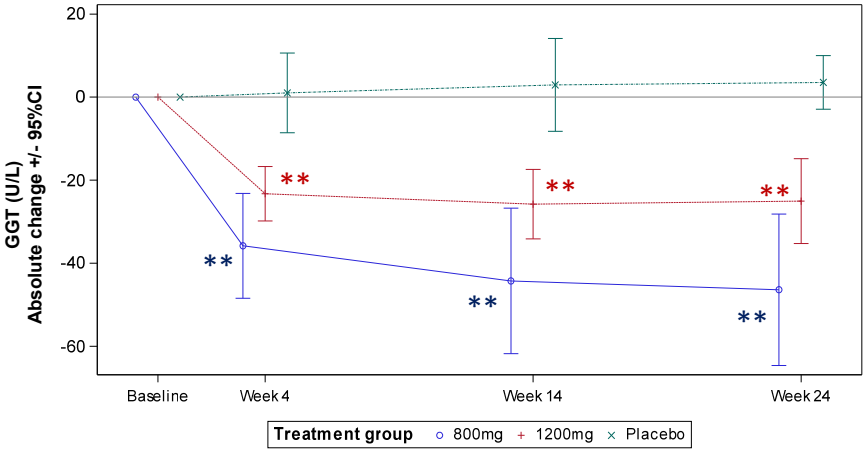


Absolute change from baseline in AST



*** p<0.01 **p<0.001**

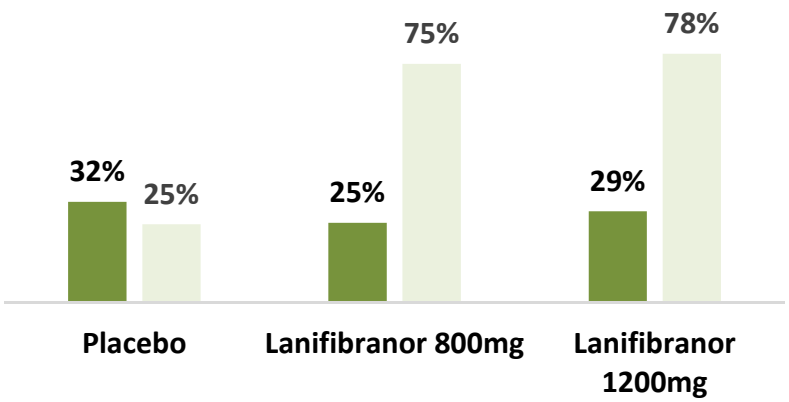
Absolute change from baseline in GGT



▶ **Statistically significant decrease of ALT, AST and GGT in both lanifibranor dose groups already at week 4**

Effect of lanifibranor therapy on liver enzymes in F2-F3

Percentage of patients with normal ALT values

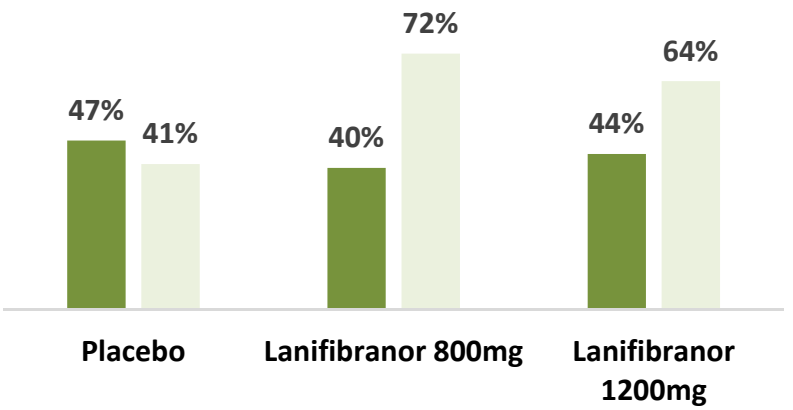


Baseline

End of treatment (Week 24)

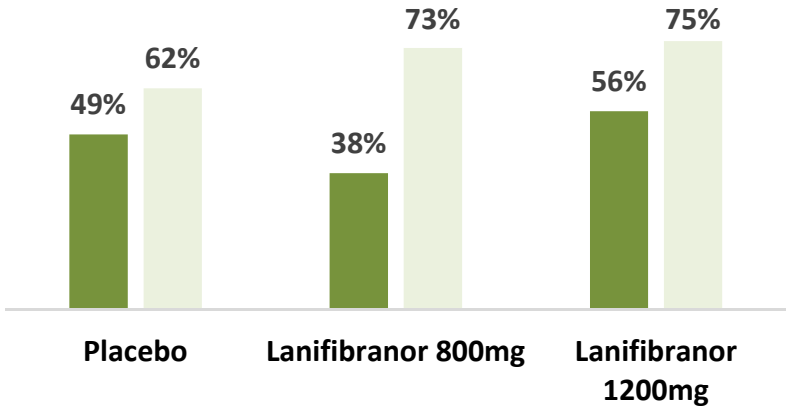
Lower Limit of Normal (LLN)= 0 U/L, Upper Limit of Normal (ULN)= 41 U/L for males, 33 U/L for females

Percentage of patients with normal AST values



LLN= 0 U/L, ULN= 40 U/L for males, 32 U/L for females

Percentage of patients with normal GGT values



LLN= 8 U/L for males, 5 U/L for females; ULN= 61 U/L for males, 36 U/L for females

▶ **Significant higher percentage of patients under lanifibranor treatment reach normal liver enzymes at end of treatment**

Effect of lanifibranor therapy on markers of lipid metabolism, inflammation and fibrosis in F2-F3

	Absolute Change from baseline at End of Treatment (Week 24): Mean (SE) P value* vs placebo			
	Lanifibranor 800 mg	Lanifibranor 1200 mg	Lanifibranor pooled	Placebo
APO-B/APO-A1	-0.09 (0.02) 0.001	-0.07 (0.02) 0.01	-0.08 (0.01) 0.001	0.01 (0.02)
Hs-CRP (mg/l)	-2.01 (0.50) 0.02	-1.00 (0.52) 0.31	-1.53 (0.36) 0.053	-0.23 (0.55)
MACK-3	-0.32 (0.03) <.001	-0.28 (0.03) <.001	-0.30 (0.02) <.001	-0.01 (0.03)
TIMP1/MMP2	-0.79 (0.10) <.001	-0.88 (0.10) <.001	-0.83 (0.07) <.001	-0.07 (0.11)

* From MMRM including absolute change from Baseline as endpoint, time, treatment, baseline diabetic status, interaction treatment * time and baseline value as fixed effects, time repeated effect within each subject.

Safety and tolerability in F2-F3

N (%) patients reporting Adverse Event (AE)	Placebo (N = 57)	800 mg (N = 68)	1200 mg (N = 63)
Any Treatment-Emergent AE (TEAE)	36 (63.2%)	50 (73.5%)	46 (73.0%)
- Drug-related TEAE	*13 (22.8%)*	*22 (32.4%)*	*18 (28.6%)*
Any Serious TEAE	2 (3.5%)	2 (2.9%)	5 (7.9%)
- Drug-related Serious TEAE	*1 (1.8%)*	*0 (0.0%)*	*0 (0.0%)*
Specific TEAE			
Weight increased [1]	-	7 (10.3%)	6 (9.5%)
Oedema peripheral	2 (3.5%)	4 (5.9%)	5 (7.9%)

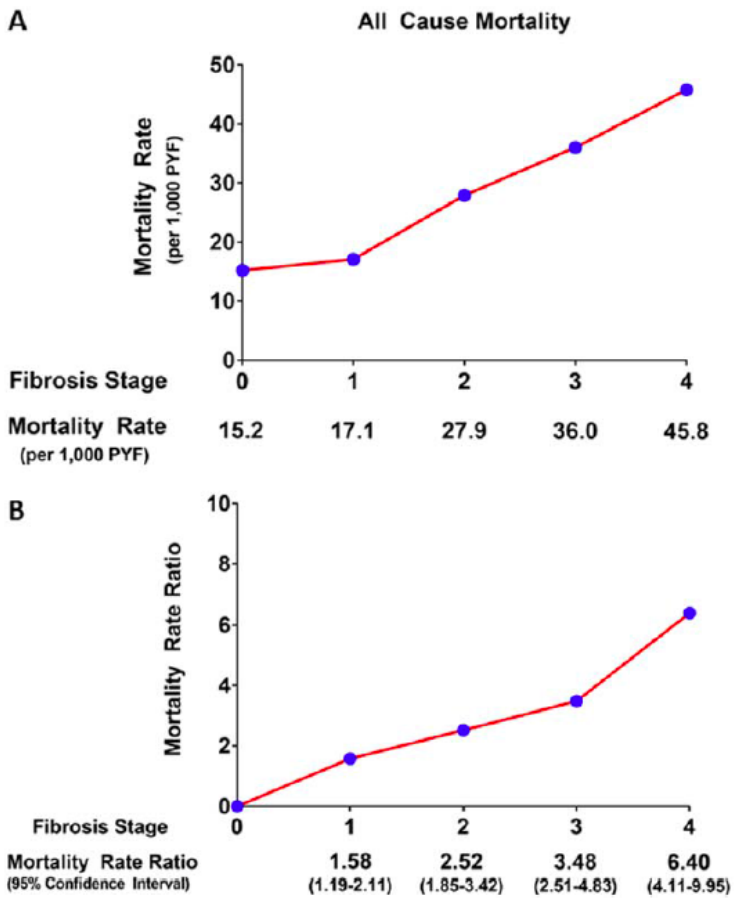
[1] Mean weight increase from baseline of 2.0 kg (2.2%) at the 800 mg/day dose and 2.7 kg (3.1%) at the 1200 mg/day dose. Reflective of improvement of adipose tissue function and shift from visceral fat to subcutaneous fat (insulin sensitizing pharmacology)

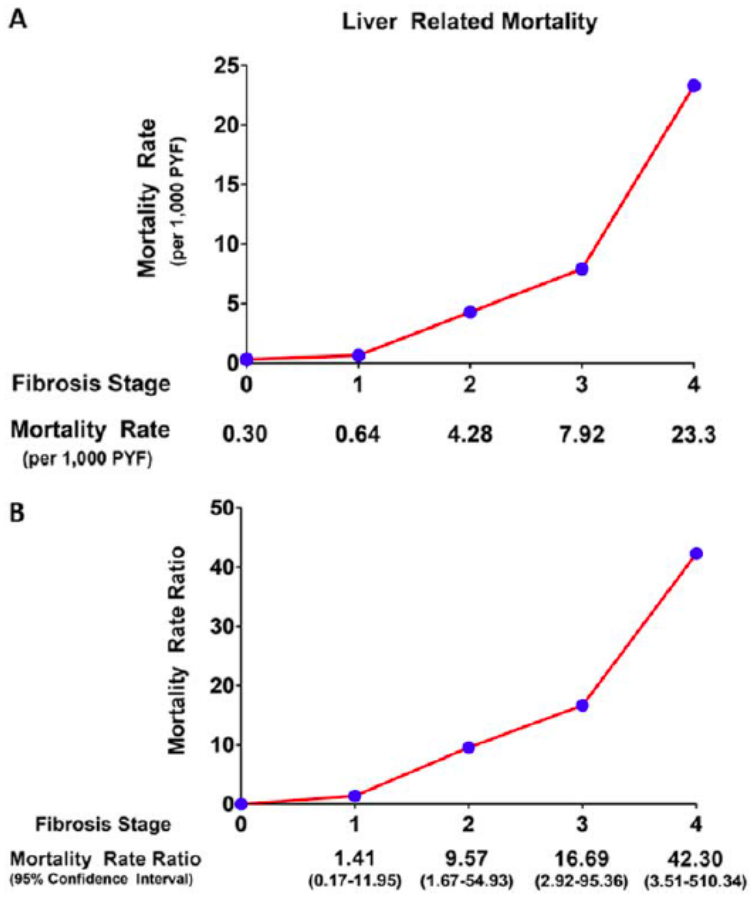
▶ **Safety profile in F2-F3 was similar to the overall population**

Lanifibranor, a pan-PPAR agonist, has beneficial effects on cardiovascular risk biomarkers in patients with NASH

Sven Francque, Michael P. Cooreman, Martine Baudin,
Philippe Huot-Marchand, Lucile Dzen, Jean-Louis Junien,
Pierre Broqua, Manal F. Abdelmalek

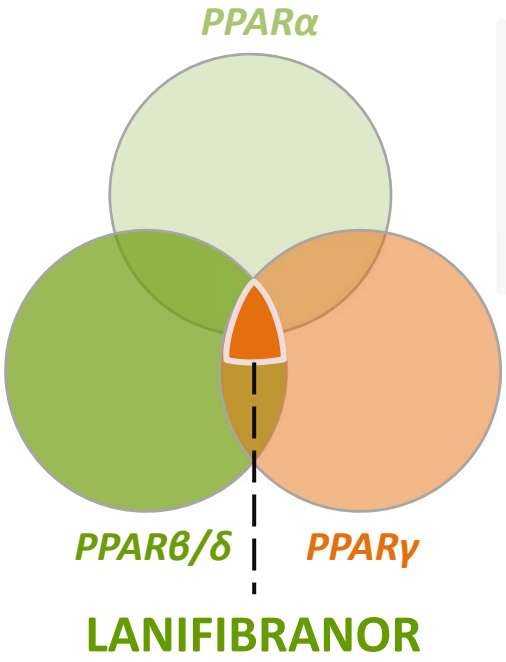
Liver fibrosis is the most important predictor of mortality in NAFLD





Dulai *et al*. Hepatology 2017

Lanifibranor: activating the 3 PPAR isotypes could lead to an optimal treatment of NASH



METABOLISM

PPARα PPARδ PPARγ

- ↑ Insulin sensitivity
- ↑ HDLc
- ↓ Triglycerides

STEATOSIS

PPARγ

- ↓ FA uptake
- ↑ FA catabolism
- ↓ Lipogenesis

INFLAMMATION AND BALLOONING

PPARα PPARδ PPARγ

- ↓ NFkB-dependent gene activation
- ↓ Inflammasome
- ↓ Ballooning

FIBROSIS

PPARδ PPARγ

- ↓ Stellate cell proliferation and activation
- ↓ Collagen and fibronectin production

VASCULAR

PPARα PPARγ

- ↓ Portal pressure
- ↓ LSEC capillarization
- ↓ Intrahepatic vascular resistance

Francque *et al.* Nat Rev Gastroenterol Hepatol 2021

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with NASH

Cardiovascular risk biomarkers considered in NASH

- **Lipids**
  - Triglycerides (mmol/L)
  - HDL-c (mmol/L)
  - LDL-c (mmol/L)
  - APO-A1 (mg/dl)
  - APO-B (mg/dl)
  - APO-B/APO-A1
  - APO-C3 (ug/ml)
- **Inflammatory marker:**
  - Hs-CRP (mg/l)
- **Glucose metabolism**
  - Fasting glucose (mmol/l)
  - Insulin (pmol/l)
- **Blood Pressure (BP)**
  - Systolic BP (mmHg)
  - Diastolic BP (mmHg)

Patient Baseline Demographics and Characteristics

Parameters (unit) n (%) or mean ± SD		Placebo - N = 81	Lanifibranor 800 mg/day N = 83	Lanifibranor 1200 mg/day N = 83	Overall - N = 247
Demographics	Female	31 (54%)	48 (71%)	35 (56%)	114 (61%)
	Age (years)	54.7 ± 12.9	55.4 ± 10.4	54.1 ± 13.2	54.7 ± 12.1
	White	52 (91%)	65 (96%)	59 (94%)	176 (94%)
	Body Mass Index (kg/m²)	33.1 ± 5.4	32.2 ± 5.5	33.2 ± 5.7	32.8 ± 5.5
	Waist circumference (cm)	109.6 ± 11.8	113.4 ± 10.2	109.4 ± 14.7	110.6 ± 12.4
	Male / Female	106.3 ± 12.1	102.8 ± 12.7	106.8 ± 13.5	105.2 ± 12.9
	Type 2 diabetes	27 (47%)	27 (40%)	29 (46%)	83 (44%)
Metabolic syndrome		**56 (69%)**	**64 (77%)**	**59 (71%)**	**179 (72%)**
	High waist circumference	78 (96%)	81 (98%)	75 (90%)	234 (95%)
	High triglycerides	54 (67%)	48 (58%)	53 (64%)	155 (63%)
	Low HDL-cholesterol	39 (48%)	36 (43%)	40 (48%)	115 (47%)
	Pre-diabetic/diabetic condition	46 (57%)	55 (66%)	52 (63%)	153 (62%)
	Hypertension	49 (60%)	53 (64%)	51 (61%)	153 (62%)

- High waist circumference: waist circumference ≥ 94 cm/37 inches in males, ≥ 80 cm/31.5 inches in females
- High triglycerides: serum triglycerides ≥ 150 mg/dL (i.e. 1.7 mmol/L) or hypertriglyceridemia / hyperlipidemia / dysplipidaemia reported as medical history
- Low HDL-cholesterol: HDL cholesterol < 40 mg/dL (i.e. 1.0 mmol/L) in males, < 50 mg/dL (i.e. 1.3 mmol/L) in females
- Pre-diabetic/diabetic condition: Presence of 'Type 2 diabetes mellitus' or Fasting glucose ≥ 100 mg/dl (5.6 mmol/L) if no type 2 diabetes mellitus
- Hypertension: reported as medical history ongoing at baseline

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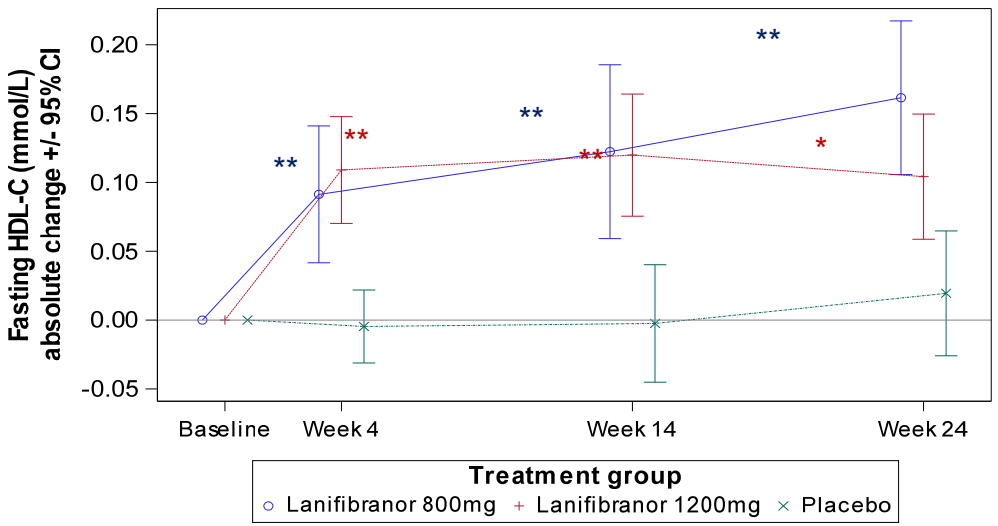
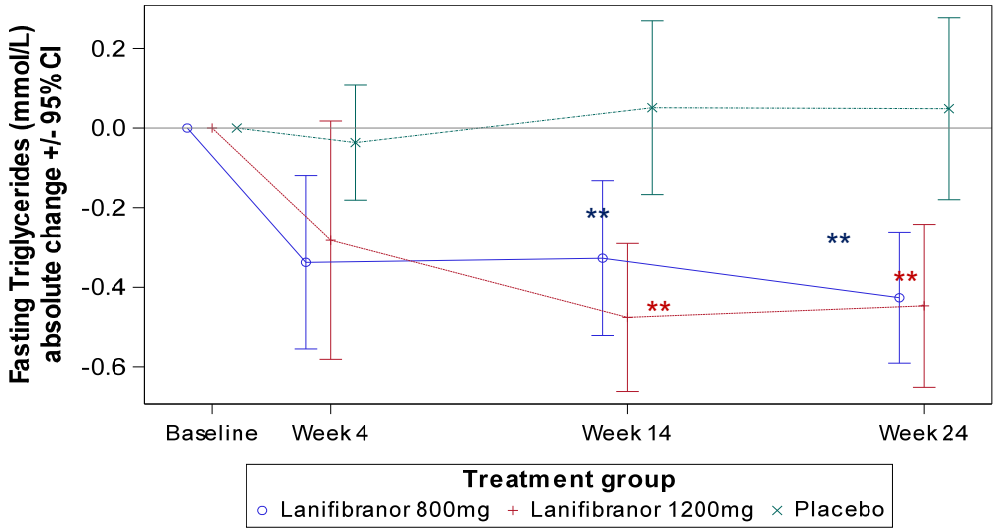
- Hypertension: reported as medical history ongoing at baseline

Effect of lanifibranor therapy on lipids

Absolute change from baseline in HDL-C



Absolute change from baseline in triglycerides



*** p<0.01 **p<0.001**

- **Statistically significant increase in HDL-C after 4 weeks**
- **Statistically significant decrease in triglycerides after 14 weeks**
- **No change in LDL-cholesterol**

Effect of lanifibranor therapy on other lipids and inflammatory markers

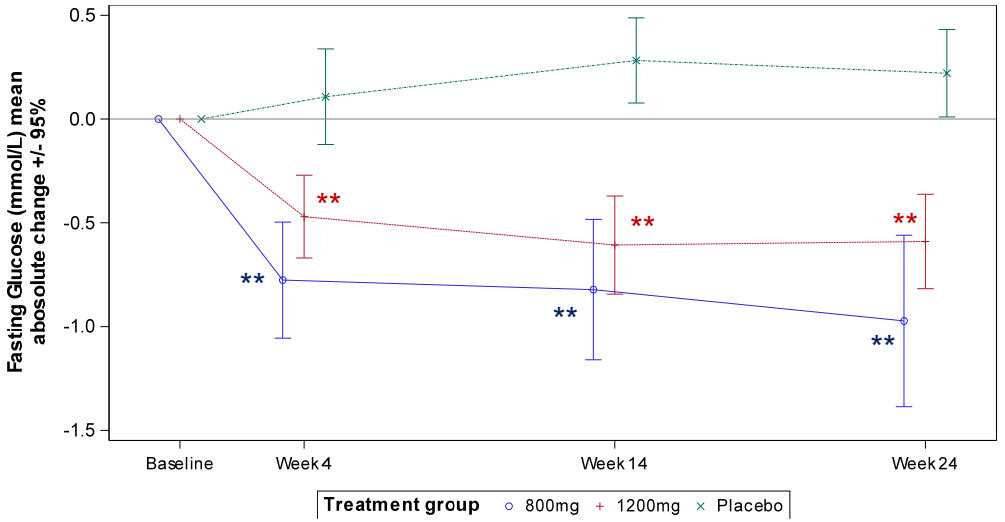
	Absolute Change from baseline at End of treatment (Week 24): Mean (SE) P value* vs placebo			
	Lanifibranor 800 mg	Lanifibranor 1200 mg	Lanifibranor pooled	Placebo
Lipids				
APO-A1 (mg/dl)	-0.29 (2.19) 0.919	-4.39 (2.16) 0.150	-2.37 (1.55) 0.365	0.03 (2.18)
APO-B (mg/dl)	-11.51 (2.08) <.001	-11.61 (2.05) <.001	-11.56 (1.46) <.001	-1.85 (2.00)
APO-B/APO-A1	-0.08 (0.02) 0.002	-0.07 (0.02) 0.013	-0.07 (0.01) 0.001	0.00 (0.02)
APO-C3 (ug/ml)	-8.08 (4.03) 0.001	-9.98 (3.94) <.001	-9.05 (2.83) <.001	10.31 (3.87)
Inflammatory marker				
Hs-CRP (mg/l)	-2.05 (0.47) 0.001	-1.37 (0.46) 0.026	-1.71 (0.33) 0.002	0.11 (0.47)

* From MMRM including absolute change from Baseline as endpoint, time, treatment, baseline diabetic status, interaction treatment * time and baseline value as fixed effects, time repeated effect within each subject.

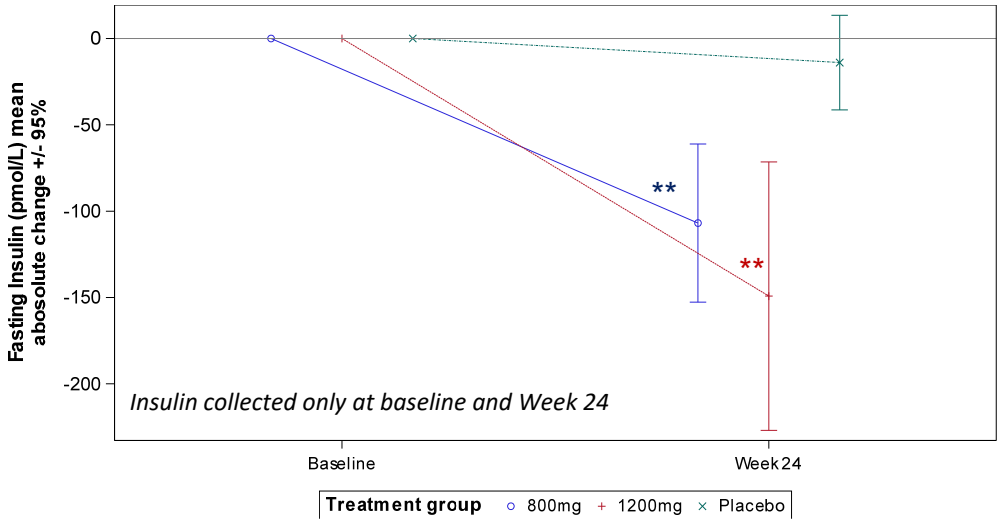
▶ **After 24 weeks, statistically significant decrease of all parameters, except for APO-A1**

Effect of lanifibranor therapy on glucose metabolism

Absolute change from baseline in Fasting Glucose (mmol/L)



Absolute change from baseline in Fasting Insulin (pmol/L)



*** p<0.01 **p<0.001**

- **Statistically significant increase in fasting glucose after 4 weeks**
- **Statistically significant decrease in fasting insulin at 24 weeks**

Glycaemic control in T2DM patients

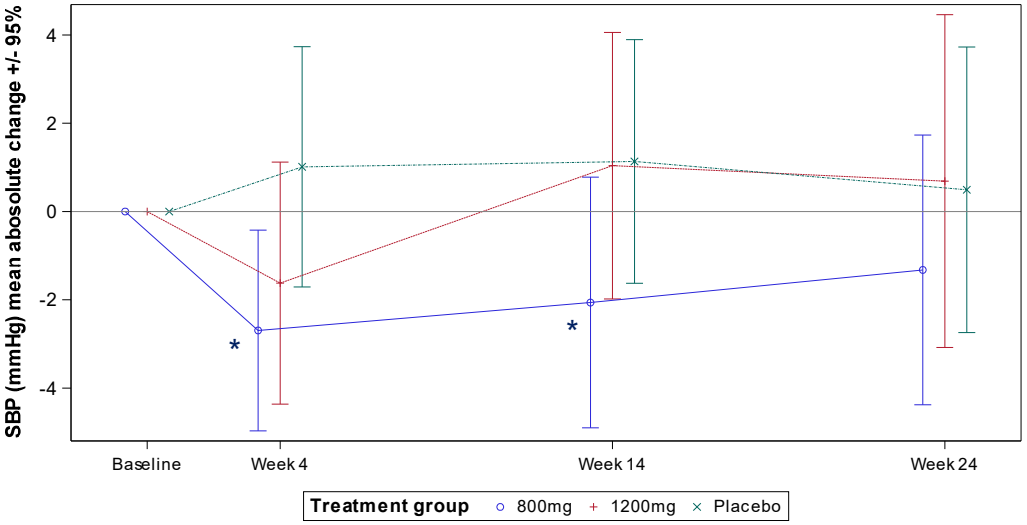
ACFB: Absolute change from baseline	Placebo N=35	Lanifibranor 800 mg N=33	p-value	Lanifibranor 1200 mg N=35	p-value
Fasting glucose (mmol/L)	0.28	-1.39	<0.001	-0.93	<0.001
Fasting insulin (pmol/L)	-40.2	-145.9	<0.001	-108.6	0.018
HbA1c (%)	0.08	-0.61	<0.001	-0.65	<0.001

▶ **Statistically significant decrease of HbA1c, fasting glucose, insulin after 24 weeks**

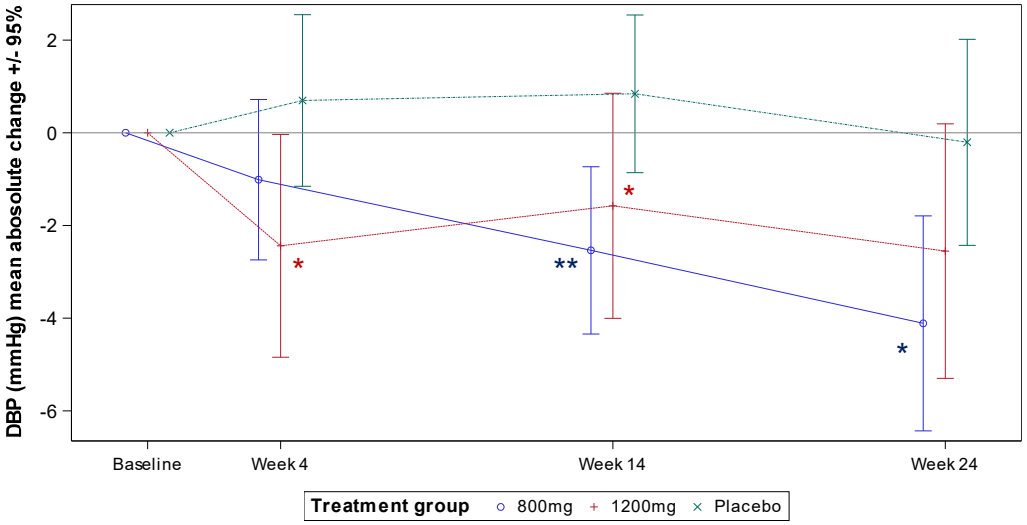
Francque *et al*. AASLD 2020

Blood pressure (BP)

Absolute change from baseline in systolic BP (mmHg)



Absolute change from baseline in diastolic BP (mmHg)



*** p<0.05 **p<0.01**

After 24 weeks:

- **No significant change in systolic BP**
- **Significant decrease in diastolic BP**

Conclusion

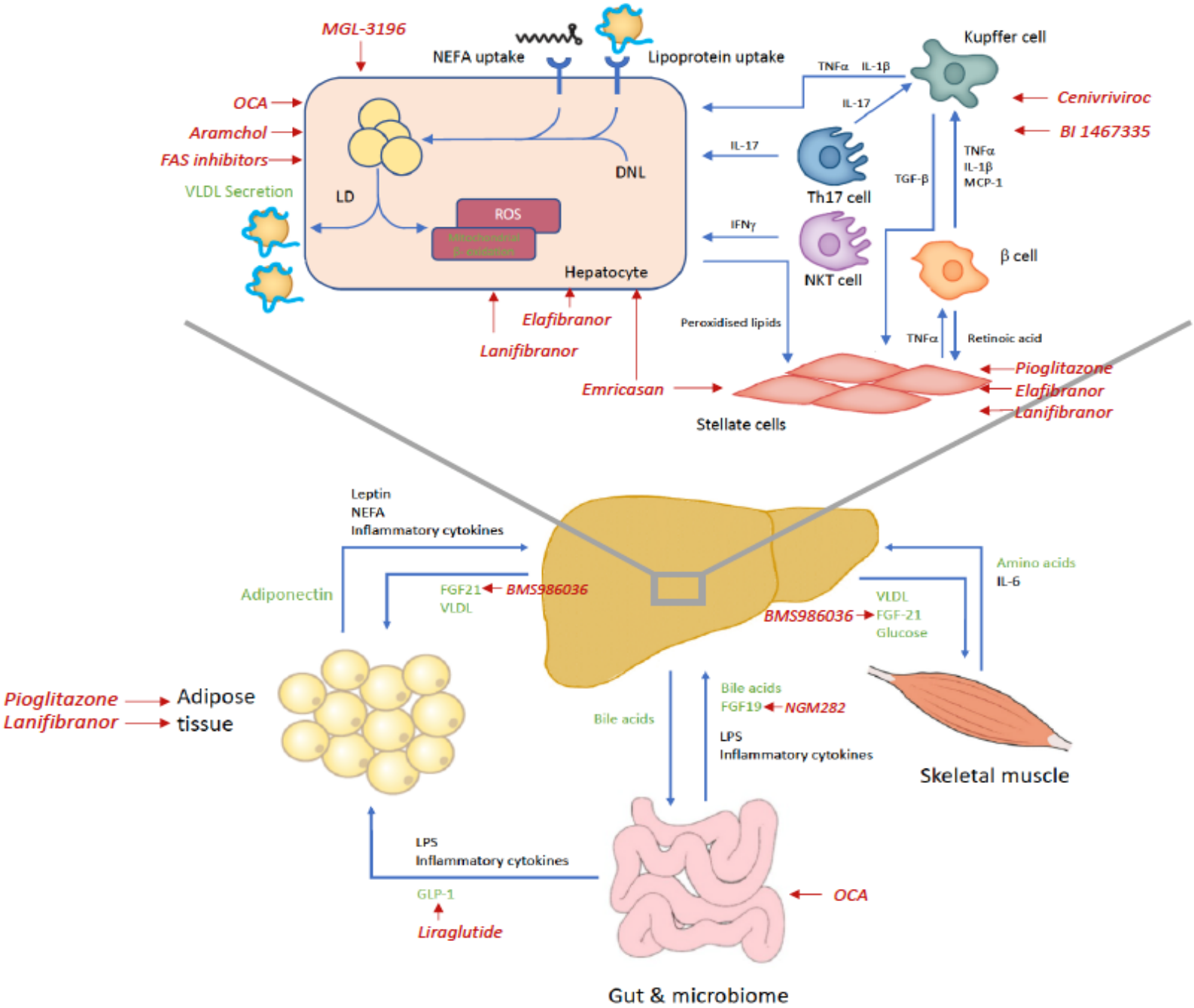
- In patients with NASH and F2/F3 fibrosis, lanifibranor showed significant efficacy on all primary and secondary histological end-points
- Efficacy was similar in patients with and without diabetes.
- Serum markers of liver injury, inflammation and fibrosis also improved with lanifibranor treatment at week 24 compared to placebo.
- Favourable safety profile.

- In patients treated for NASH during the phase 2b NATIVE trial, lanifibranor has demonstrated beneficial effects on a broad panel of cardiovascular disease biomarkers.
- Significant improvements were in addition seen in markers of lipid metabolism, insulin-resistance, inflammation and blood pressure.

- These findings support the phase 3 trial NATIV3 with lanifibranor for the treatment of patients with NASH and F2-F3 fibrosis.

Combination therapy of lanifibranor and firsocostat further improves steatohepatitis and fibrosis compared to monotherapy in a diet-induced murine model of NASH

Authors, G. WETTSTEIN [1], F. BRIAND [2], T. SULPICE [2], J-L. JUNIEN [1], P. BROQUA [1]
1 Inventiva, Daix, France
2 Physiogenex, Escalquens, France

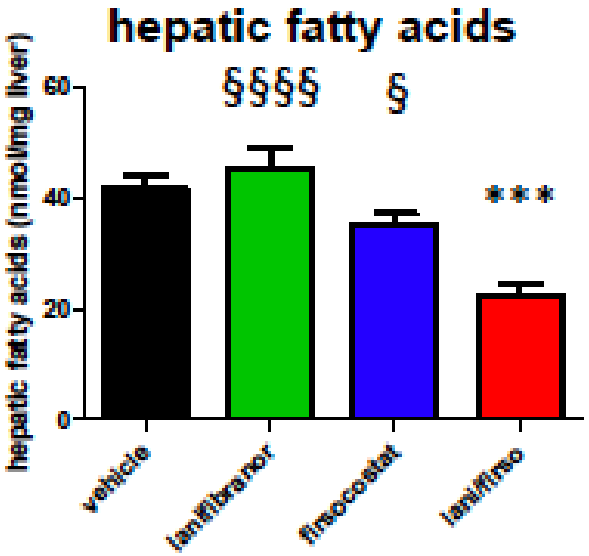


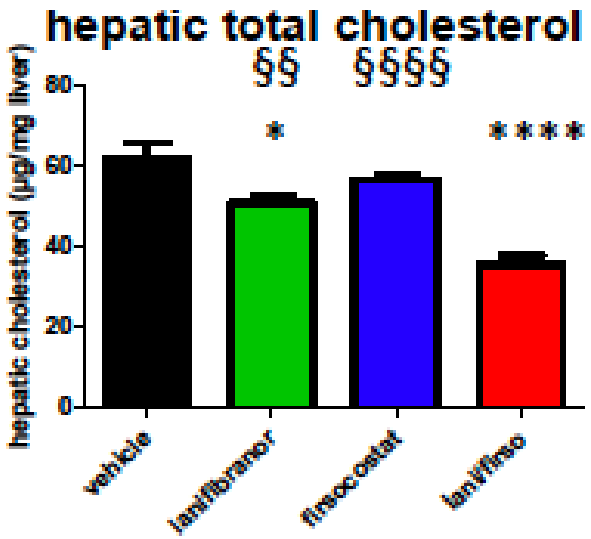
Haas, Francque & Staels. Ann Rev Physiol 2016
Francque & Vonghia. Advances in Therapy 2019

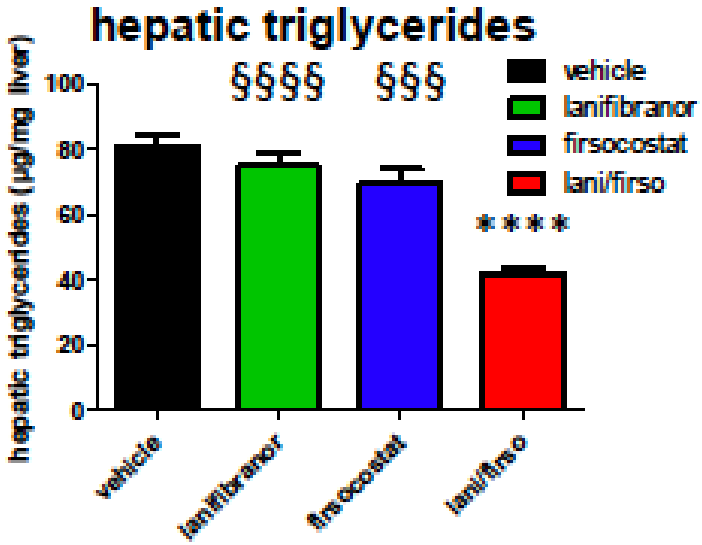
Study design

Group 1: vehicle 1 p.o. QD + vehicle 2 p.o. QD; n=10
Group 2: lanifibranor p.o. QD + vehicle 2 p.o. QD; n=10
Group 3: vehicle 1 p.o. QD + firsocostat p.o. QD; n=10
Group 4: lanifibranor p.o. QD + firsocostat 2 p.o. QD; n=10

Effect of lanifibranor and firsocostat alone, or in combination, on hepatic lipids content

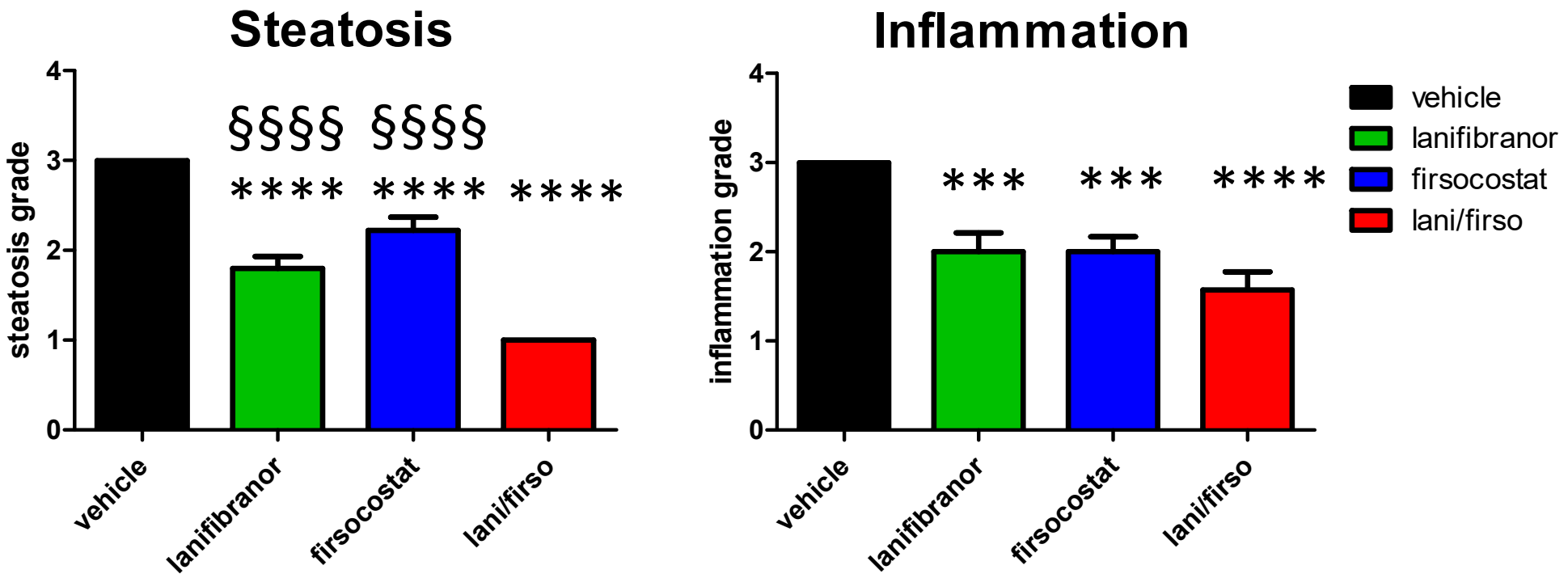






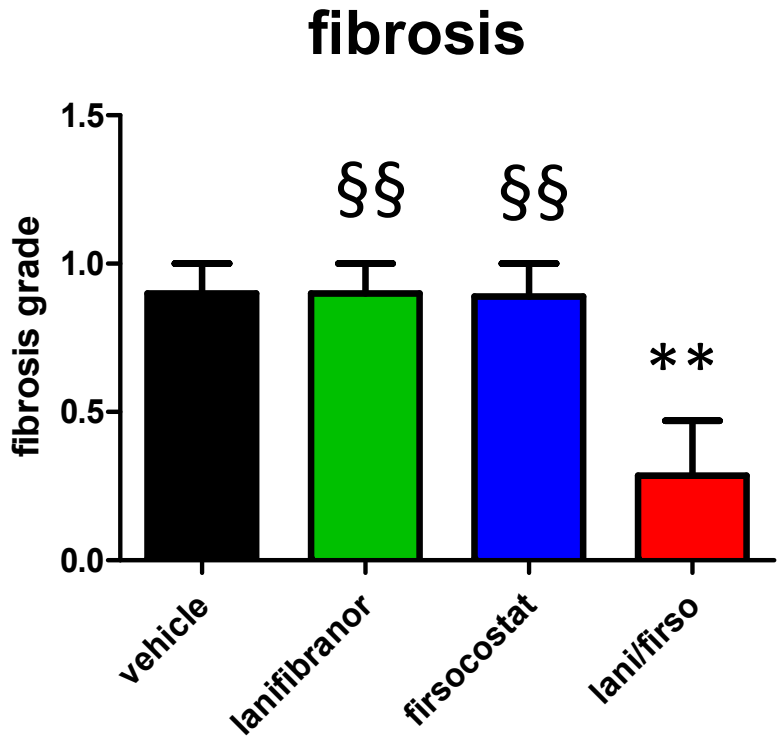
* Vs vehicle with * p<0.05; **p<0.01; ***p<0.001; ****p<0.0001
§ Vs combination lani/firso with § p<0.05; §§p<0.01; §§§p<0.001; §§§§p<0.0001

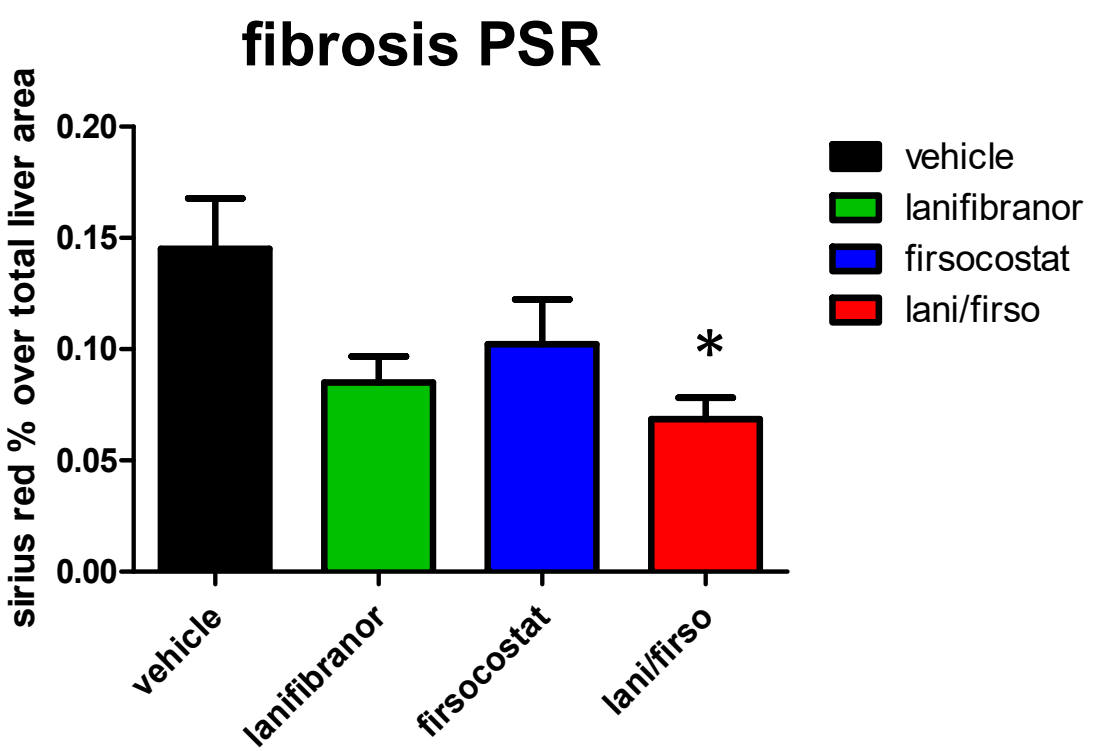
Effect of lanifibranor and firsocostat alone, or in combination, on steatosis and inflammation



* Vs vehicle with * p<0.05; **p<0.01; ***p<0.001; ****p<0.0001
§ Vs combination lani/firso with § p<0.05; §§p<0.01; §§§p<0.001; §§§§p<0.0001

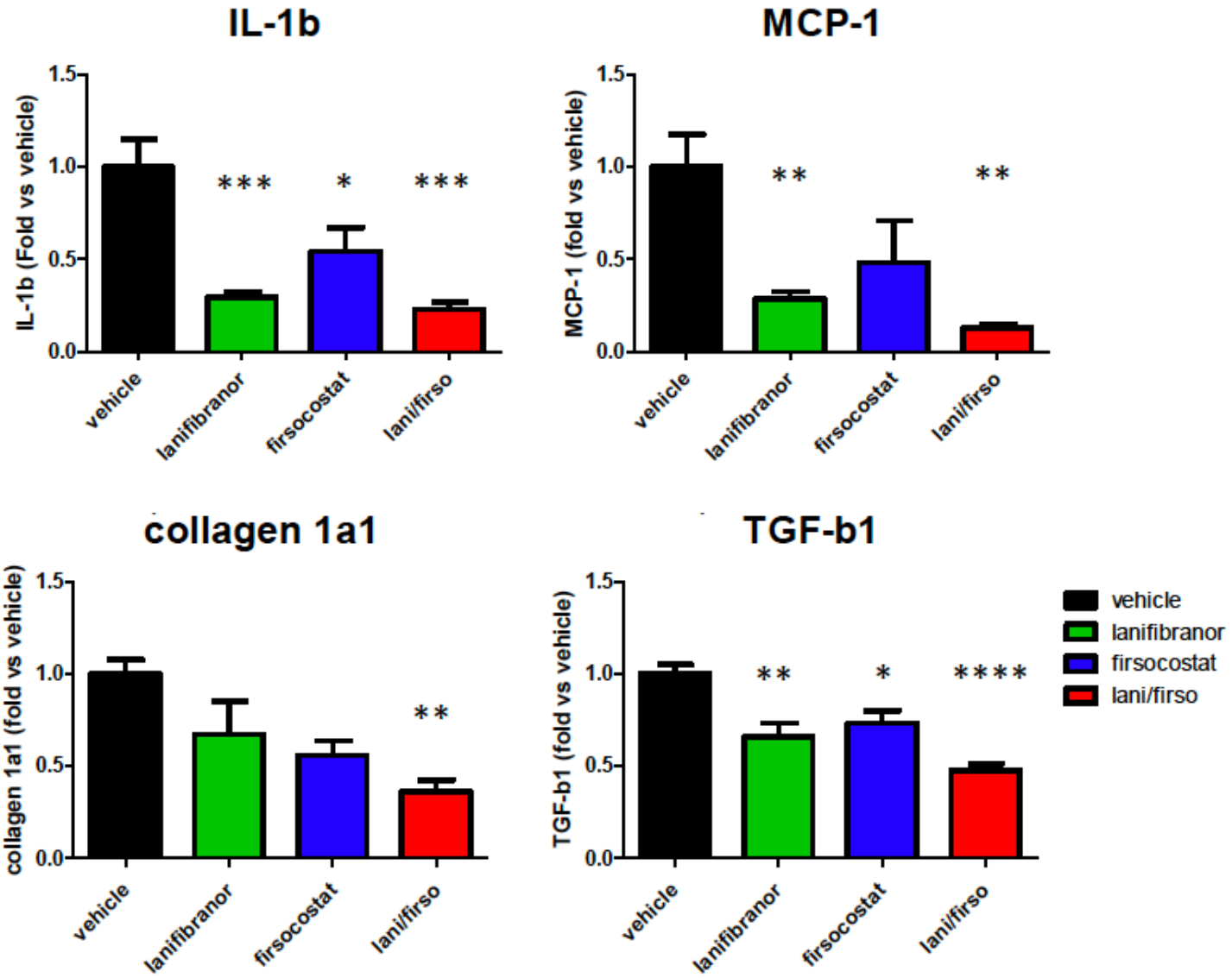
Effect of lanifibranor and firsocostat alone, or in combination, on fibrosis





* Vs vehicle with * p<0.05; **p<0.01; ***p<0.001; ****p<0.0001
§ Vs combination lani/firso with § p<0.05; §§p<0.01; §§§p<0.001; §§§§p<0.0001

Effect of lanifibranor and firsocostat alone, or in combination, on markers of inflammation and fibrosis



* Vs vehicle with * p<0.05; **p<0.01; ***p<0.001; ****p<0.0001
§ Vs combination lani/firso with § p<0.05; §§p<0.01; §§§p<0.001; §§§§p<0.0001

Conclusion

- Lanifibranor and firsocostat combination reached greater efficacy than monotherapy on
  - hepatic lipid content
  - steatosis
  - fibrosis
  - total scoring.
- These data emphasize the complementary effect of these two compounds on lipid metabolism leading to further improvement of NASH and fibrosis.
- These data would support clinical investigation of a combination of lanifibranor and firsocostat in patients with NASH.

Lanifibranor: overview of phase III NASH trial

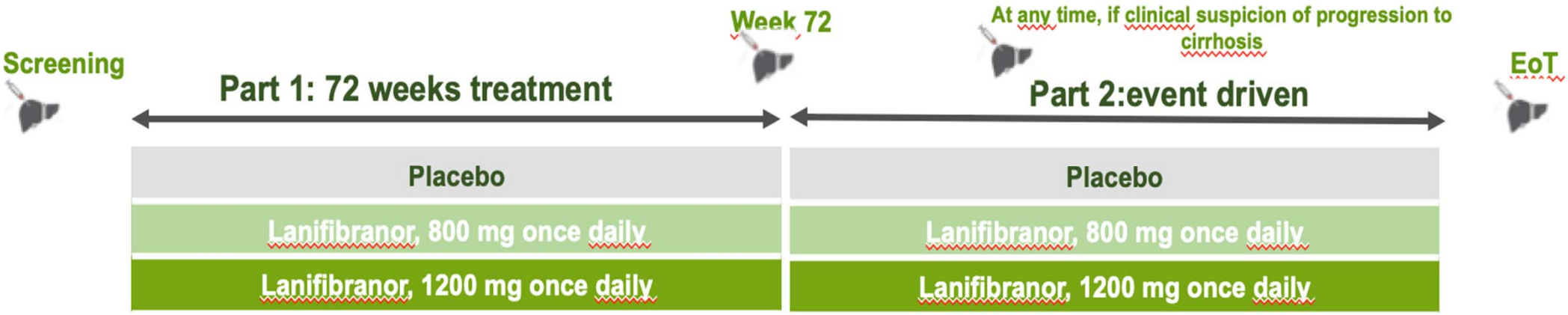
Michael Cooreman, MD, CMO

NATiV3 Trial - Overview

- **Design**
  - Part 1: accelerated (FDA) and conditional (EMA) approval
  - Part 2: full approval
  - Central reading of liver histology
- **Clinical Operations**
  - Status
  - Time frame

NATiV3 Study Design

A randomised, double-blind, placebo-controlled, multicentre, Phase 3 study evaluating long-term efficacy and safety of lanifibranor in adult patients with non-cirrhotic non-alcoholic steatohepatitis (NASH) and fibrosis 2 (F2)/fibrosis 3 (F3) stage of liver fibrosis



NATiV3 study design

Randomization and stratification

- Randomisation 1:1:1
- Stratification on T2DM
- Stratification on F2/F3 patients

Statistical powering: 90% considered for sample size

Main inclusion criteria

- Adults ≥18 years of age DIAGNOSED with NASH using SAF scoring (steatosis ≥1, activity ≥3 and fibrosis score of F2-F3)

Central biopsy review done by two pathologists plus a third one involved in case of discrepancies on biopsies required for Part 1 analysis

NATiV3 – Part 1

- **Primary efficacy endpoint**
  - Evaluated at Week 72 in ca 900 patients
  - Composite endpoint of patients having both ***NASH resolution*** and ***improvement of fibrosis*** of at least one stage
- **Key secondary endpoints**
  - NASH resolution and no worsening of fibrosis
  - Improvement of fibrosis and no worsening of NASH
- **Additional secondary endpoints (selection)**
  - Liver tests
  - Biomarkers of glucose metabolism
    - Incl. in patients with T2D and HbA1c ≥ 6.5%: proportion of patients with HbA1c < 6.5% at Week 12 and Week 24
  - Biomarkers of lipid metabolism, adiponectin
  - Quality of Life (NASH-CLDQ, SF-36, WPAI)
- **Safety**
- **Exploratory endpoints**
  - Cardiovascular events: major adverse cardiovascular events (MACE)
  - Biomarkers of disease biology

Eligible for U.S. ACCELERATED APPROVAL and EU CONDITIONAL APPROVAL

NATiV3 – Part 2

- **Primary efficacy endpoint based on 'time to first clinical event'**
- **Clinical events**
  - Progression to cirrhosis (histological diagnosis)
  - All cause mortality
  - Hepatic decompensation
    - Hepatic encephalopathy
    - Upper gastrointestinal variceal bleeding
    - Ascites (requiring treatment)
  - Worsening of liver function
    - MELD score ≥ 15
  - Liver transplantation

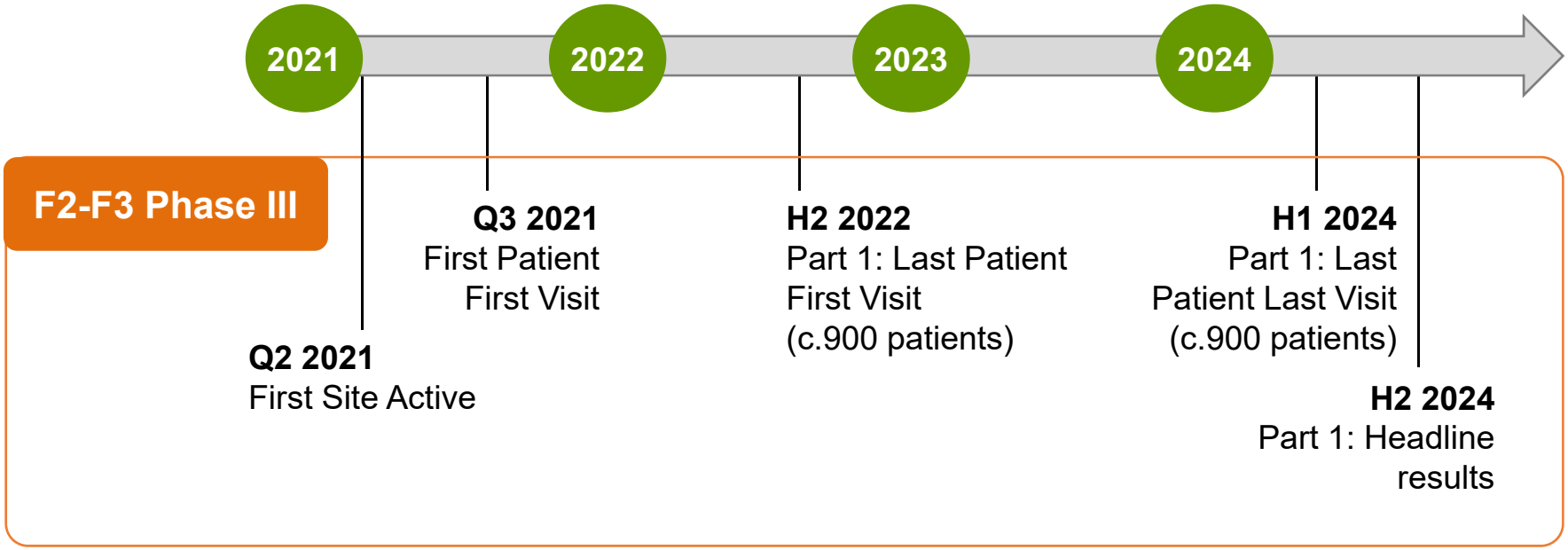
Full approval based on outcome improvement

Central Reading of liver biopsies - process

	Pathologist A	Pathologist B	Pathologist C
Screening	**Glass slide**	**Digital slide**	-
	Glass slides sent at random to one of the 3 pathologists, review on glass and digital slides done in parallel by a second one Patient randomized if both agree on eligibility		-
Part I week 72 (for the first approx. 900 randomised, histologically eligible patients)	**Glass slide**	**Glass slide**	-
	Glass slides, sent by batches of 80 slides (20 patients, screening & week 72) reviewed by 2 pathologists at random		
	Digital slide	**Digital slide**	**Digital slide**
	Digital slides reviewed by 3 pathologists at random if first 2 pathologists are not aligned on steatosis, inflammation or fibrosis		
If **suspicion of cirrhosis and End of Treatment**	**Glass slide**		
	Glass slides sent at random to one of the pathologists who scores stage F4 yes/no		

NATiV3 – Timelines to submission for accelerated approval

PHASE III **MILESTONES**



NATiV3 – Status today

- The study is conducted with our CRO partner PRA Health Sciences
- Protocol finalized
- Target number of sites: approx. 300
- Site feasibility started
- Qualified sites (as of June 14): >150
  - Enrollment potential for Part 1: >1000 patients
  - Approx. 60% expected from the U.S. and Canada
  - Approx. 35% expected from Europe
- First site activated and first patient in (FPI, screened) expected Q3 2021

Q & A