inventiva

KOL Webcast Event From AASLD 2021

November 19, 2021

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Today’s speakers

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

Pierre Broqua, Ph.D., Chief
Scientific Officer and cofounder

Michael Cooreman, MD,
Chief Medical Officer

Prof. Nezam Afdhal
Charlotte and Irving Rabb Distinguished Professor of Medicine, Harvard Medical School
Chief of Gastroenterology, Hepatology and Nutrition, Beth Israel Deaconess Medical Center

Dr. Kenneth Cusi
Chief of the Division of Endocrinology, Diabetes & Metabolism in the Department of Medicine, University of Florida

Dr. Michelle Lai
Associate Professor of Medicine, Harvard Medical School
Director of Transplant Hepatology Fellowship
Director of BIDMC NAFLD Center

Prof. Jörn Schattenberg
Professor of Medicine
Director Metabolic Liver Research Program - Department of Medicine, University Medical Center Mainz

Agenda

- Corporate update
- Update on Inventiva's NATIV3 Phase III clinical trial in NASH
- Update on the NASH field
- Overview of the five lanifibranor scientific abstracts presented during the AASLD Liver Meeting
- Update on Phase II clinical trial evaluating lanifibranor in patients with T2D and NAFLD
- Presentation of Phase IIa combination study with lanifibranor and SGLT2 inhibitor empagliflozin in patients with NASH and T2D

Lanifibranor: overview of the phase III NASH trial NATiV3

Michael Cooreman, MD, CMO

Lanifibranor overall development in NASH

Phase I → Phase IIa → Phase IIb (NATIVE) → F2-F3 Phase III → Registration

IIb DESIGN

- *24 weeks*
- *800 mg and 1200 mg once-daily lanifibranor*

IIb EFFICACY

- *First candidate to achieve statistically significant results on the two Phase III FDA and EMA primary endpoints*

IIb SAFETY

- *Favourable profile*

III OVERVIEW

- *72 week Part 1 + Part 2 extension period*
- *Inclusion criteria and patient profile in line with NATIVE Phase IIb*
- *Primary composite endpoint combining NASH resolution and fibrosis improvement*

Lani Phase II in NAFLD patients with T2D

Lani + SGLT2i Phase II in NASH patients with T2D

Phase II/III in NASH patients with compensated cirrhosis

Completed clinical trials

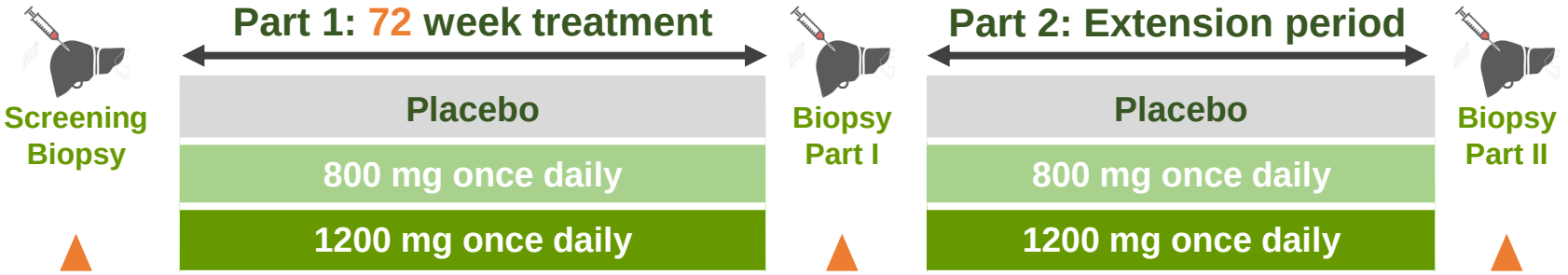
Ongoing clinical trials

Potential clinical trials

NATiV3 study design

A randomized, double-blind, placebo-controlled, multicenter, Phase III study evaluating long-term efficacy and safety of lanifibranor in adult patients with NASH with liver fibrosis

Main inclusion criteria **ALIGNED TO** Phase IIb NATIVE trial



PRINCIPAL INVESTIGATORS

- Prof. Francque and Prof. A. Sanyal

INCLUSION CRITERIA

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

RANDOMISATION AND STRATIFICATION

- Randomisation 1:1:1
- Stratification on T2D and F2/F3 patients
- At least 30% of U.S. patients

STATISTICAL POWERING: 90% considered for sample size

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

PRIMARY ENDPOINT *week 72, c.900 patients*

- Composite endpoint of patients having both NASH resolution and fibrosis improvement of at least one stage

KEY SECONDARY ENDPOINTS

- NASH resolution and no worsening of fibrosis
- Fibrosis improvement and no NASH worsening

SECONDARY ENDPOINTS

- Glycaemic parameters at week 12 and 24 in patients with T2D not well controlled: proportion of patients with HbA1c back to normal
- Composite endpoint of diabetic patients having both NASH resolution and fibrosis improvement
- Improvement in renal function
- Reduction of cardiovascular risk
- Quality of life

- Endpoints based on time to first clinical event on c.2,000 patients
  - histological progression to cirrhosis
  - all cause mortality
  - hepatic decompensation events
  - MELD score ≥15
  - liver transplant

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

Potential for **FULL APPROVAL** in **U.S.** and **EU**

Central reading of liver biopsies

- **Central pathologists**
  - Zack Goodman, Inova, VA
  - Carolin Lackner, Medical University of Graz, Austria
  - Dina Tiniakos, Newcastle University, UK

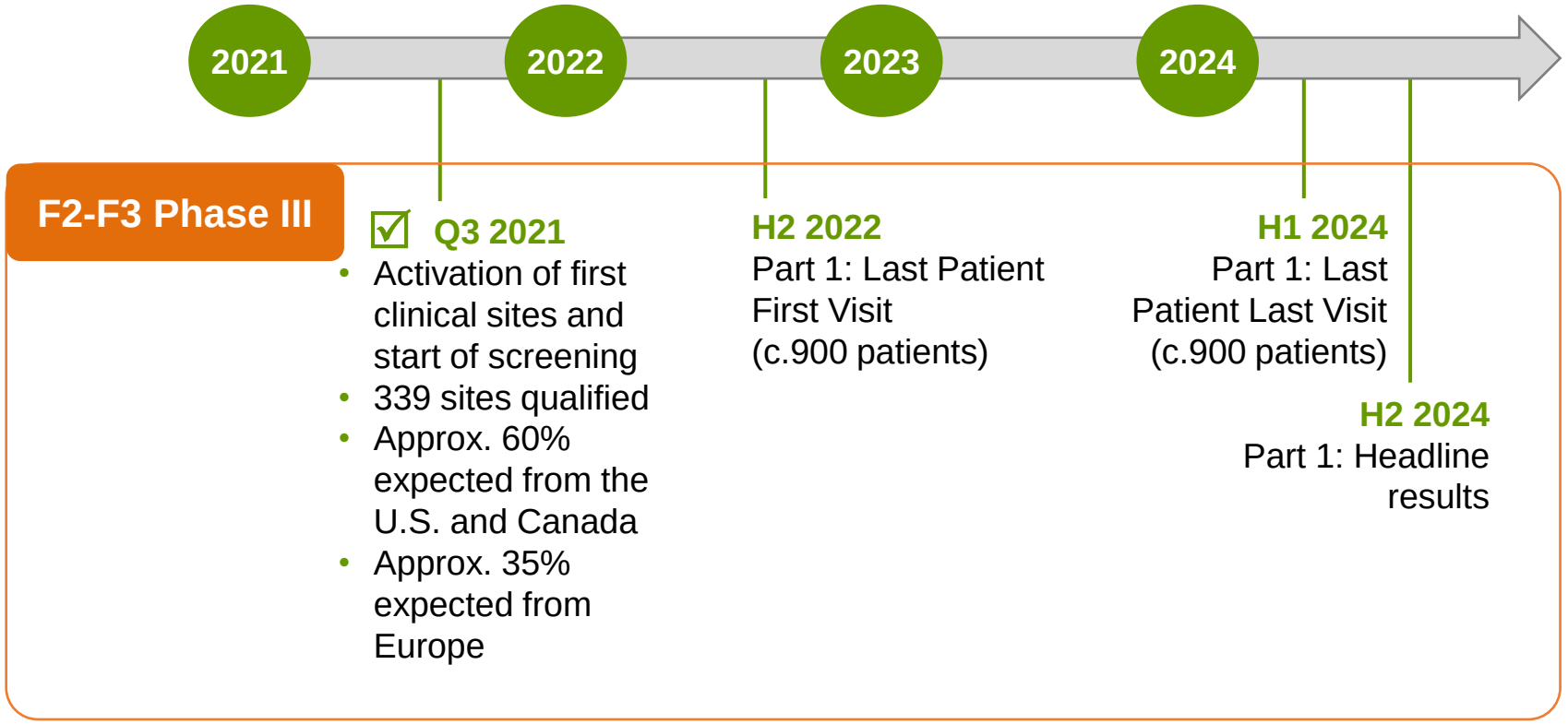
- **Reading on digitalized biopsy images at central lab (PorPath, Dallas, Tx)**

- **Eligibity process:**
  - Slides reviewed in parallel by 2 pathologists at random
  - Patient randomised if both agree on eligibility criteria (S≥1, A≥3, F2-3)

- **Part 1 analysis: for the first 882 randomised, histologically eligible patients**
  - Histologically eligible = eligibility confirmed when screening biopsy read again when the Week 72 biopsy is available
  - Slides reviewed in parallel by 2 pathologists at random
  - Alignement with third pathologist whenever needed for S or I or B or F

- **Part 2 analysis: for all biopsies performed beyond Week 72 (suspicion of cirrhosis or end-of-study)**
  - Slides reviewed in parallel by 2 pathologists at random
  - Alignement with third pathologist whenever needed for F

Key milestones of the Phase III study in NASH (Part 1)



Update on the NASH field

Prof. Nezam Afdhal

Charlotte and Irving Rabb Distinguished Professor of Medicine,
Harvard Medical School
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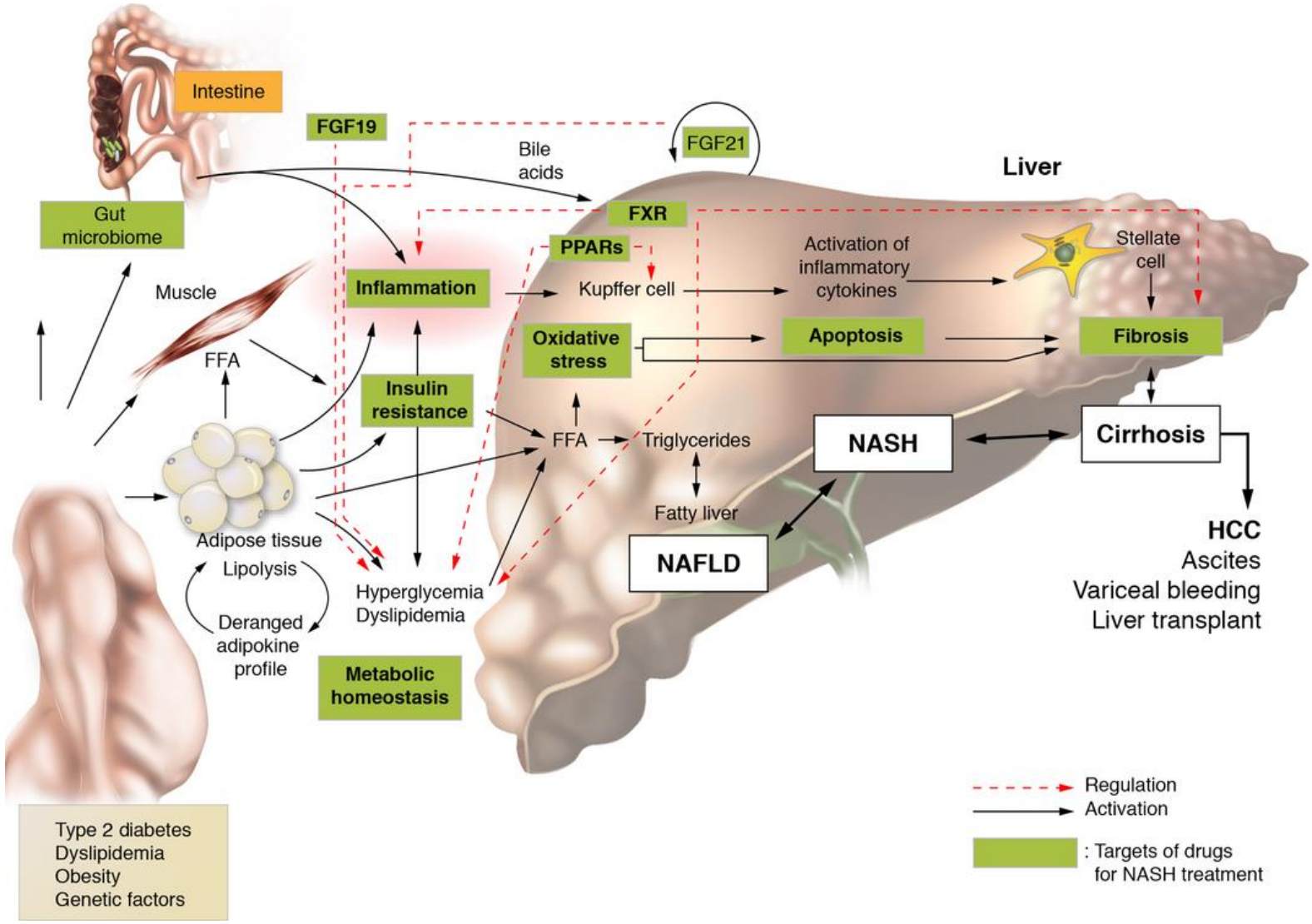
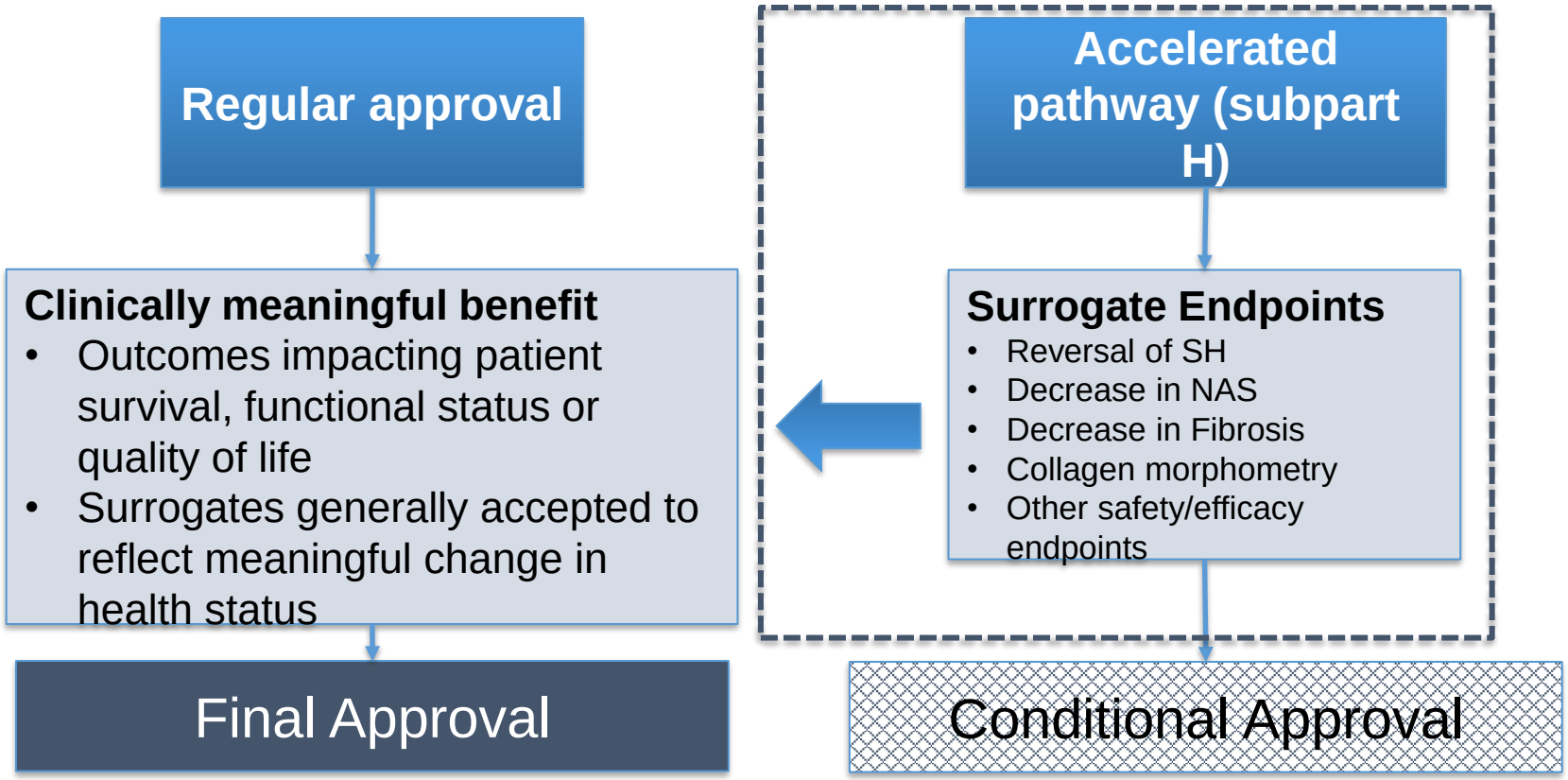
Pathophysiology & Therapeutic Targets

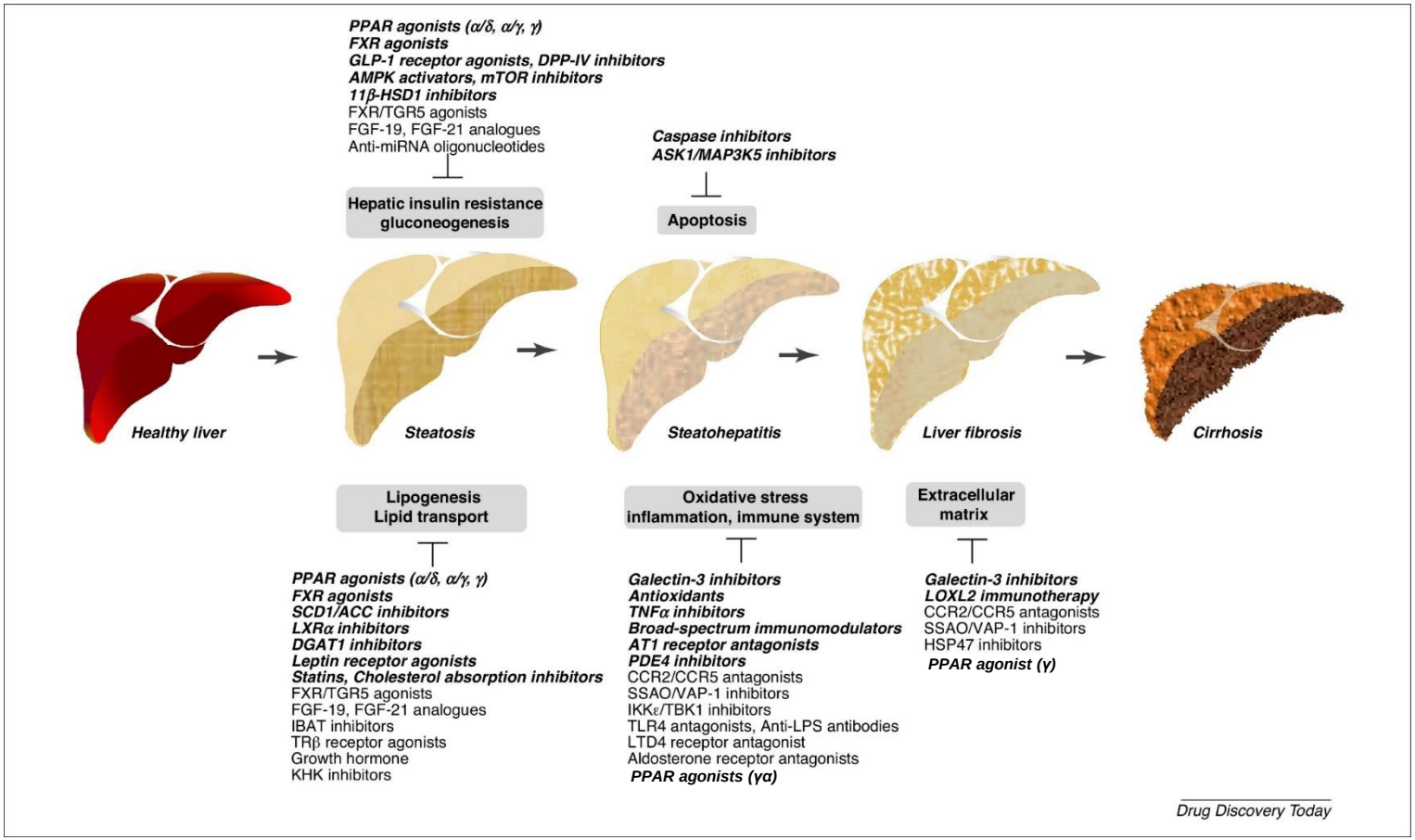


Modified from Perrazo & Dufour, Liver International 2017

Pathways for drug development

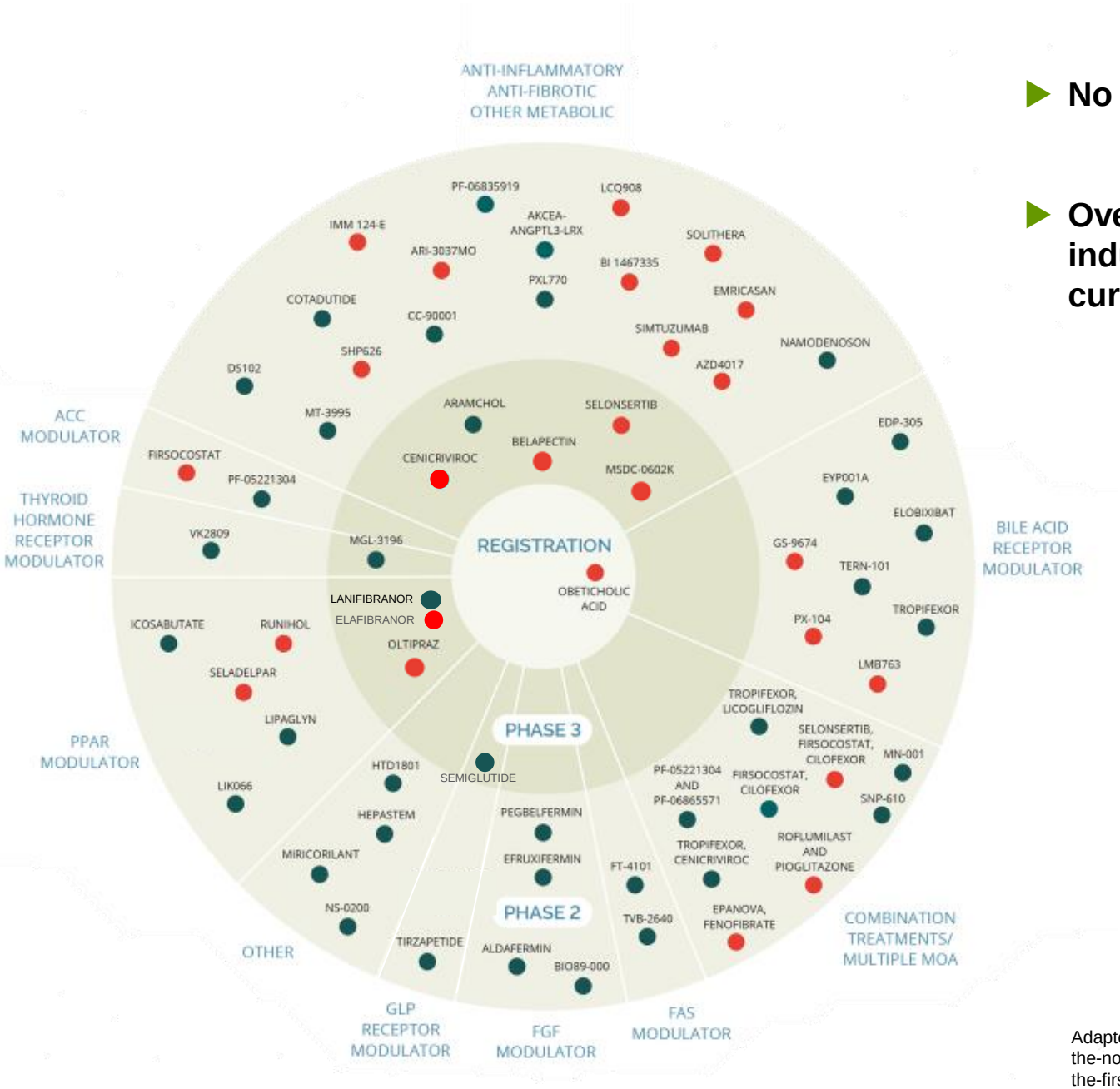


Targets and disease stages



Henrik H. Hansen, and al. Mouse models of nonalcoholic steatohepatitis in preclinical drug development, Drug Discovery Today,Volume 22, Issue 11.

Competitive Landscape

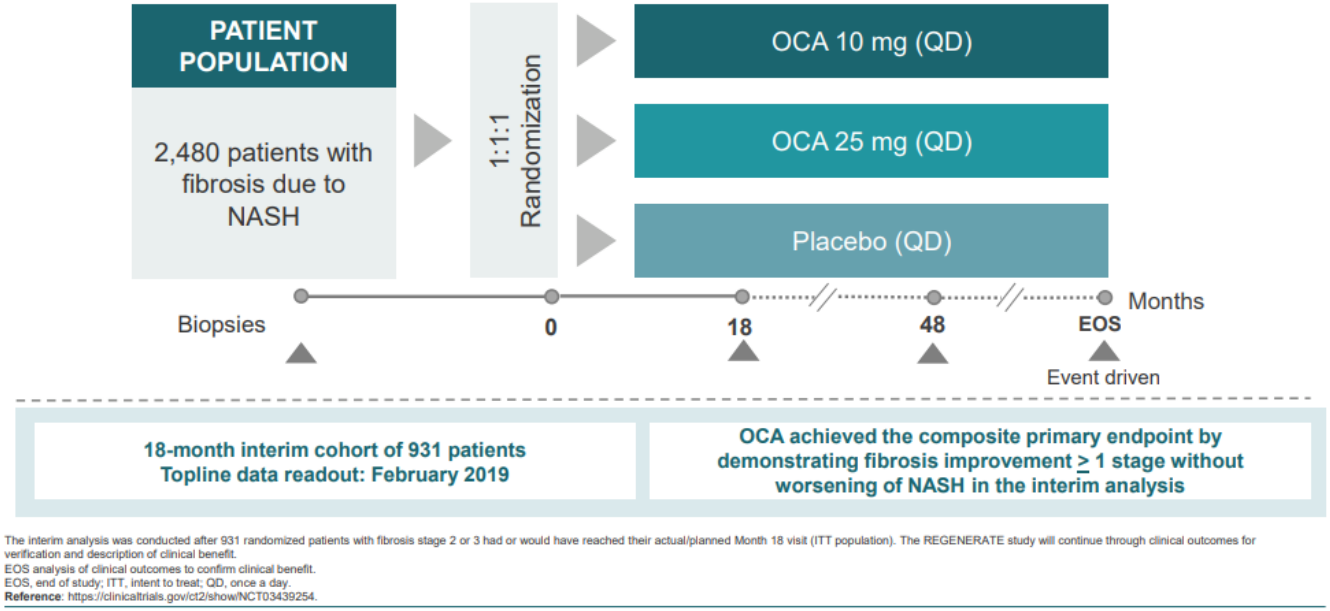


- No FDA- or EMA-approved drug
- Over 90 Phase2 and Phase3 industry-sponsored studies currently active

- Ended
- Ongoing

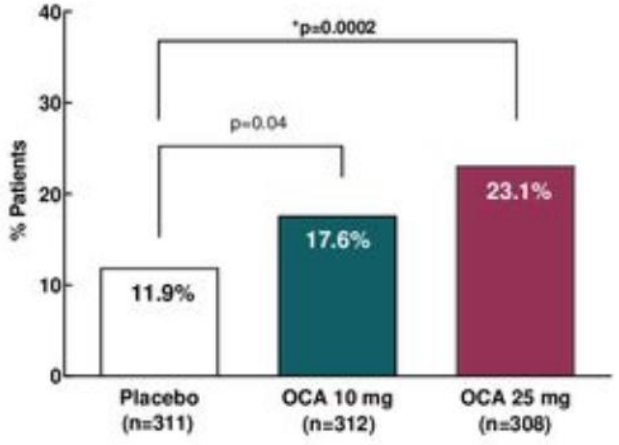
Adapted from https://www.pharmaceuticalonline.com/doc/analysis-of-the-non-alcoholic-steatohepatitis-nash-drug-pipeline-market-sizing-up-the-first-wave-0001

FXR agonist: REGENERATE PhaseIII clinical trial

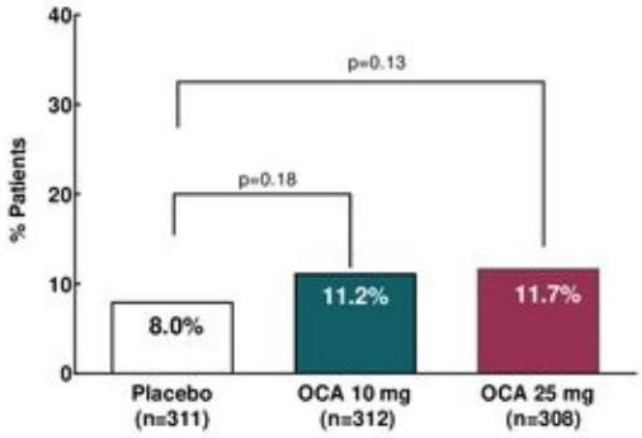


The interim analysis was conducted after 931 randomized patients with fibrosis stage 2 or 3 had or would have reached their actual/planned Month 18 visit (ITT population). The REGENERATE study will continue through clinical outcomes for verification and description of clinical benefit.
EOS analysis of clinical outcomes to confirm clinical benefit.
EOS, end of study; ITT, intent to treat; QD, once a day.
Reference: https://clinicaltrials.gov/ct2/show/NCT03439254.

Primary endpoint (ITT): fibrosis improvement by ≥1 stage with no worsening of NASH



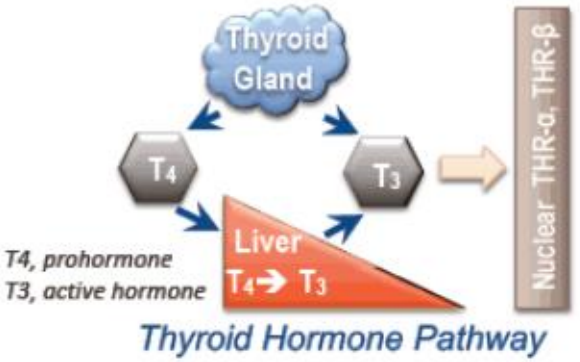
Primary endpoint (ITT): NASH resolution with no worsening of fibrosis



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

*Statistically significant in accordance with the statistical analysis plan agreed with the FDA. All other p values are nominal.
Younossi Z, et al. ILC 2019; GS-06

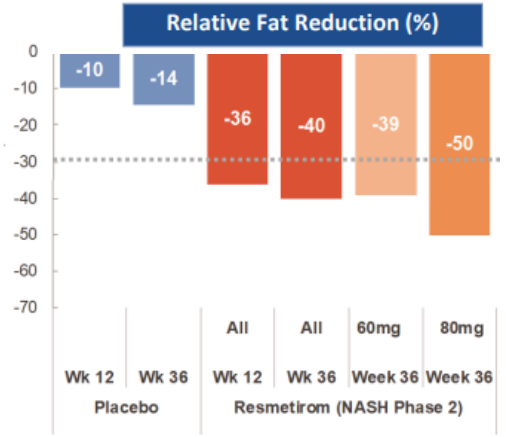
THR β agonist - RESMETIROM

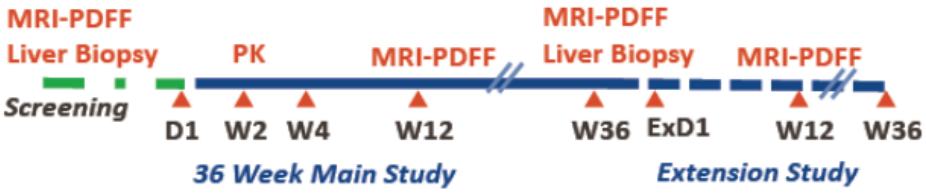


In humans, thyroid hormone receptor-β (THR-β) agonism:

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

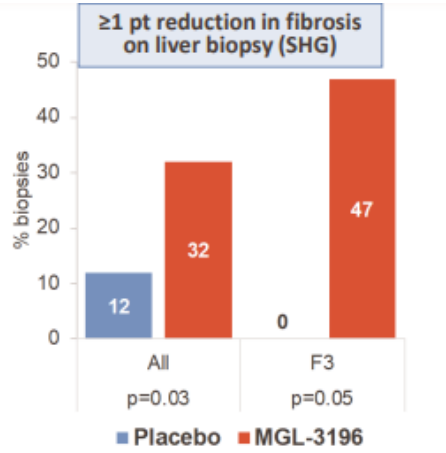
No thyrotoxicosis (THR-α effect)





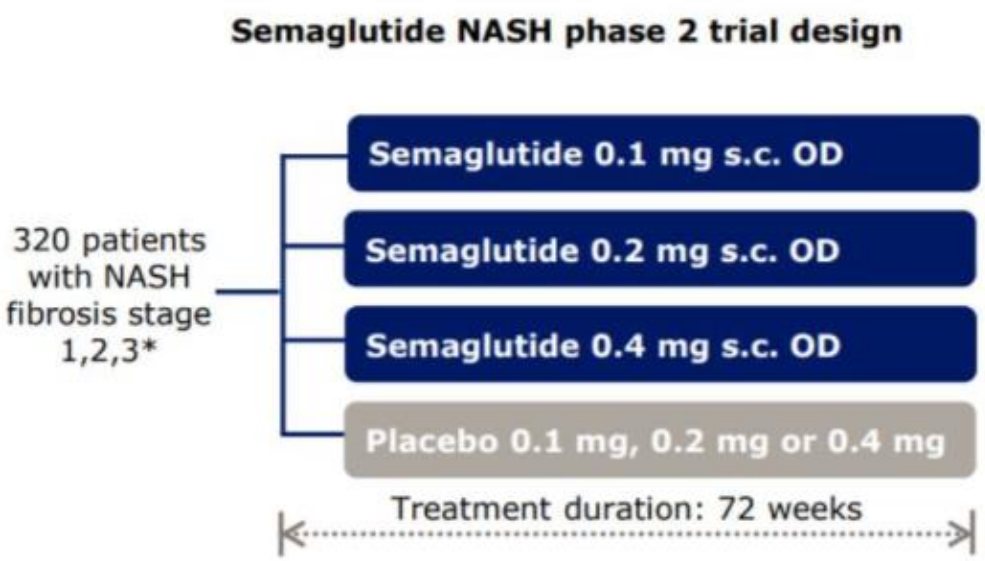
Comparator/Arms

- 2:1 MGL-3196 to placebo
- 125 patients enrolled in USA, 18 sites
- MGL-3196 or placebo, oral, once daily; dose 80 mg (+/-20 mg dose adjustment possible at Week 4)

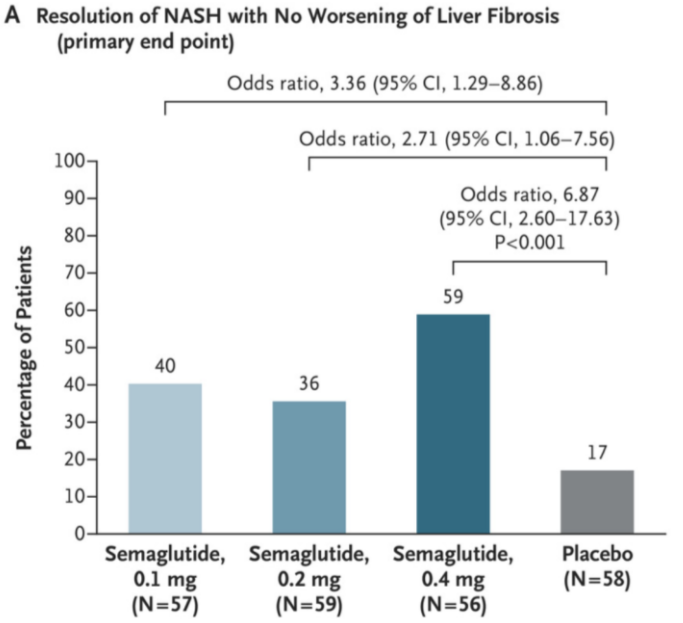


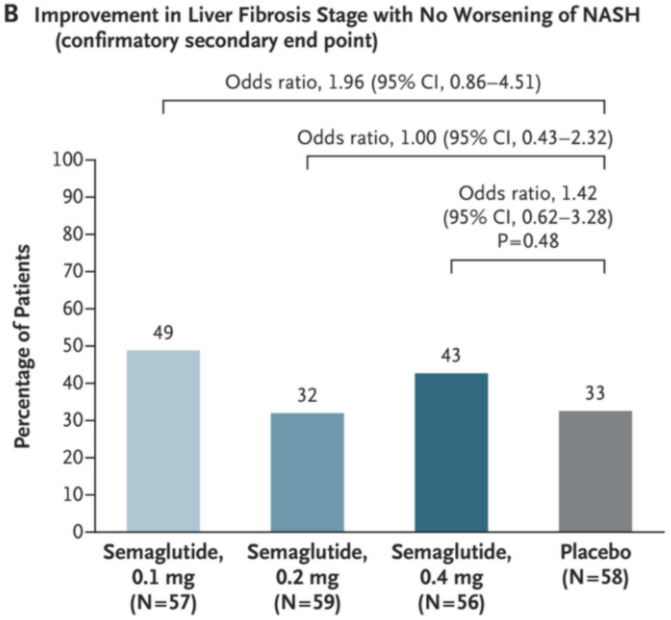
https://www.madrigalpharma.com/wp-content/uploads/2021/10/HCWainwright-NASH-Conf-Madrigal-12Oct2021.pdf

GLP1 agonist - Semaglutide



*Full list of inclusion criteria: Age 18-
10%; No other chronic liver disease other than NASH
NASH: Non-alcoholic steatohepatitis; s.c.: subcutaneous; OD: once-daily





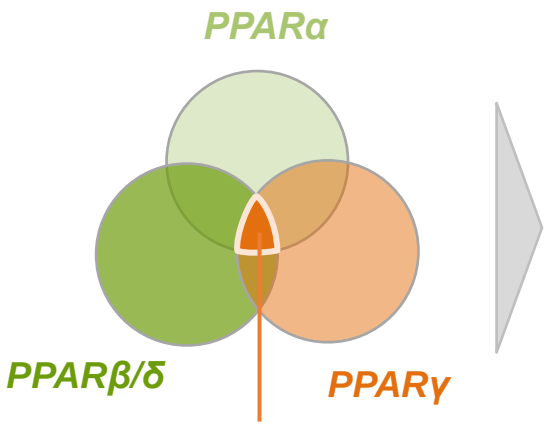
Novo Nordisk Q1 2020 presentation

Newsome PN et al. N Engl J Med 2021;384:1113-1124

Lanifibranor's activation of the three PPAR isoforms addresses the key features of NASH

LANIFIBRANOR

Pan-PPAR activity expected to ensure improved efficacy



LANIFIBRANOR

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

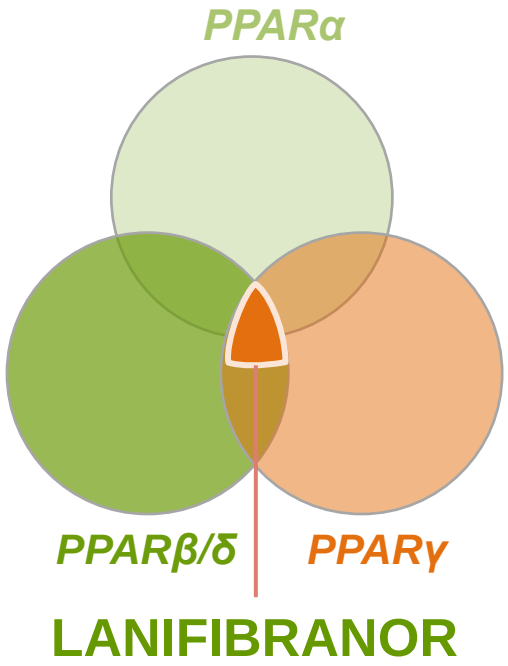
VASCULAR

PPARα PPARγ

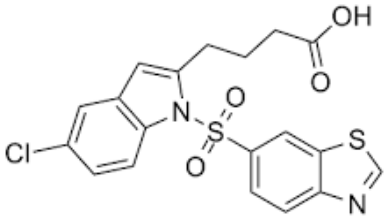
- ↓ Portal pressure
- ↓ LSEC capillarization
- ↓ Intrahepatic vascular resistance

Lanifibranor: a pan-PPAR agonist in Phase3 clinical trial 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

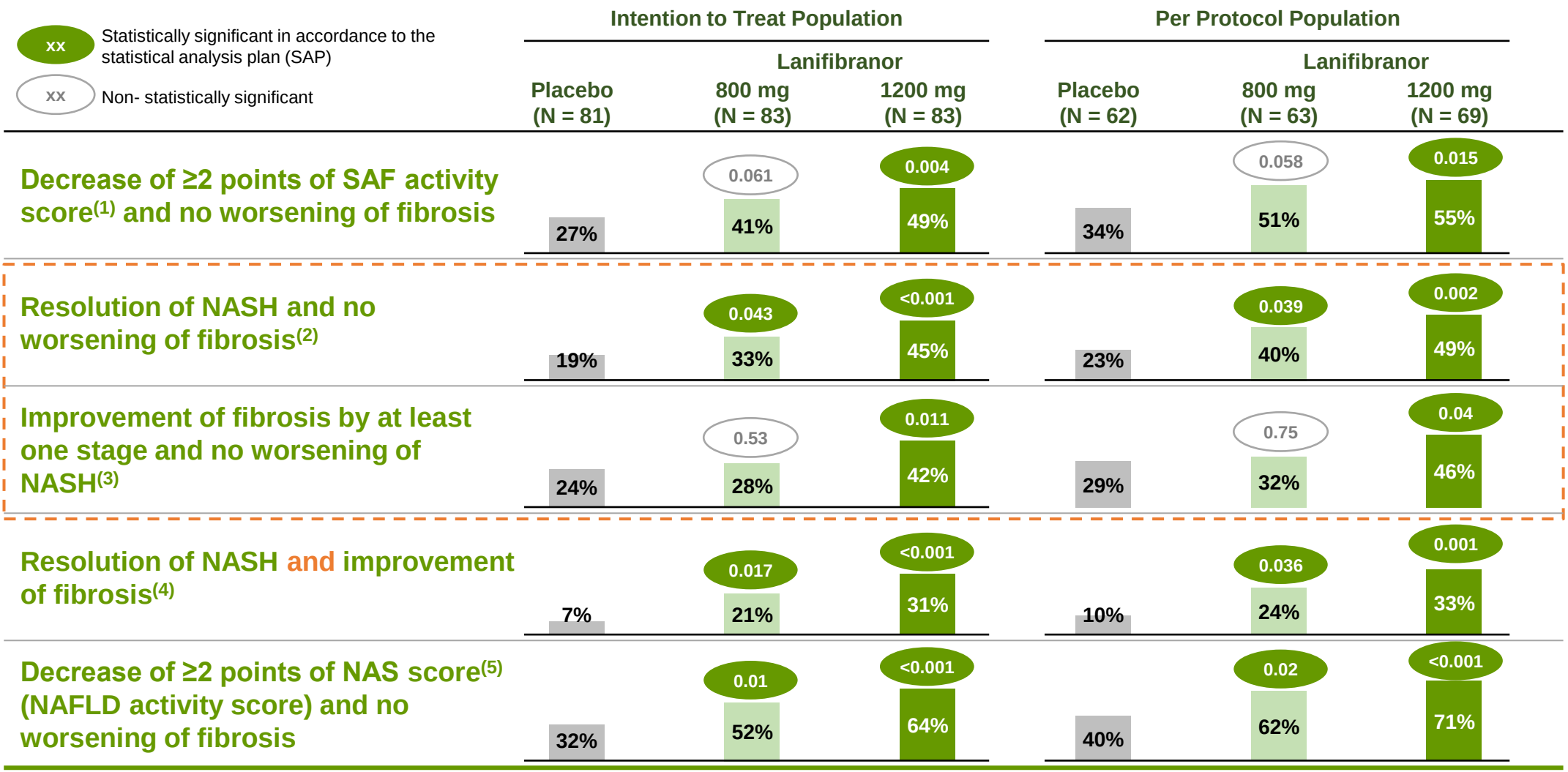


*Francque *et al*. AASLD 2020

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**

Lanifibranor is the first drug candidate to achieve statistically significant results on the two Phase III FDA and EMA primary endpoints



(1) Response is defined as a decrease from baseline to week 24 of at least 2 points of the SAF Activity score (SAF-A) with no worsening of the NAS Fibrosis score (NAS-F). No worsening means that score remains stable or decreases ; (2) Resolution of NASH with no worsening of fibrosis at week 24: NAS-I = 0 or 1 (NAS-Inflammation), NAS-B = 0 (NAS-Ballooning) and no worsening of NAS-F from baseline; (3) Improvement of liver fibrosis ≥ 1 stage and no worsening of NASH at week 24; (4) Resolution of NASH and improvement of fibrosis at week 24: NAS-I = 0 or 1, NAS-B = 0 and an improvement of NAS-F ≥ 1 stage; (5) NAS score is a commonly accepted, semi-quantitative evaluation of biopsy results that assesses the severity of steatosis, inflammation and ballooning in the liver.

Comparison of efficacy

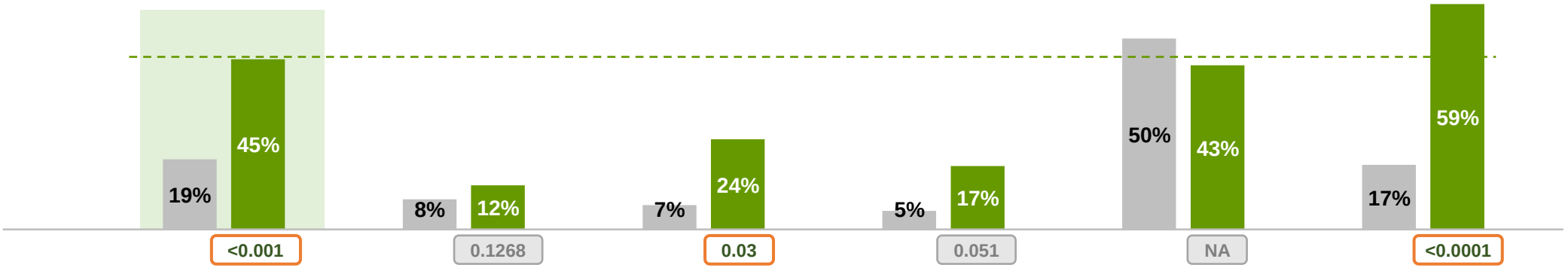
EFFICACY — Active | Placebo | xx Statistically significant | xx Non-statistically significant

Only drug achieving statistical significance on both endpoints

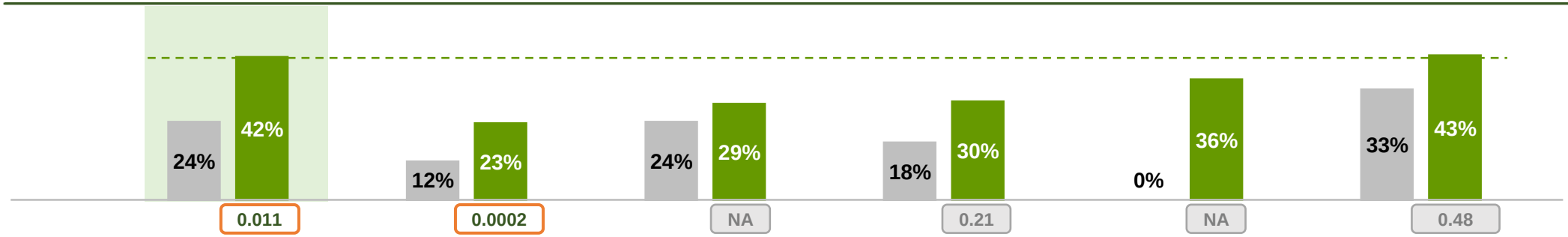
Injectables

	Lanifibranor (inventiva)	Ocaliva (Intercept)	Resmetirom (Madrigal Pharmaceuticals)	Aramchol (Galmed Pharmaceuticals)	Efruxifermin* (akero)	Semaglutide (novo nordisk®)
Time point of data collection	**Phase IIb 6 months**	Phase III 18 months	Phase IIb 9 months	Phase IIb 12 months	Phase IIa 4 months	Phase IIb 18 months
# of patients	**247**	931	125	247	80	320

NASH resolution with no worsening of fibrosis



Fibrosis improvement with no worsening of NASH



No head-to-head clinical trials have been conducted; results obtained from different trials, with different designs, endpoints and patient populations. Results may not be comparable.
**** Efruxifermin 70mg results only. Placebo N = 2. No information available regarding statistical significance of trial results; histology results reported only for patients achieving a ≥30% reduction of hepatic fat at week 12***

Source: lanifibranor native results 1200 mg/day, ITT population; ocaliva 25mg : REGENERATE Phase II trial: company press release February 19, 2019; Newsome et al., 2020: Ratziu et al, Gastorenterology 2016; 150:1147-1159 ; resmetirom 80mg ± 20mg: Harrison et al, Lancet 2019 ; S0140-6736(19) 32517-6; Aramchol 600mg :AASLD 2018 presentation

Review of lanifibranor AASLD 2021 abstracts

Prof. Nezam Afdhal

Charlotte and Irving Rabb Distinguished Professor of Medicine,
Harvard Medical School
Chief of Gastroenterology, Hepatology and Nutrition,
Beth Israel Deaconess Medical Center

Lanifibranor treatment improves hepatic steatosis in patients with NASH, evaluated by histological grading and Controlled Attenuation Parameter

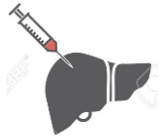
Cooreman MP, Abdelmalek MF, Baudin M, Huot-Marchand P, Dzen L, Fournier C, Junien JL, Broqua P, Francque S

NATIVE Phase 2b trial: design

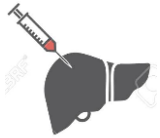
Screening
- **Liver biopsy**

24-week treatment + 4-week follow-up
Double blind, randomized, placebo-controlled

End of treatment
- **Liver biopsy**



- **Placebo**
- **lanifibranor, 800 mg once daily**
- **lanifibranor, 1200 mg once daily**



- Randomisation 1/1/1
- Stratification on type 2 diabetes mellitus (T2D)

- **Main inclusion criteria**: patients with biopsy-proven NASH confirmed by central reader having Steatosis-Activity-Fibrosis (SAF) scores of 1-3 for steatosis, 3-4 for activity, and <4 for fibrosis
- **Results published on**:

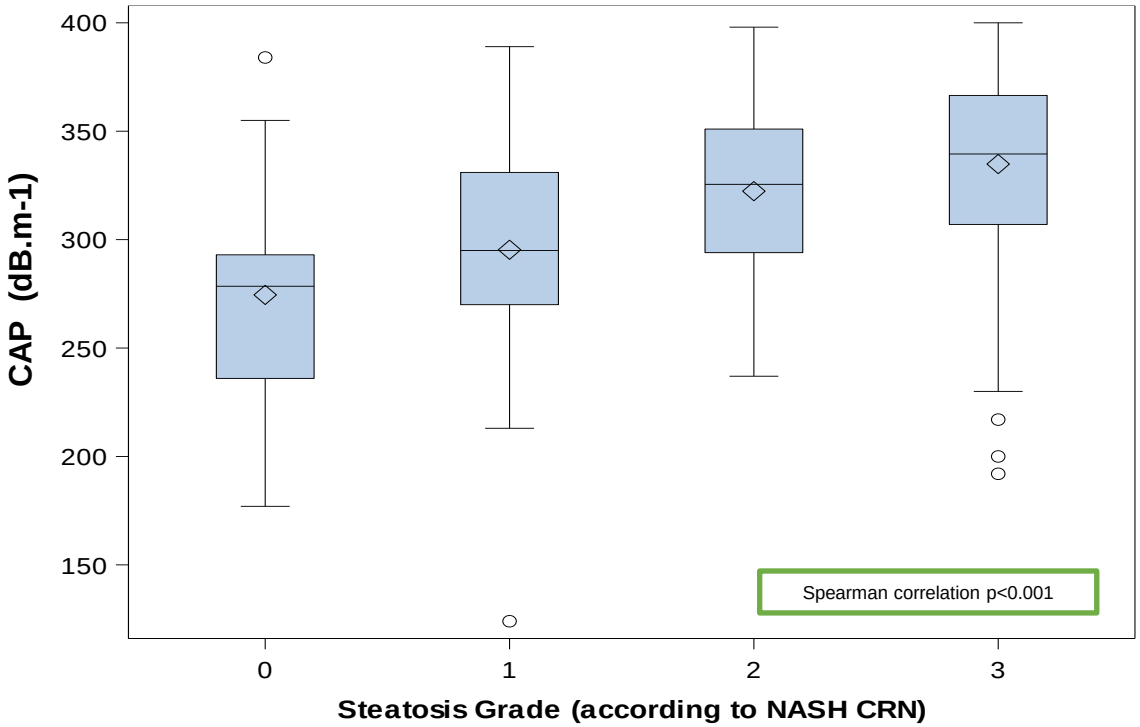
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2021 VOL. 385 NO. 17

A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH

- Primary endpoint met with a statistically significant reduction of SAF score
- Key secondary endpoints also met, including
  - **NASH resolution with no worsening of fibrosis**
  - **Improvement of liver fibrosis with no worsening of NASH**
  - **Composite endpoint of NASH resolution and improvement of liver fibrosis**

Positive correlation between CAP and histological grading of steatosis in the overall population



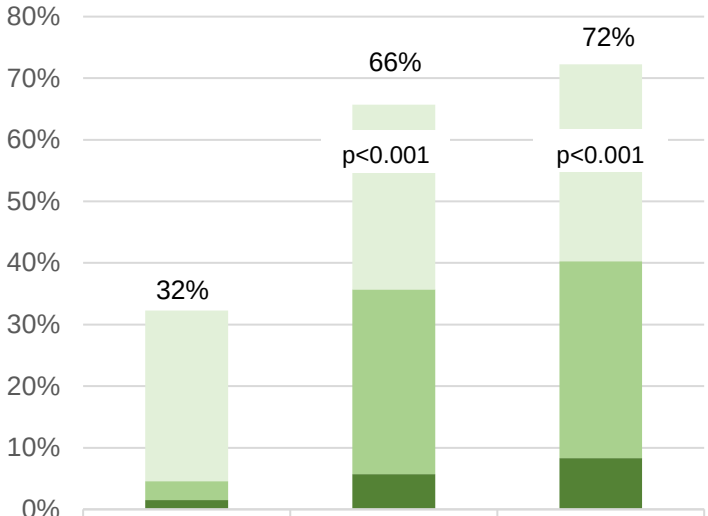
	Histological steatosis grade			
	S0	**S1**	**S2**	**S3**
N	18	81	86	168
Mean ± SD	274.5 ± 50.4	295.3 ± 48.7	322.3 ± 43.4	334.8 ± 43.0
Median	279	295	326	340
Min ; Max	177; 384	124; 389	237; 398	192; 400

- **Controlled Attenuation Parameter (CAP™), assessed with Fibroscan (Echosens), is a quantitative surrogate of liver steatosis. The cutoff value of 302dB/m was defined as a diagnostic marker of Steatosis ≥S1 (presence) versus S0 (absence)(1)**
- **Significant correlation between CAP and histological steatosis grade was observed at screening and EOT (pooled data all treatments)**

(1) Reference: Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease.

Lanifibranor decreases histological steatosis grading and CAP

Improvement of histological steatosis grade

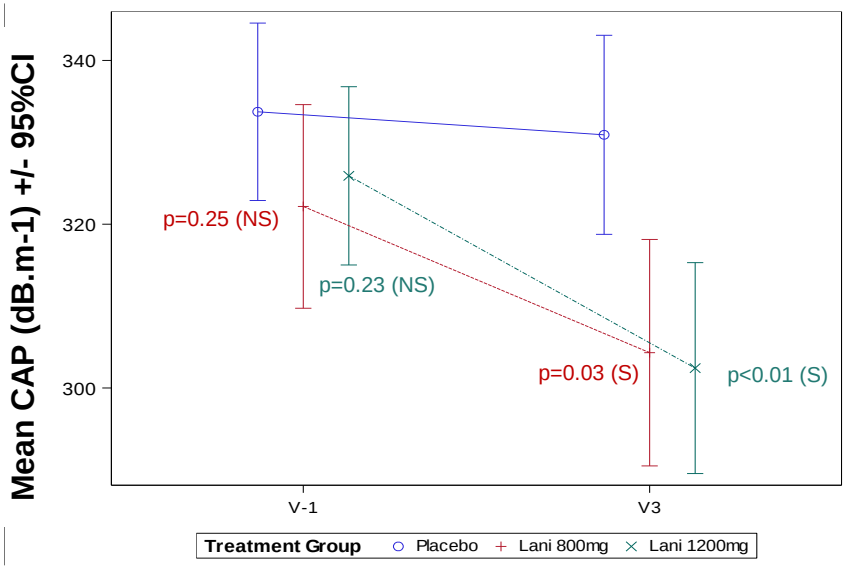


	Placebo N=65	Lanifibranor 800 mg N=70	Lanifibranor 1200 mg N=72
Improvement of 1 point	28%	30%	32%
Improvement of 2 points	3%	30%	32%
Improvement of 3 points	2%	6%	8%

P-values are calculated using a Cochran–Mantel–Haenszel test stratified by diabetic status at baseline.

- **Significant improvements of histological steatosis grade after 24 weeks under lanifibranor compared to placebo**
- **More than 35% of at least 2 stages improvers in both lanifibranor arms, versus 5% in placebo.**

Mean CAP over time



- **Significant decreases of CAP under lanifibranor treatments**

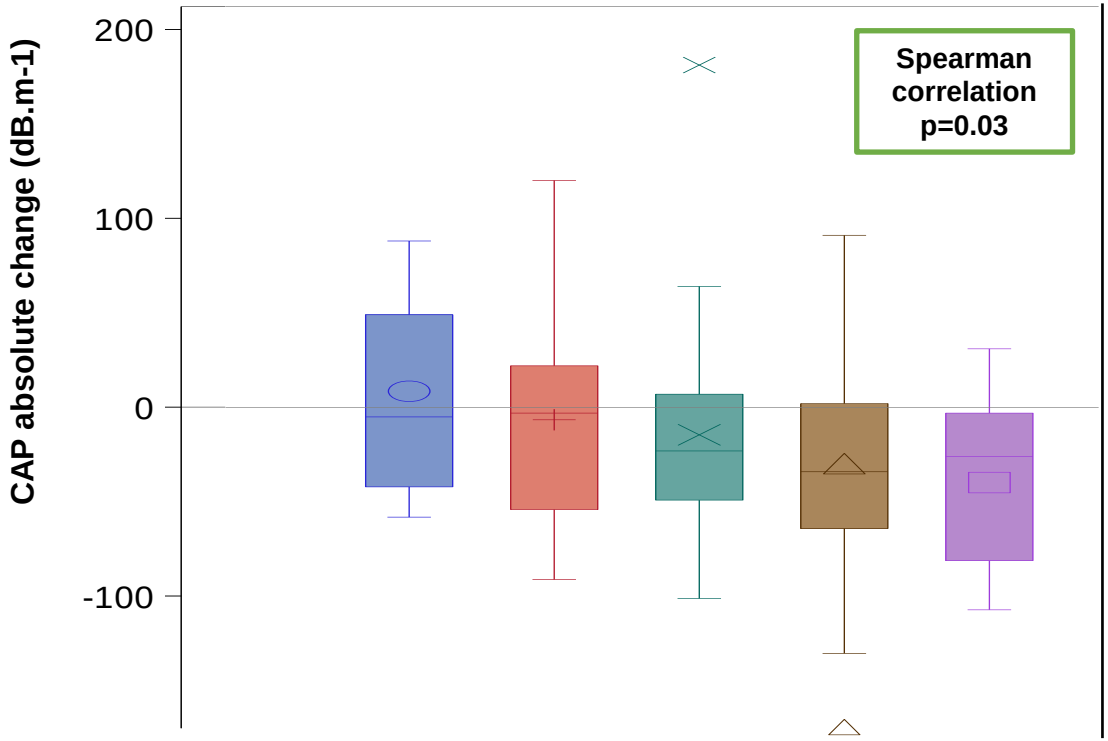
	Placebo	Lani 800mg	Lani 1200mg
$CAP_{Screening}$ ≤ 302[a] dB/m	26.4%	29.6%	32.6%
Pvalue[b] vs. Placebo	-	**0.711 (NS)**	**0.499 (NS)**
CAP_{EOT} ≤ 302[a] dB/m	13 (24.5%)	25 (46.3%)	23 (50.0%)
Pvalue[b] vs. Placebo	-	**0.019 (S)**	**0.009 (S)**

[a]Youden optimal cutoff of the CAP as a diagnosis marker of Steatosis ≥S1 versus S0. Reference: Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology. 2019 May;156(6):1717-1730. doi: 10.1053/j.gastro.2019.01.042. Epub 2019 Jan 25. PMID: 30689971, Eddowes P and Al, [b]Chi² test.

- **Significantly higher proportion of patients in treated arms had CAP_{EOT} ≤ 302 dB/m compared to placebo**

Significant correlation between CAP and histological steatosis grade in lanifibranor treated arms

Correlation between CAP and steatosis grade changes in lanifibranor treated arms



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

Conclusions

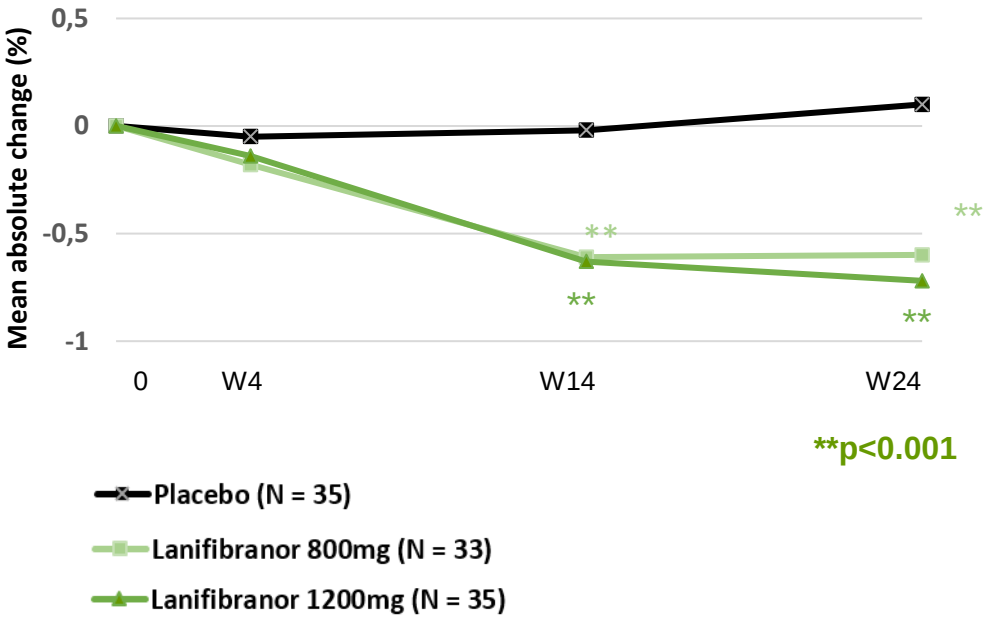
- Histological steatosis grading showed a good correlation with CAP by Fibroscan
- Lanifibranor induced a significant reduction in hepatic steatosis
- Changes in CAP over time correlates with changes in histological grading of steatosis

Lanifibranor reverses fasting glucose levels to normoglycemia in prediabetic patients with nonalcoholic steatohepatitis (NASH)

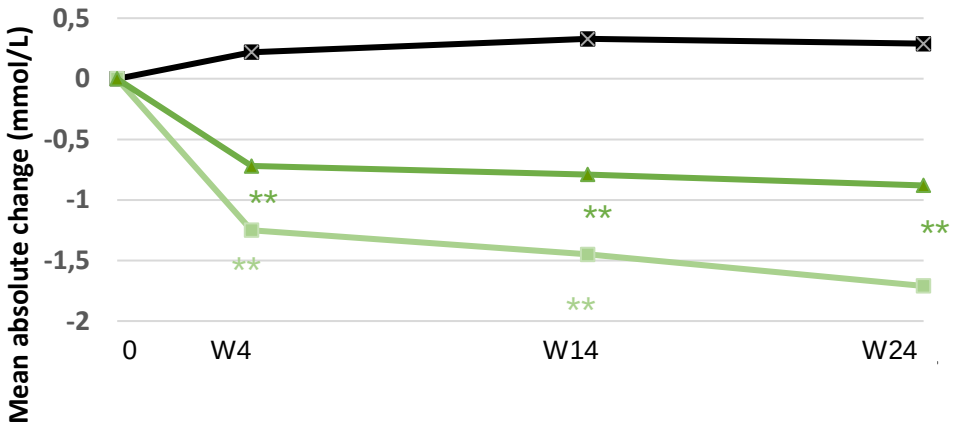
Cooreman MP, Francque S, Baudin M, Huot-Marchand P, Dzen L, Junien JL, Broqua P, Abdelmalek MF

Lanifibranor significantly improves glycaemic control in patients with NASH and T2D

Absolute change from baseline in HbA1c

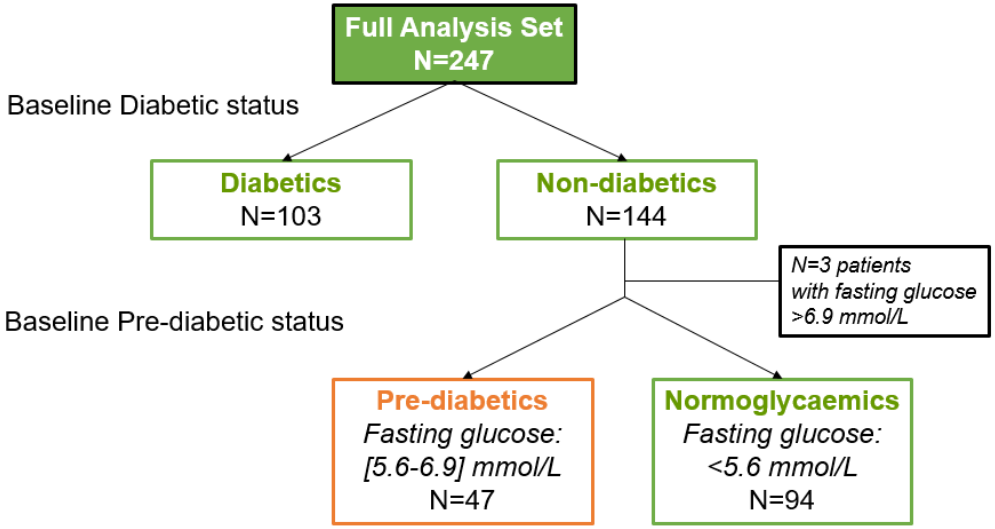


Absolute change from baseline in fasting glucose



Lanifibranor improves glycemia in pre-diabetic patients

- NASH is associated with manifestations of metabolic syndrome that share a common disease biology, including type 2 diabetes (T2D) and cardiovascular disease (CVD)
- Patients with prediabetes also have an increased risk for CVD. Reversal of prediabetes diminishes the risk for subsequent T2D and therefore may also reduce the risk for CVD



At baseline:

Pre-diabetics

Fasting glucose (EOT)	Placebo	Lanifibranor 800mg	Lanifibranor 1200mg
N	9	18	14
<5.6 mmol/L	**1 (11%)**	**12 (67%)**	**10 (71%)**
[5.6-6.9] mmol/L	6 (67%)	5 (28%)	4 (29%)
>6.9 mmol/L	2 (22%)	1 (6%)	0 (0%)

Normoglycemic patients

Placebo	Lanifibranor 800mg	Lanifibranor 1200mg
31	24	28
23 (74%)	24 (100%)	28 (100%)
8 (26%)	**0 (0%)**	**0 (0%)**
0 (0%)	0 (0%)	0 (0%)

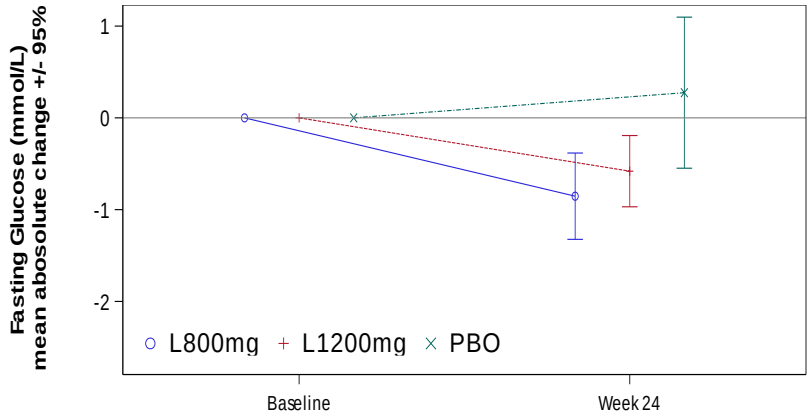
- Among prediabetics at baseline, **67% and 71% in the lanifibranor 800 and 1200mg/d arms reversed to normoglycemia** at EOT, versus 11% in the placebo arm
- Among normoglycemics at baseline, **0% in the lanifibranor arms progressed to prediabetes at EOT, versus 26% in placebo arm**

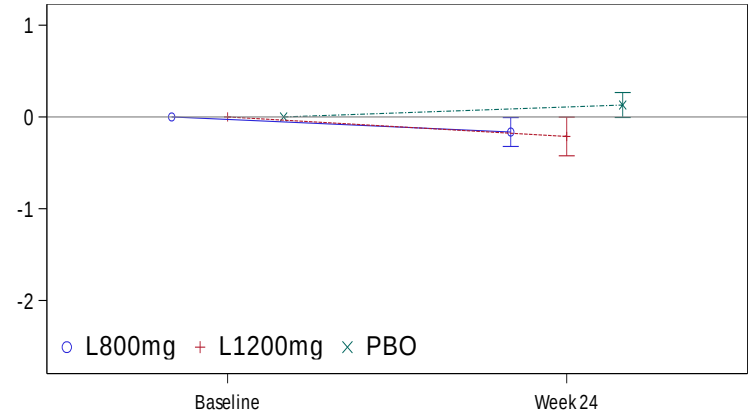
Lanifibranor improves markers of glucose metabolism in pre-diabetic patients

Pre-diabetic patients

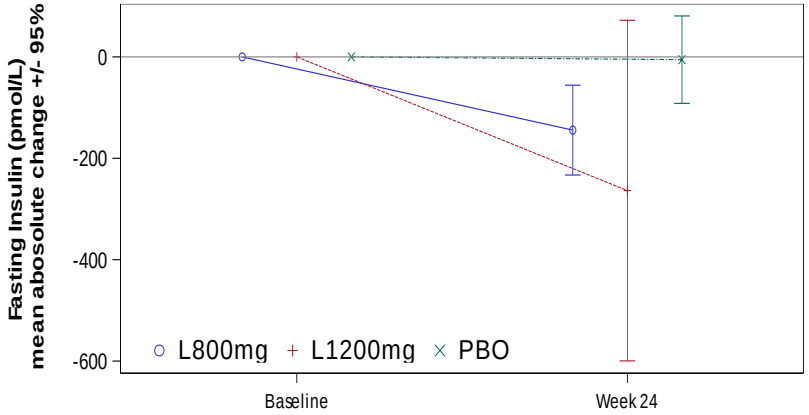
Normoglycemic patients

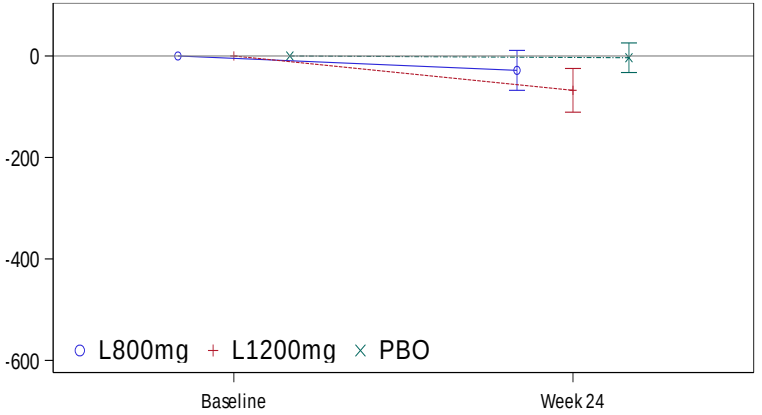
Fasting glucose





Fasting insulin





Insulin levels status (EOT)	Placebo	Lanifibranor 800mg	Lanifibranor 1200mg
N	8	18	14
Abnormal (>173 pmol/L)	5 (63%)	4 (22%)	2 (14%)
Normal (≤173 pmol/L)	3 (37%)	14 (78%)	12 (86%)

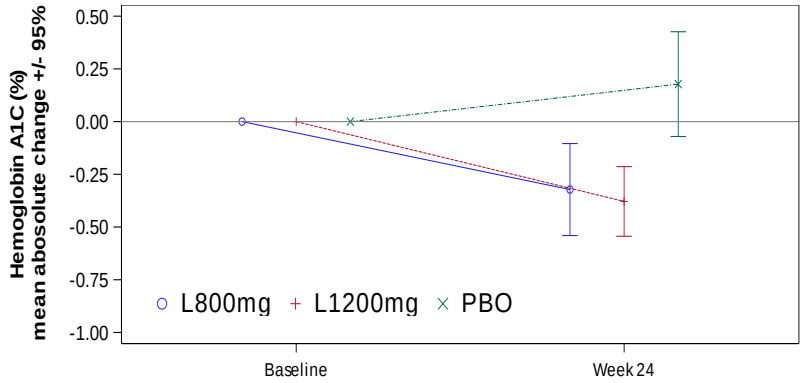
Placebo	Lanifibranor 800mg	Lanifibranor 1200mg
30	24	26
11 (37%)	4 (17%)	2 (8%)
19 (63%)	20 (83%)	24 (92%)

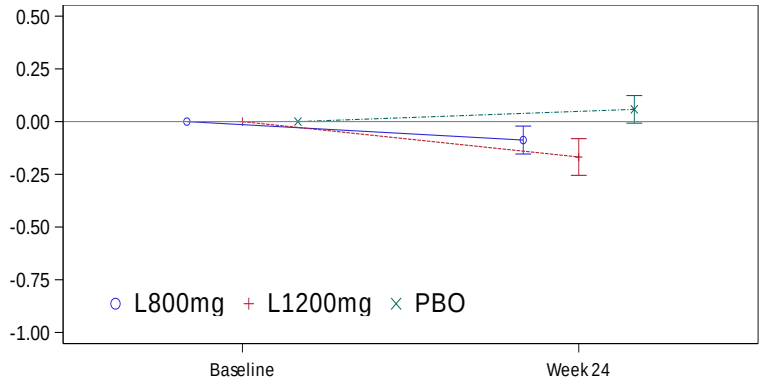
Lanifibranor improves markers of glucose metabolism in pre-diabetic patients

Pre-diabetic patients

Normoglycemic patients

HbA1c

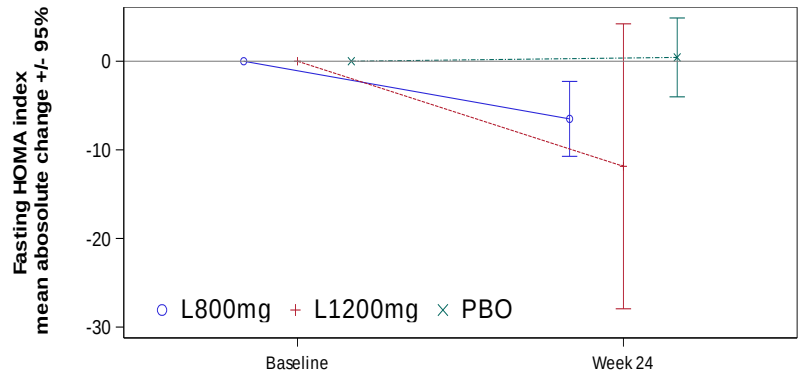


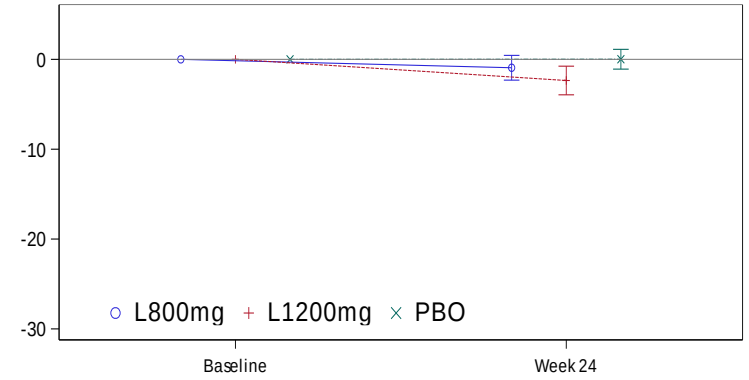


HbA1c (EOT)	Placebo	Lani. 800mg	Lani. 1200mg
N	9	18	14
Abnormal (>6.5%)	5 (56%)	1 (6%)	1 (7%)
Normal (≤6.5%)	4 (44%)	17 (94%)	13 (93%)

Placebo	Lani. 800mg	Lani. 1200mg
31	24	28
2 (7%)	0 (0%)	0 (0%)
29 (93%)	24 (100%)	28 (100%)

HOMA IR





HOMA-IR (EOT)	Placebo	Lani. 800mg	Lani. 1200mg
N	8	17	14
Abnormal (>3)	8 (100%)	13 (77%)	11 (79%)
Normal (≤3)	0 (0%)	4 (23%)	3 (21%)

Placebo	Lani. 800mg	Lani. 1200mg
28	24	26
23 (82%)	14 (58%)	11 (42%)
5 (18%)	10 (42%)	15 (58%)

Conclusions

- **The effect size on reversal to normoglycemia and improvement of insulin resistance suggest a therapeutic benefit of lanifibranor on glucose metabolism in prediabetic patients with NASH that warrants further study.**
- **These data also further support the relevance of screening patients with NASH for both overt T2D and prediabetes.**
- **Effective interventions on pre-diabetics could prevent or delay the apparition of diabetes and its morbid complications.**

Review of lanifibranor AASLD 2021 abstracts

Prof. Jörn Schattenberg, MD
Professor of Medicine
Director Metabolic Liver Research Program - Department of Medicine
University Medical Center Mainz

Liver sinusoidal endothelial cell (LSEC) capillarization in NASH and its evolution following lanifibranor treatment: an exploratory study of the NATIVE clinical trial

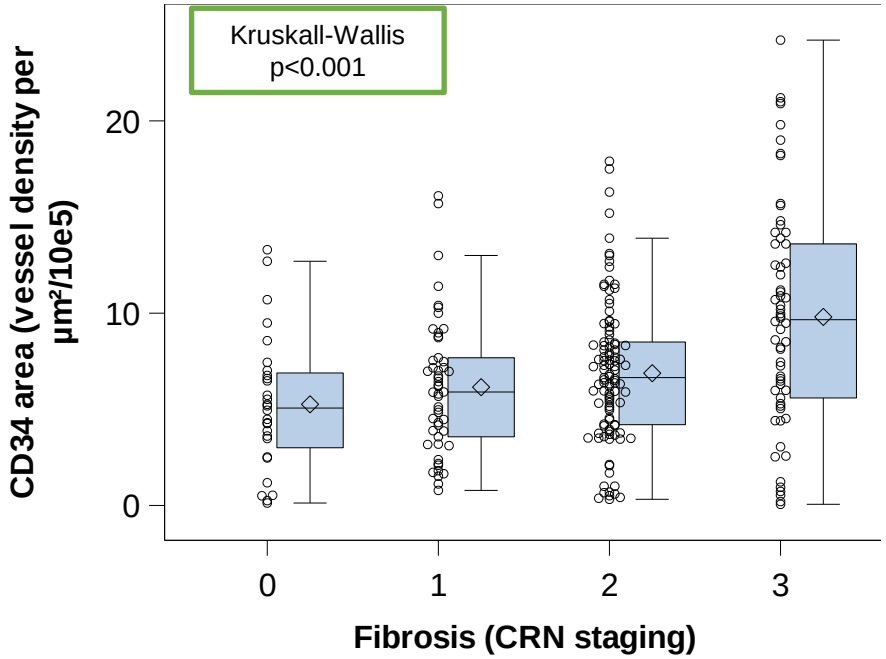
Rautou PE, Wettstein G, Bedossa P, Cooreman MP, Baudin M, Huot-Marchand P, Dzen L, Albuquerque M, Broqua P, Junien JL, Abdelmalek MF, Francque S, Paradis V

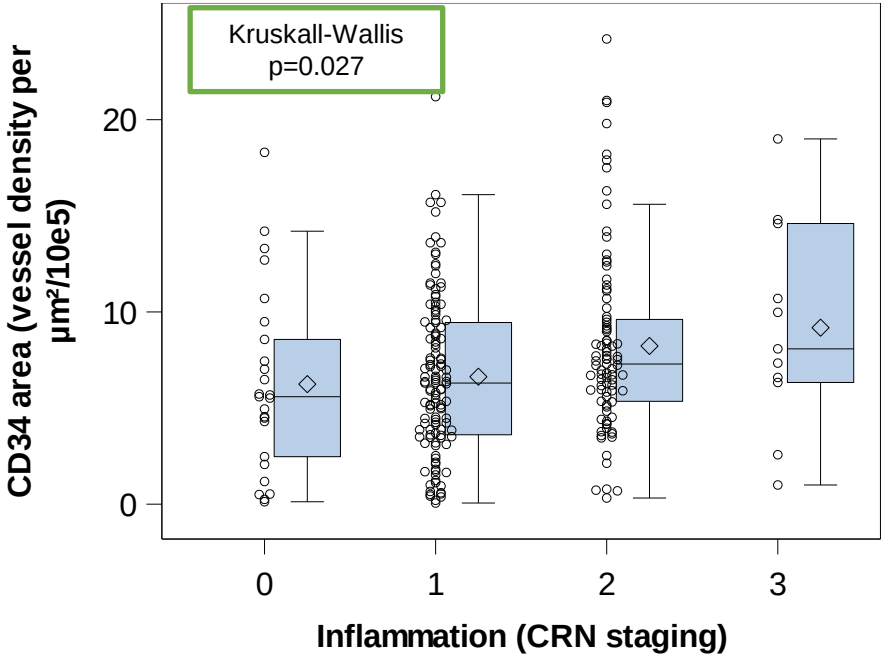
LSEC capillarization and fibrosis

- LSEC are specialized endothelial cells which are permeable because of their fenestrae and lack of basal membrane. LSECs maintain hepatocyte homeostasis, hepatic stellate cell quiescence and hepatic vascular tone contributing to maintenance of low portal pressure.
- LSEC capillarization in chronic liver disease has been associated with increased hepatic fibrosis and portal pressure. Limited clinical studies showed that LSEC capillarization occurs at early stages of NASH.
- Preclinical models suggest that this change contributes to steatosis, liver inflammation and fibrosis.
  - In preclinical study, lanifibranor has been shown to induce a regression of LSEC capillarization.*
- Exploratory study using trial liver biopsies specimens obtained during the NATIVE determine:
  - (a) the features of NASH associated with LSEC changes using liver biopsies performed at baseline in 249 patients considered for inclusion in NATIVE;
  - (b) the evolution of LSEC changes following lanifibranor treatment in liver biopsies of 162 patients included in NATIVE.
- CD34 immunostaining was quantified by morphometric analysis (using dedicated algorithm of microvessel density Imagescope APerio) and by 2 semi-quantitative scores (centrilobular and periportal, defined as 0=0%, 1/3:< 33%, 2/3: 33-66% and 3/3: >66% of the lobular surface).
- CD34 and ERG costaining was performed on 20 slides and ensured endothelial specificity of CD34 staining.

Boyer-Diaz Z,et al. *J Hepatol*. 2021;74(5):1188-1199.

Correlation between morphometric CD34 and histological features of NASH

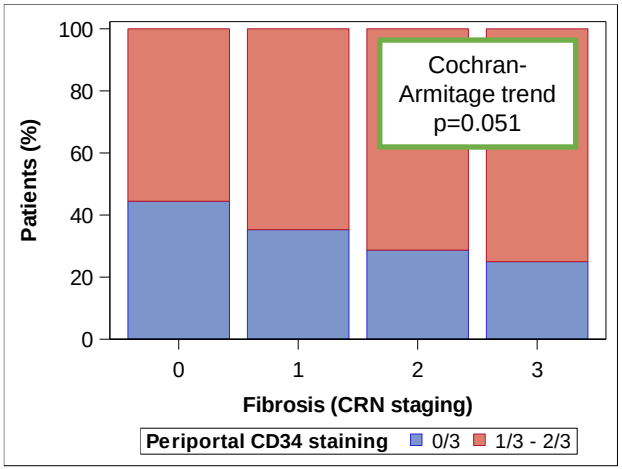


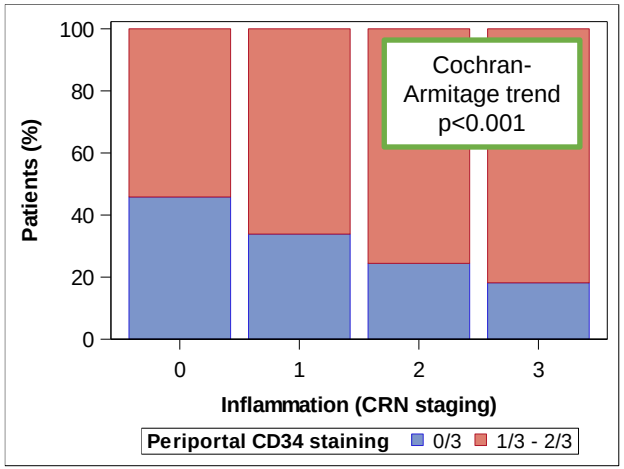


- CD34 staining strongly associated with liver fibrosis and lobular inflammation (to a lesser extent)
- CD34 staining was not associated with steatosis or hepatocellular ballooning (data not shown)

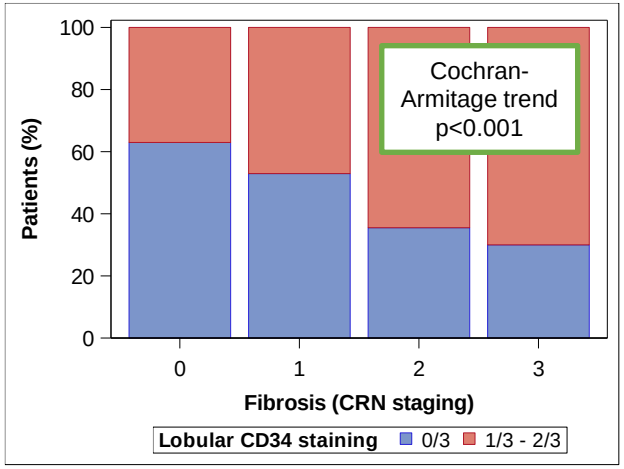
Correlation between semi-quantitative CD34 scoring and features of NASH

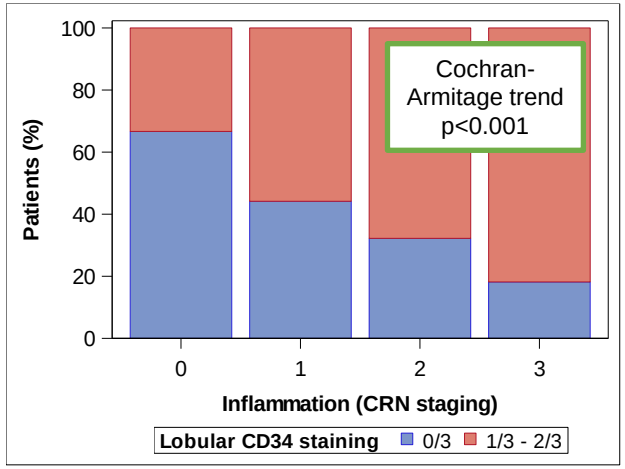
Periportal CD34 score





Lobular CD34 score

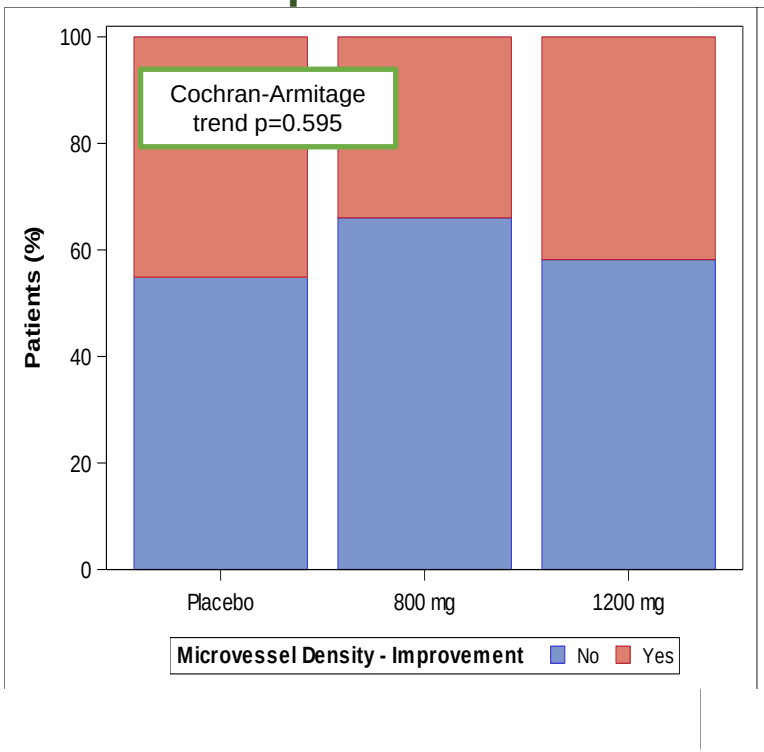




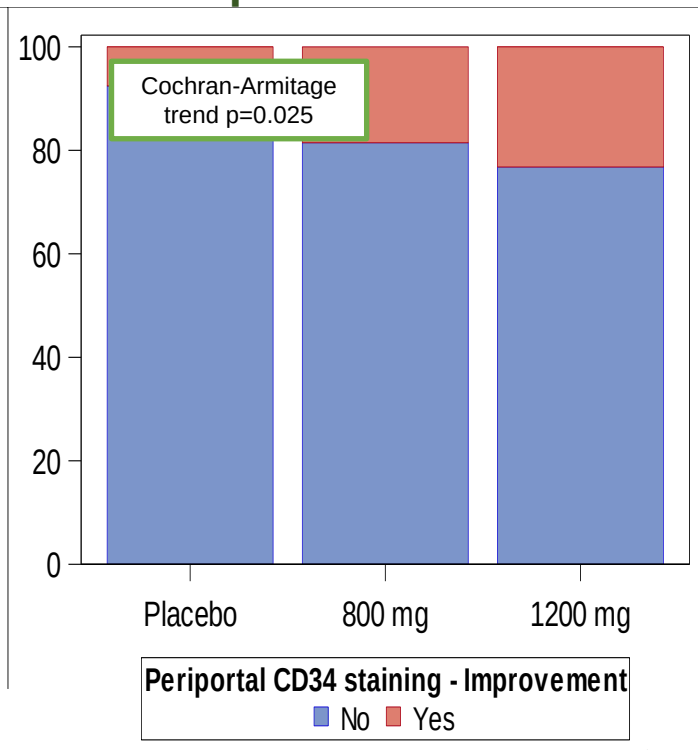
- **Semi-quantitative scores for CD34 staining were associated with liver fibrosis and lobular inflammation.**

Lanifibranor reduces the expression of CD34 in the periportal area

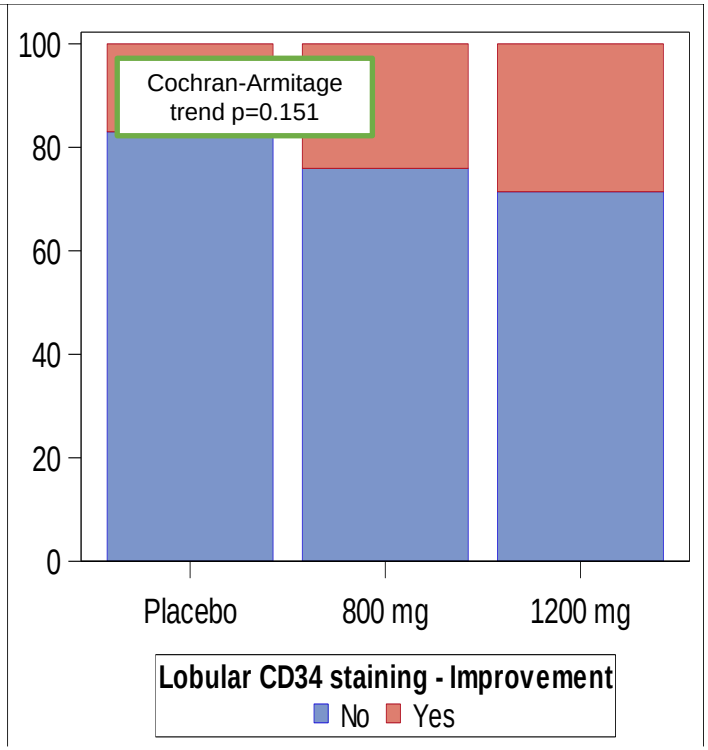
Morphometric CD34



Periportal CD34 score



Lobular CD34 score



- **No difference between treated arms and placebo regarding improvement in CD34 staining by morphometry (defined as a decrease of 20% compared to baseline)**
- **Lanifibranor treatment is associated with a lower, dose-dependent, expression of CD34, significantly different in the periportal area, but not in the centrilobular area**

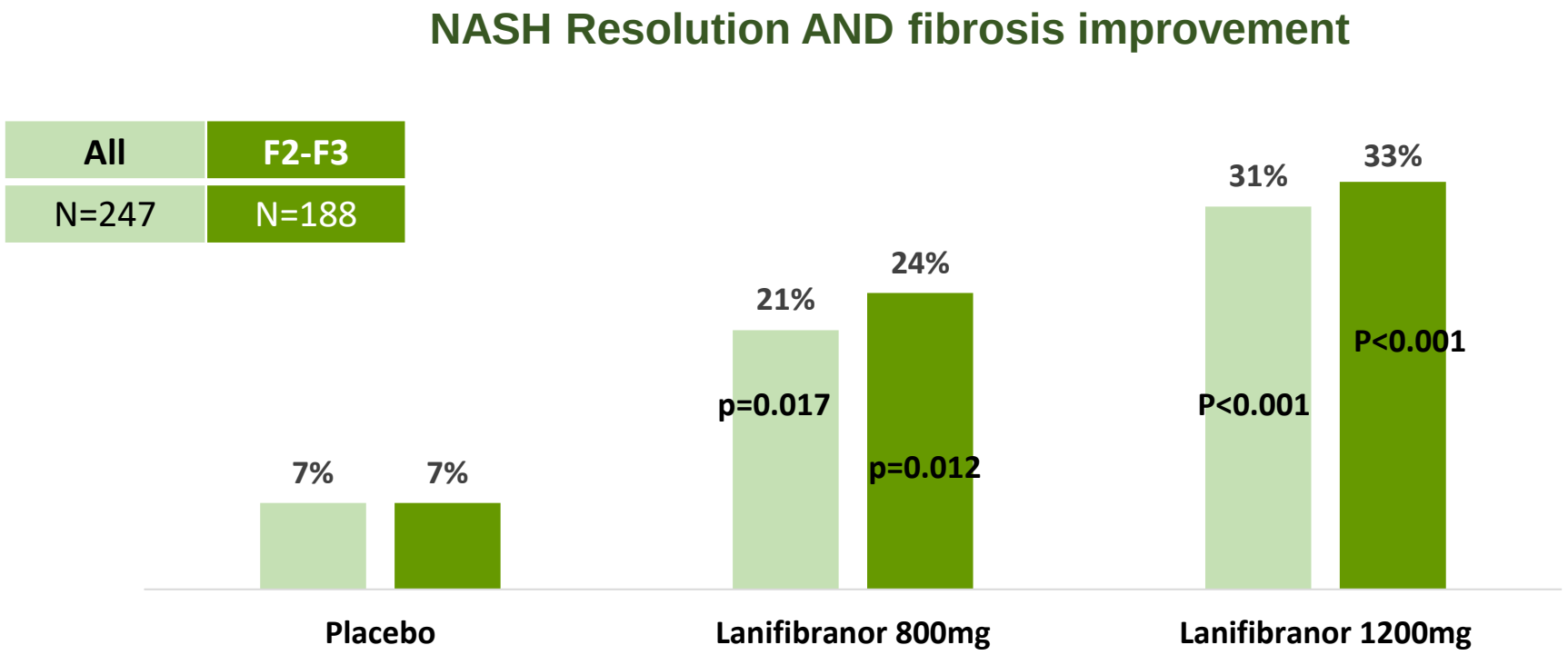
Conclusions

- In patients with NASH, LSEC capillarization (i.e. CD34 expression) increases with liver fibrosis and lobular inflammation, but not with steatosis or ballooning.
- Lanifibranor treatment is associated with a dose-dependent reduction of CD34 staining which reached statistical significance in periportal area.
- Whether this effect of lanifibranor is due to a direct effect on endothelial cells or a consequence of its anti-inflammatory and anti-fibrotic activity will require further studies.

Treatment Response to the pan-PPAR agonist Lanifibranor in the NATIVE Study: NASH Resolution and Fibrosis Improvement are correlated

Sanyal AJ, Cooreman MP, Baudin M, Huot-Marchand P, Dzen L, Junien JL, Broqua P, Francque S, Abdelmalek MF

Lanifibranor treatment induces NASH resolution AND improvement of fibrosis

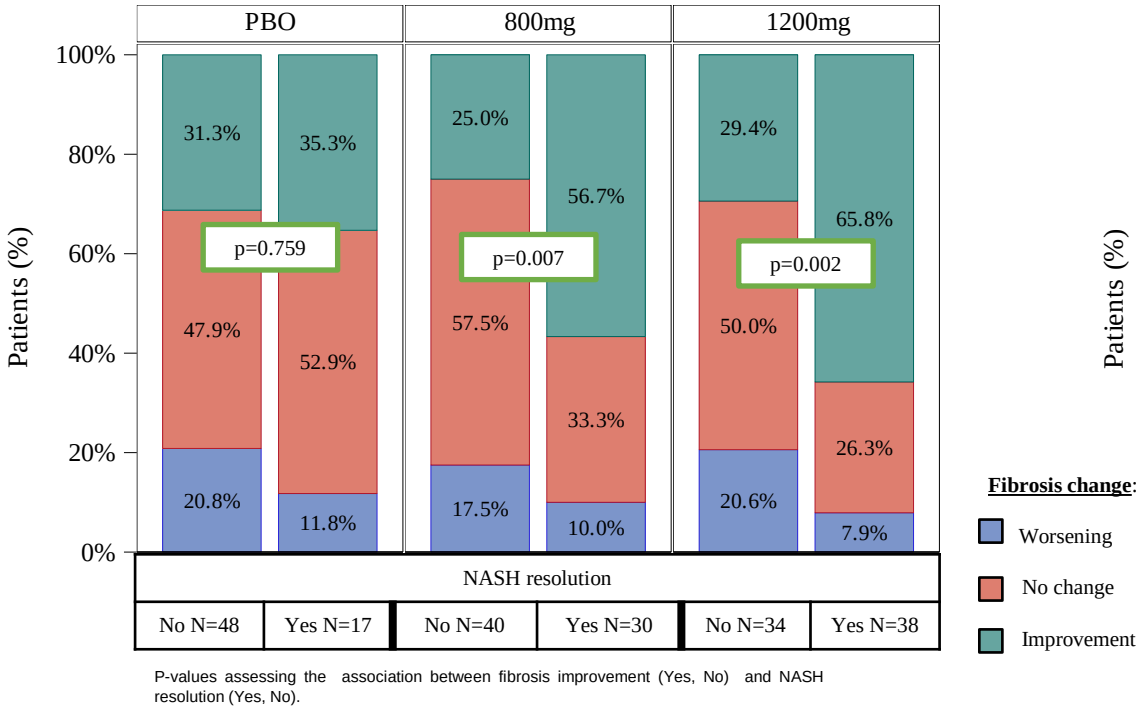


- **In NATIVE, both lanifibranor dose groups met the composite endpoint of resolution of NASH and fibrosis improvement**

Francque et al. N Engl J Med 2021; 385:1547-1558

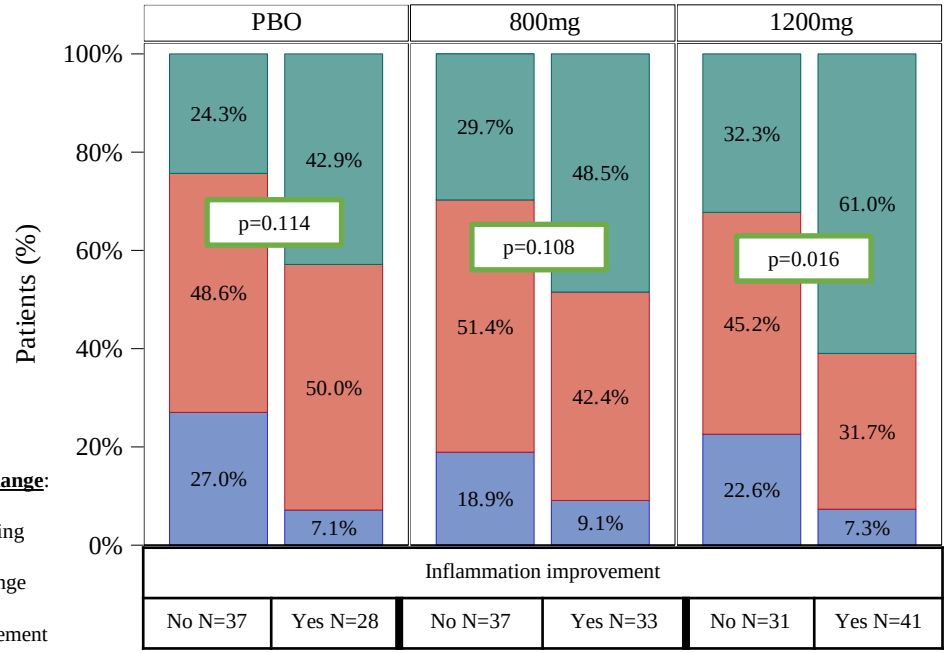
Correlation between fibrosis improvement and NASH resolution

NASH Resolution



P-values assessing the association between fibrosis improvement (Yes, No) and NASH resolution (Yes, No).

Lobular Inflammation Improvement

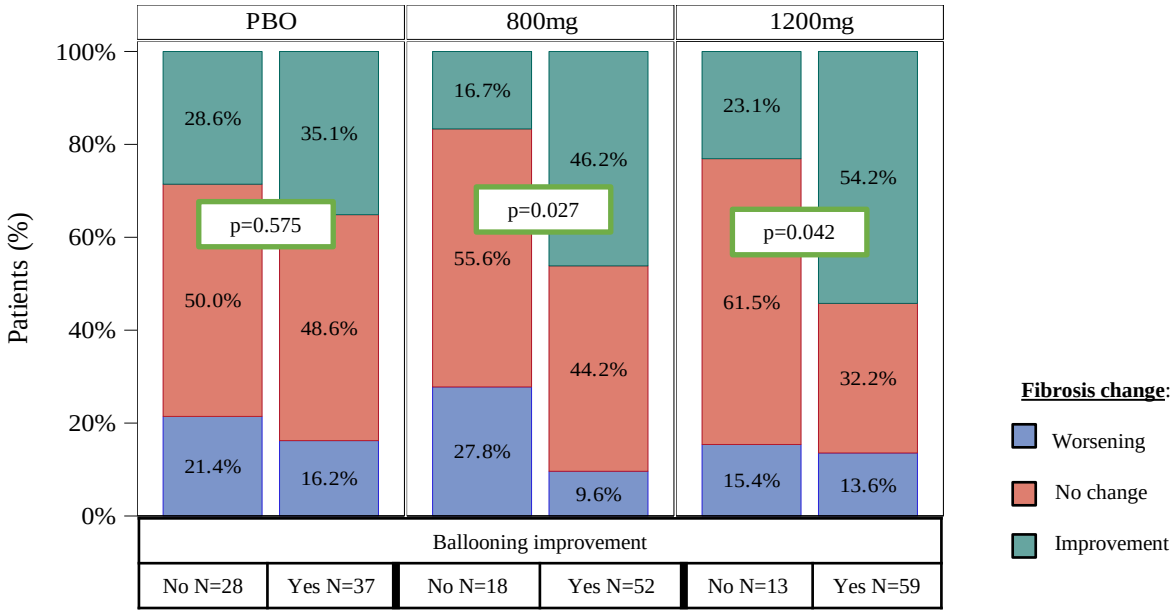


P-values assessing the association between fibrosis improvement (Yes, No) and inflammation improvement (Yes, No).

- **NASH resolution responders were significantly more likely to be fibrosis improvers than non-improvers for lanifibranor arms, but not with placebo.**
- **Inflammation improvers were significantly more likely to be fibrosis improvers than non-improvers in lanifibranor 1200 mg, but not for lanifibranor 800 mg and placebo.**

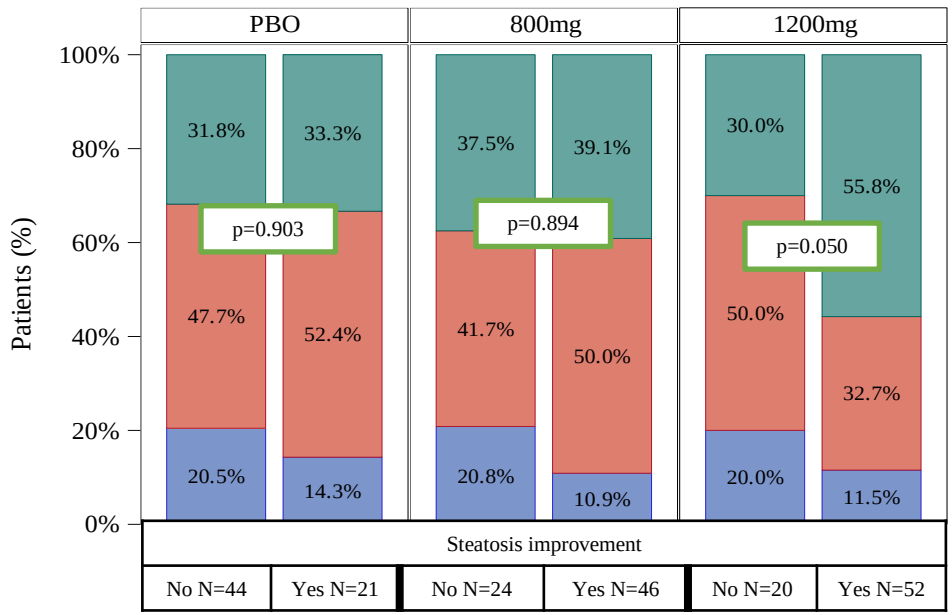
Correlation between fibrosis improvement and NASH resolution

Ballooned Hepatocyte Improvement



P-values assessing the association between fibrosis improvement (Yes, No) and ballooning improvement (Yes, No).

Steatosis Improvement



P-values assessing the association between fibrosis improvement (Yes, No) and steatosis improvement (Yes, No).

- **Ballooned hepatocyte improvers were significantly more likely to be fibrosis improvers than non-improvers for both lanifibranor arms, but not with placebo.**
- **Steatosis improvers were significantly more likely to be fibrosis improvers than non-improvers for lanifibranor 1200 mg, but not for 800 mg and placebo.**

Conclusions

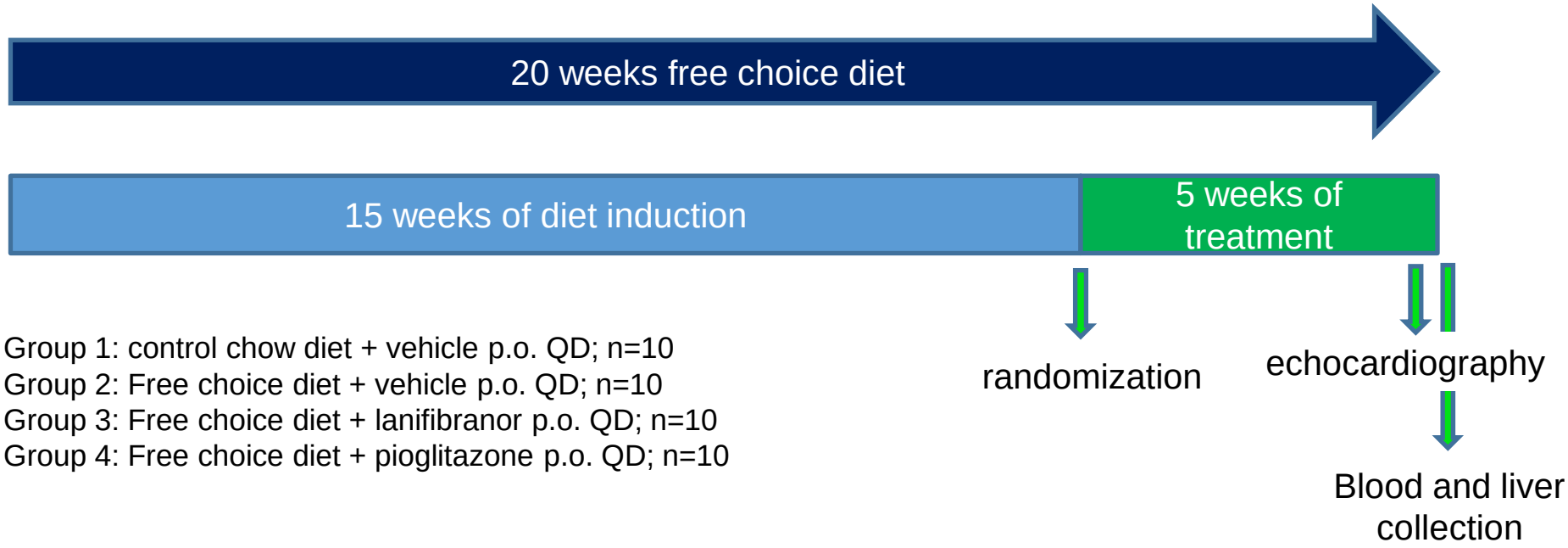
- **With lanifibranor 800 or 1200 mg, NASH resolution and improvement in ballooned hepatocytes are associated with improvement in hepatic fibrosis.**
- **These analyses support a biologically plausible link between NASH resolution and fibrosis.**
- **The specific pathogenic link between ballooned hepatocytes and fibrosis warrants further investigation.**

Lanifibranor improves NASH, fibrosis and diastolic dysfunction in a hamster preclinical model of diet induced NASH

Wettstein G, Briand F, Sulpice T, Junien JL, Broqua P

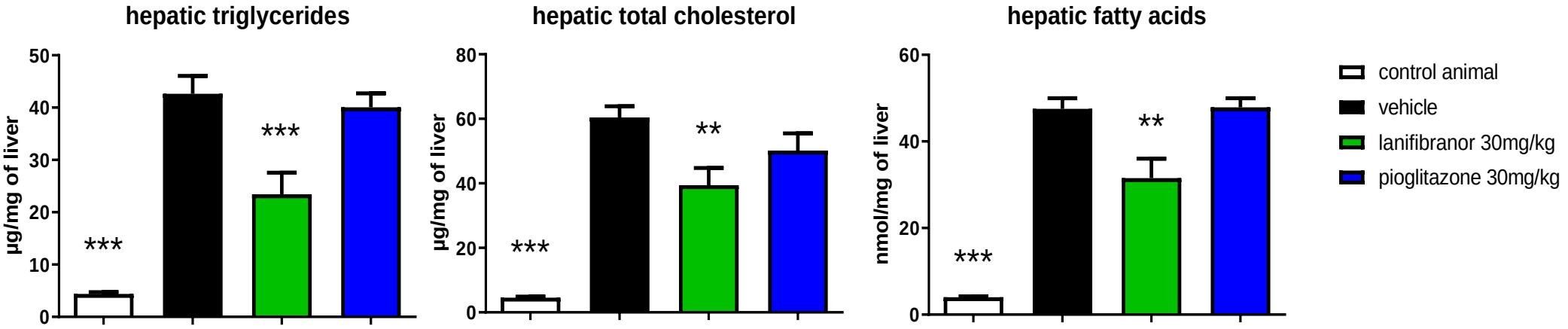
Introduction

- **Lanifibranor is a well-balanced agonist of the 3 PPAR isotypes with anti-inflammatory and anti-fibrotic effects in pre-clinical models of NASH.**
- **The NATIVE phase 2b trial (NCT03008070) in non-cirrhotic NASH patients demonstrated beneficial effects of lanifibranor treatment on several histological endpoints including NASH resolution and improvement of fibrosis.**
- **It has been reported in several studies that NASH increases the risk for cardiovascular diseases and that NASH patients are at higher risk of developing diastolic dysfunction.**
- **We evaluated in this study the potential of lanifibranor in preventing metabolic changes and diastolic dysfunction in a preclinical model of NASH, in comparison with the PPARγ agonist pioglitazone.**

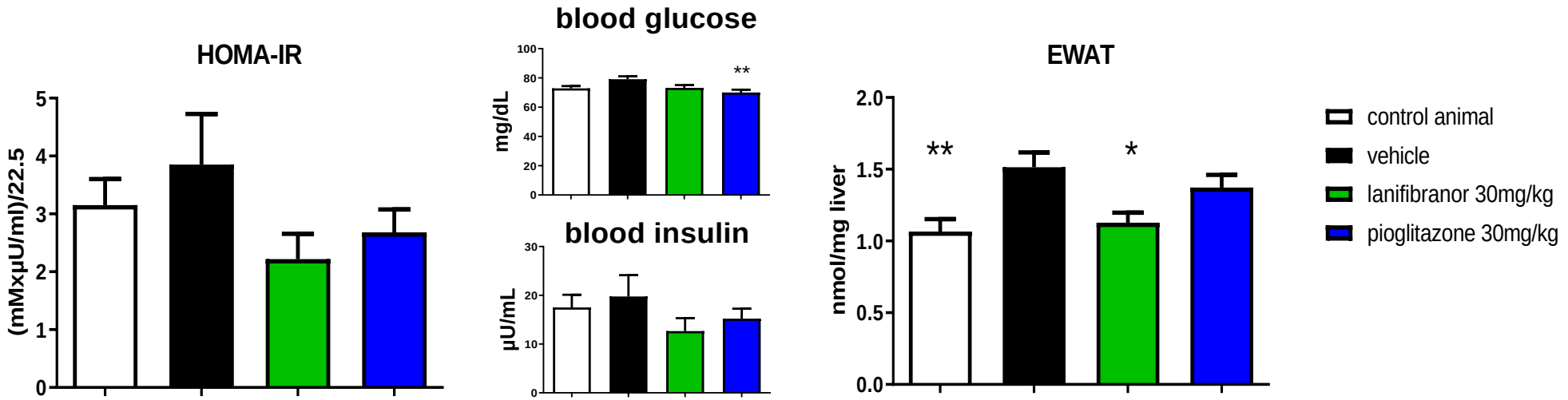


Group 1: control chow diet + vehicle p.o. QD; n=10
Group 2: Free choice diet + vehicle p.o. QD; n=10
Group 3: Free choice diet + lanifibranor p.o. QD; n=10
Group 4: Free choice diet + pioglitazone p.o. QD; n=10

Positive effects of lanifibranor on glucose and lipids markers in a NASH model inducing diastolic dysfunction

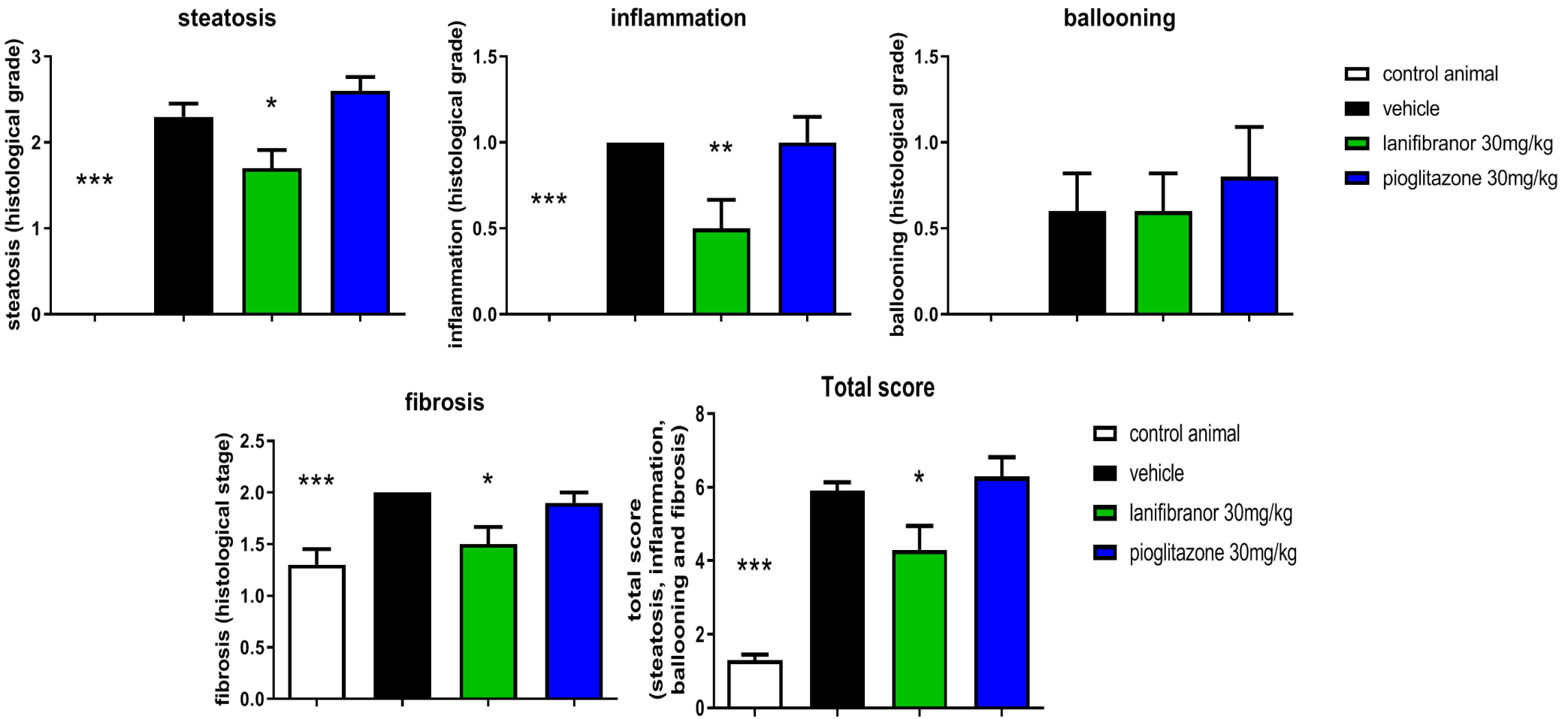


- Lanifibranor, but not pioglitazone, reduced hepatic cholesterol, hepatic triglycerides and hepatic fatty acids increase due to High Fat Diet.



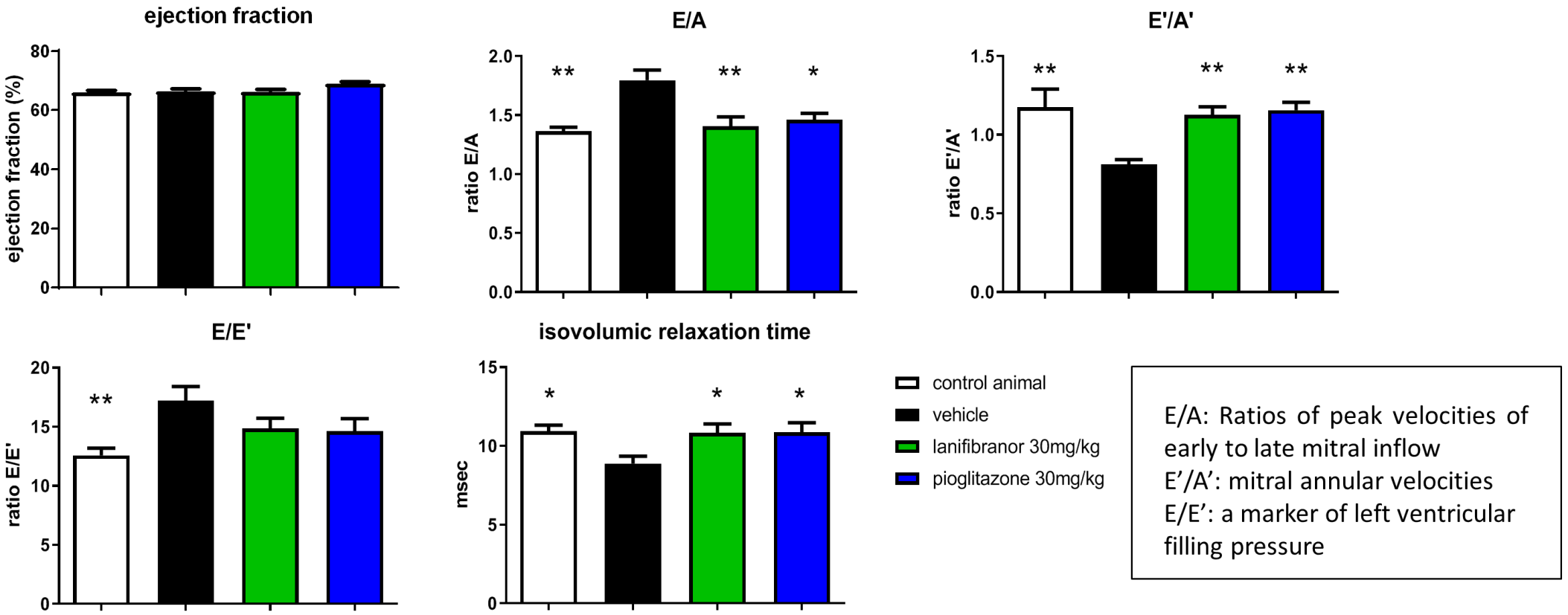
- Lanifibranor and pioglitazone tend to reduced blood glucose, blood insulin and the resultant HOMA-IR index.
- Lanifibranor, but not pioglitazone, significantly reduced epididymal white adipose tissue increase due to High Fat Diet.

Positive effect of lanifibranor on NASH features and fibrosis in a NASH model inducing diastolic dysfunction



- High Fat diet produced a significant increase in steatosis, liver inflammation and fibrosis but not ballooning.
- Lanifibranor, but not pioglitazone, significantly decreased steatosis, inflammation, fibrosis and consequently the total score taking into account the 3 NASH features and fibrosis.

Positive effect of lanifibranor on cardiovascular function in a NASH model inducing diastolic dysfunction



E/A: Ratios of peak velocities of early to late mitral inflow
E'/A': mitral annular velocities
E/E': a marker of left ventricular filling pressure

- **Diastolic dysfunction is a cardiac condition associated with left ventricular relaxation or compliance abnormalities and a preserved ejection fraction. High Fat Diet induced an advanced diastolic dysfunction.**
- **Lanifibranor and pioglitazone normalized E/A and E'/A' ratio as well as the isovolumic relaxation time and tend to reduced E/E' ratio.**

Conclusions

- **Lanifibranor but not pioglitazone led to improvement in NASH and fibrosis suggesting that a panPPAR activation leads to a greater efficacy than a PPARγ activation alone for the treatment of NASH-related liver features.**
- **Lanifibranor also markedly and significantly improved diastolic dysfunction similarly to pioglitazone.**
- **Activation of PPARγ is therefore sufficient to correct the diastolic dysfunction in this model.**
- **However lanifibranor limits the development of diastolic dysfunction.**
- **This new data further support the development of lanifibranor as a treatment for patients with NASH who are at risk for cardiovascular diseases.**

Lanifibranor Phase II study on Non-Alcoholic Fatty Liver Disease in Patients with Type 2 Diabetes in the United States

Dr. Kenneth Cusi

Chief of the Division of Endocrinology, Diabetes & Metabolism in the Department of Medicine, University of Florida

NASH and Type 2 Diabetes

- **Nonalcoholic fatty liver disease (NAFLD) develops in ~70% of patients with type 2 diabetes mellitus (T2D):**
  - Diabetes becomes more difficult to control and often needs more medication
  - About 35-40% develop the more severe form of the disease with hepatocyte necrosis (ballooning) and liver inflammation (steatohepatitis or NASH)
  - About 15-20% develop moderate to severe fibrosis (Lomonaco/Cusi et al, Diabetes Care February , 2021)
- **Coexistence of T2D and NAFLD leads to worse insulin resistance at multiple levels:**
  - In adipose tissue, insulin resistance increases the flux of fatty acids to the liver with hepatocyte « lipotoxicity » and development of NASH
  - Hepatic insulin resistance is associated with a failure to suppress hepatic VLDL secretion, increased de novo lipogenesis (DNL) and more severe atherogenic dyslipidemia characterized by
    - Elevated plasma triglyceride levels
    - Low plasma HDL-cholesterol concentration
    - Smaller and denser LDL particles
- **STUDY AIM: To investigate the mechanism(s) of action of lanifibranor to reduce intrahepatic triglyceride accumulation (IHTG) in relation to changes in adipose tissue, hepatic and muscle insulin resistance, as well as improvement in the cardiometabolic risk profile of patients with T2D and NAFLD**

Lanifibranor Phase II study in Patients with Type 2 Diabetes and NAFLD

Main inclusion criteria

- A total of 34 patients with type 2 diabetes (T2D) with a fasting plasma glucose (FPG) ≤ 250 mg/dL and HbA1c ≤ 9.5% (not on insulin or pioglitazone) with NAFLD.
- Hepatic steatosis (intrahepatic triglycerides or IHTG) > 10 % determined by ^{1}H-MRS.
- Stable weight

Main procedures performed in the study

- Imaging: VCTE/Fibroscan, ^{1}H-MRS/MR-PDFF, MRE, iron-corrected T1 MRI (cT_1 MRI) mapping
- Determination of adipose tissue/hepatic/muscle insulin sensitivity, and de-novo lipogenesis (DNL) will be done with use of labeled glucose, deuterium labeled water (D2O), combined with a low- and high- dose insulin infusion during the euglycemic hyperinsulinemic clamp to measure glucose and lipid turnover and substrate oxidation (with indirect calorimetry).
- Glycemic control (HbA1c), biomarkers of adipose tissue metabolism (i.e., plasma adiponectin and adipokine panels measured by the gold-standard Millipore multiplex platform).
- Plasma biomarkers of liver fibrosis

Main imaging and metabolic results

- Intrahepatic triglycerides (IHTG), liver fibrosis (MRE), liver cT1 (fibroinflammatory activity)
- Adipose tissue/hepatic/muscle insulin sensitivity, DNL
- Cardiometabolic profile/advanced lipid testing and, biomarkers of liver fibrosis

Lanifibranor clinical trial in patients with NAFLD and T2D

Objective: Establish the efficacy/safety and mechanism of action of lanifibranor in patients with T2D and NAFLD.
Specifically determine if lanifibranor decreases IHTG, improves adipose tissue, hepatic and muscle insulin sensitivity, endogenous (hepatic) glucose production, and cardiometabolic health.

Principal investigator

- Prof. Kenneth Cusi (University of Florida)

Randomization

- Randomized (1:1), double-blind, placebo-controlled
- N=34 and 10 healthy non-obese as “normal” controls for all the metabolic and imaging tests
- Sample calculated assuming a >50% relative reduction of IHGT (updated based on the NATIVE trial results reported in 2020)

Primary endpoint

- Change in IHTG quantified by 1H-MRS from baseline to week 24

Key secondary endpoints

- Change in the key metabolic defects of patients with NAFLD: Insulin resistance in adipose tissue, liver and muscle
- Proportion of responders (patients with a IHTG decrease ≥ 30%)
- NAFLD resolution (patients with IHTG ≤ 5%)
- Change in hepatic fibrosis (MRE[4], fibroscan, biomarkers)
- Safety

Study update

Data to become available in 3rd quarter or 2022:

- Estimated recruitment completion in Dec 2021/January 2022
- We have completed treatment on 22 patients; 4 controls
- Seven patients in different stages of run-in or on-treatment

LEGEND STUDY

Lanifibranor in Combination with the SGLT2 Inhibitor empagliflozin in patients with NASH and Type 2 Diabetes

LEGEND Study

Dr. Michelle Lai, MD, MPH

Associate Professor of Medicine, Harvard Medical School
Director of Transplant Hepatology Fellowship
Director of BIDMC NAFLD Center
Division of Gastroenterology/Hepatology

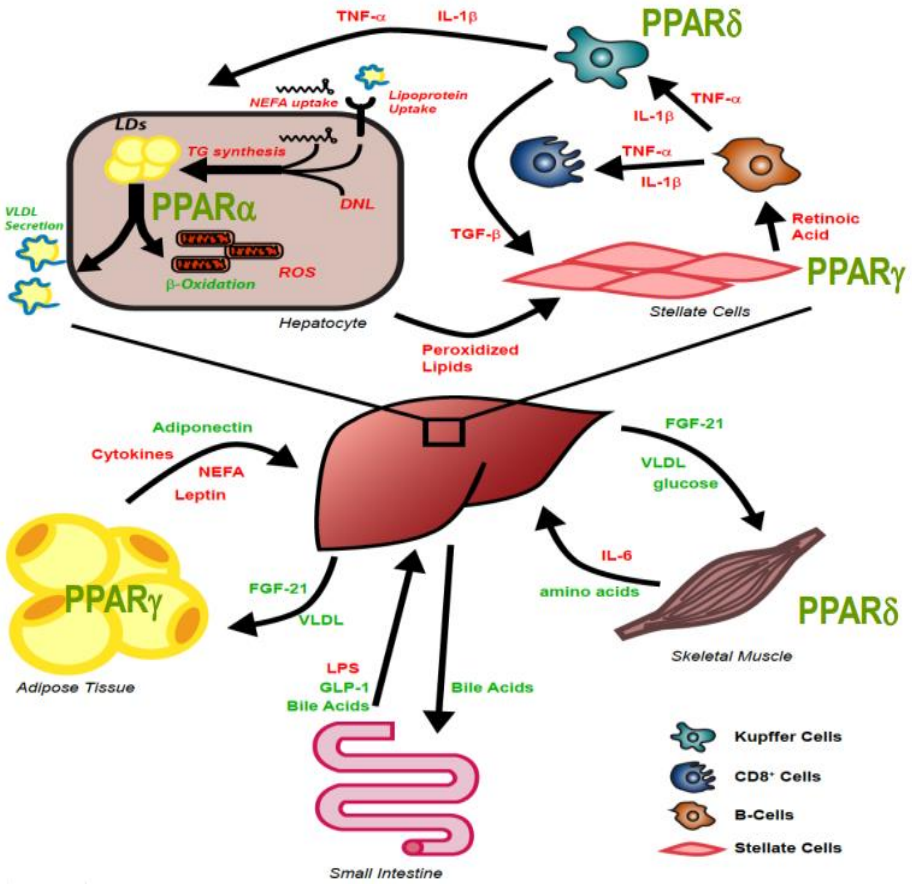
Background

- A large portion of patients with T2D and NASH display typical features of Metabolic Syndrome including abdominal obesity, dyslipidemia, hypertension and insulin resistance.[1]
- T2D accounts for 90 to 95% of all cases of diabetes and is an increasingly prevalent disease with an estimated 462 million affected people worldwide.[2]
- The prevalence of liver biopsy diagnosed NASH among patients with T2D has been observed to be 37.3%.[3]
- Insulin resistance is the key pathophysiological event leading to the clinical manifestations of the metabolic syndrome leading to both NASH and T2D. [1]
- Therapeutic compounds that address the upstream metabolic and immune mediated pathways of NASH are also expected to be beneficial for T2D. [4]
- There is a rationale to assess combination therapy with drugs that have a complementary mechanism of action in the complex disease pathophysiology of patients with NASH who also have T2D.

References : 1. Godoy-Matos et al. Diabetol Metab Syndr 2020, 2. IDF Diabetes Atlas 9th Edition 2019, 3. Younossi ZM, et al. Diabetes Care 2020, 4. Lillich FF et al Front. Pharmacol 2021

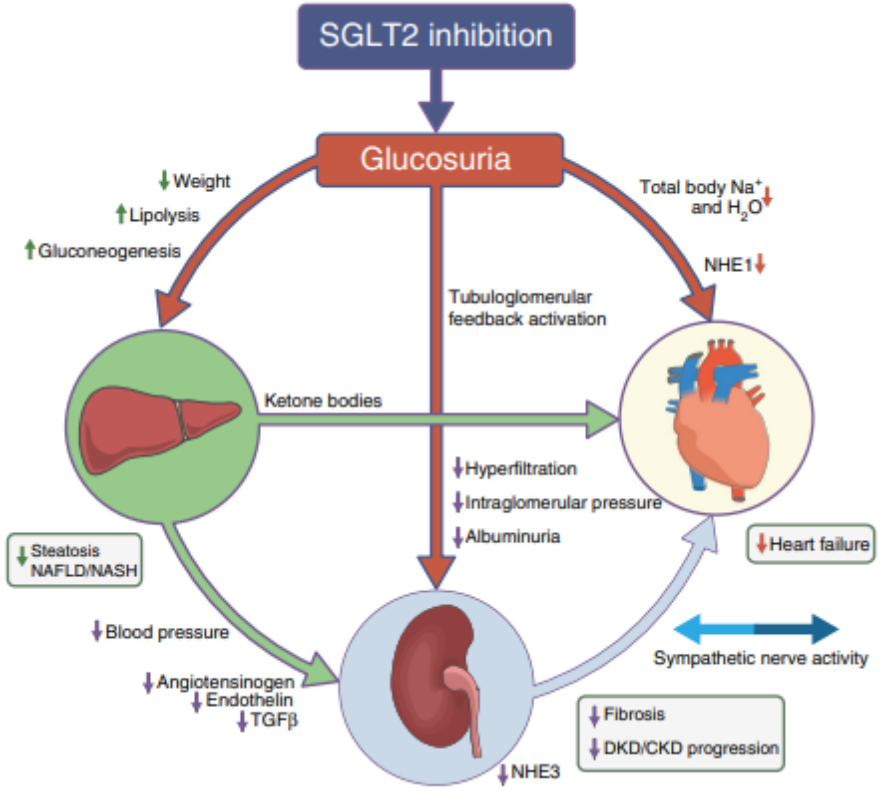
Lanifibranor and a SGLT2 inhibitor (SGLT2i) : rationale

Lanifibranor: balanced pan-PPAR agonist (PPARα, PPARγ and PPARδ)[1]



Lanifibranor shown to improve insulin sensitivity, macrophage activation, liver fibrosis and inflammation

Empagliflozin: SGLT2i reduces proximal tubule reabsorption of sodium and glucose[2]



Empagliflozin shown to improve glycaemia, body weight and fat mass, insulin sensitivity, fluid overload

References : 1. Haas, Francque & Staels. Ann Rev Physiol 2016, 2. Wanner & Marx. Diabetolgia 2018

LEGEND trial: rationale

Target biology

- Utilizing drug combinations targeting multiple aspects of the metabolic syndrome has the potential to address the clinical outcomes in *both* T2D and NASH
- Complex NASH pathophysiology requires targeting multiple mechanisms
- Potential for additive effects

Body composition assessment

- Data to support lanifibranor related fat re-distribution toward a more 'metabolically healthy' fat profile[1]
- Combination (with a SGLT2i) may help mitigate lanifibranor related body weight increase

Evaluation of combination on metabolism & liver parameters

- Study can assess potential additive effects on metabolic and non invasive liver parameters
- Liver Steatosis, inflammation and fibrosis assessed via LiverMultiScan[2]
- HbA1c the gold standard biomarker for glycaemic control also predicts severity of ballooning hepatocytes and hepatic fibrosis[3]

1. Goossens G Obes Facts 2017
2. Pavlides et al Journal of Hepatology 2016
3. Alexopoulos et al Hepatology 2021

LEGEND trial: design

Lanifibranor in Combination with the SGLT2 Inhibitor empagliflozin in patients with NASH and Type 2 Diabetes

LEGEND Study

Principal investigator

- Prof. M. Lai, gastroenterologist-hepatologist, associate professor of medicine; Beth Israel Deaconess Medical Center (USA)
- Prof. O. Holleboom, academic medical specialist (diabetes and metabolism) at the Amsterdam University Medical Center (NL)

Status

- **First site activated:** H1 2022
- **Headline results**: H2 2023

Inclusion criteria

- Adult patients with diabetes and NASH

Design

- Double-blind comparison of lanifibranor vs. placebo will allow controlled assessment of body composition changes (MRI)
- Open-label arm of lanifibranor+empagliflozin will allow *'Proof of Concept'* data to be developed on the use of this combination

Primary outcome measures

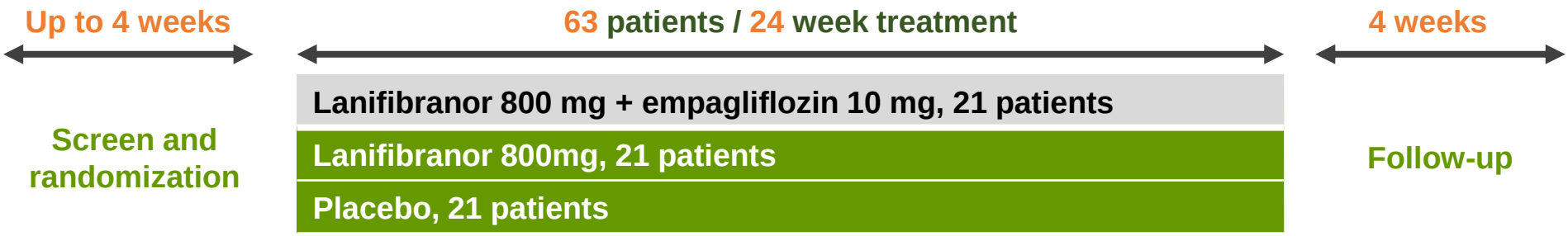
- HbA1c change

Secondary outcome measures

- MRI-based imaging to collect non-invasive data on hepatic fat, inflammation and fibrosis
- Glycaemic/lipid parameters, inflammatory markers
- Changes in body fat composition

Other outcome measures (safety/exploratory)

- AEs, body weight, PK, IHTG, cT1, biomarkers



LEGEND trial: summary

- Lanifibranor and empagliflozin is an attractive combination to study in patients with NASH and T2D
- LEGEND trial will develop important *'Proof of Concept'* data on the combination :
  - Metabolic function :
    - Lanifibranor addresses disease pathways across the spectrum, from lipid and glucose metabolism to fibrosis
    - Empagliflozin acts upstream on metabolic pathways which may work synergistically with lanifibranor
    - HbA1c, in addition to being the gold standard biomarker for glycaemic control also predicts severity of ballooning hepatocytes and hepatic fibrosis
  - Body composition :
    - Based on the MOA, and available data from pioglitazone in combination with several SGLT2i's[1,2], the weight reducing effect of empagliflozin may balance out the weight gain observed with lanifibranor
    - Data to support that lanifibranor induces a fat re-distribution favoring subcutaneous fat that is more 'metabolically healthy'
  - Liver parameters:
    - Impact of combination on non-invasive markers of NASH/fibrosis
    - Liver Steatosis, inflammation and fibrosis assessed via LiverMultiScan
  - Characterise safety profile of combination (lanifibranor + empagliflozin)

1. Rosenstock et al Diabetes Care 2021,
2. Kovacs et al Clinical Therapeutics 2015

Q & A