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THE LIVER MEETING®
NOVEMBER 8-12 2019 BOSTON

Lanifibranor KOL Breakfast

Boston
November 2019

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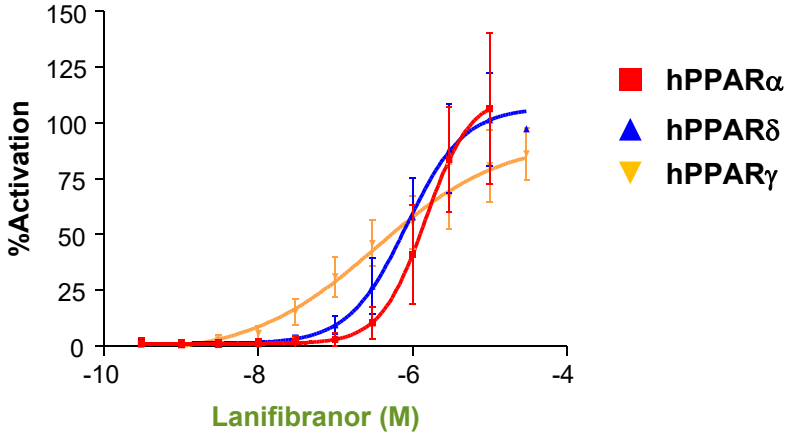
Lanifibranor: a pan-PPAR Agonist with Therapeutic Potential in NASH and NASH Cirrhosis

November 9, 2019

Lanifibranor is a next generation panPPAR with moderate and well balanced activity on PPARα,δ and γ

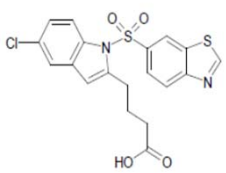
Lanifibranor dose response curves and EC50s for hPPARs (nM)

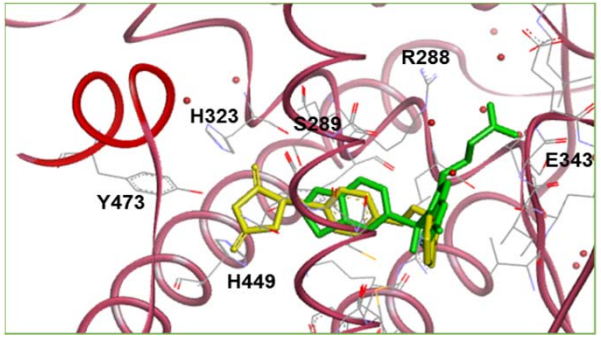
Lanifibranor presents a similar profile for the 3 rodent PPAR isoforms

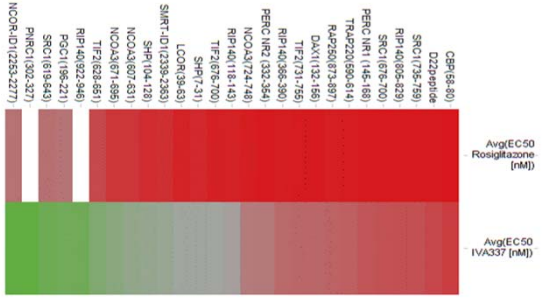


Compound	PPARα EC50 (nM)	PPARδ EC50 (nM)	PPARγ EC50 (nM)
▶ **Lanifibranor[1]**	**1630**	**850**	**230**
▶ Fenofibrate	2400	-	-
▶ Pioglitazone	-	-	263
▶ Rosiglitazone	-	-	13
▶ Elafibranor[2]	10	100	-
▶ Seladelpar[3]	-	2	-

Lanifibranor binds differently than rosiglitazone to PPARγ inducing a different coactivator recruitment[4]







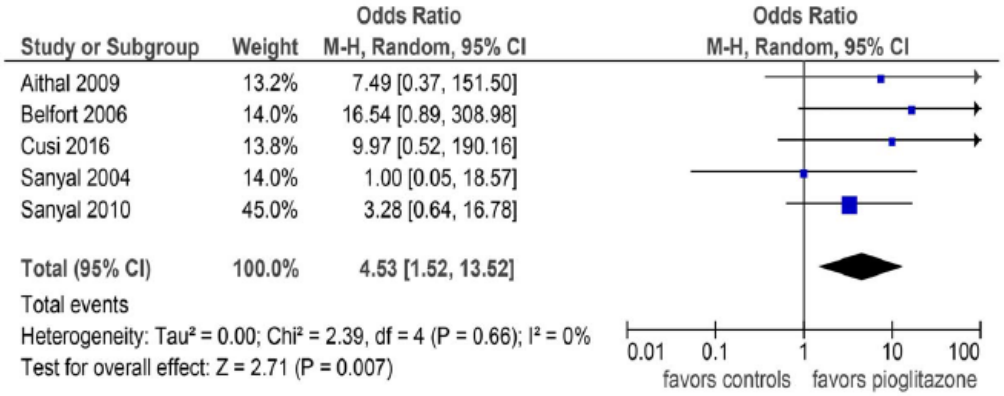
Potency scale: red 10 nM; grey: 500 nM; green 5 000 nM

Source: (1) Company data (2) Hanf R et al, Diabetes & Vascular Dis Res 2014 (3) Cimabay company presentation (4) J Med Chem. 2018 Feb 15. doi: 10.1021/acs.jmedchem.7b01285

PPARγ efficacy is well established in NASH

- **PPARγ activation by pioglitazone significantly improves steatosis, ballooning and inflammation** as well as metabolic markers in NASH patients after 6 or 18 months of treatment:

Pioglitazone (PPARγ)	Belfort NASH study 6 month treatment			Cusi NASH study 18 month treatment		
	Placebo	Pio	p	Placebo	Pio	p
Steatosis (% patients improved)	38%	65%	< 0.001	26%	71%	< 0.001
Inflammation (% patients improved)	29%	65%	< 0.001	22%	49%	< 0.001
Ballooning (% patients improved)	24%	54%	< 0.001	24%	51%	< 0.001
NASH resolution (% patients)	-	NA	-	19%	51%	< 0.001
Fibrosis (mean change in score)	-	NS	-	0	- 0.5	= 0.039



- **Pioglitazone improves advanced fibrosis** (stage F3-F4) as indicated by an increase in the number of NASH patients whose fibrosis stage changed from F3-F4 to F0-F2 at the end of treatment

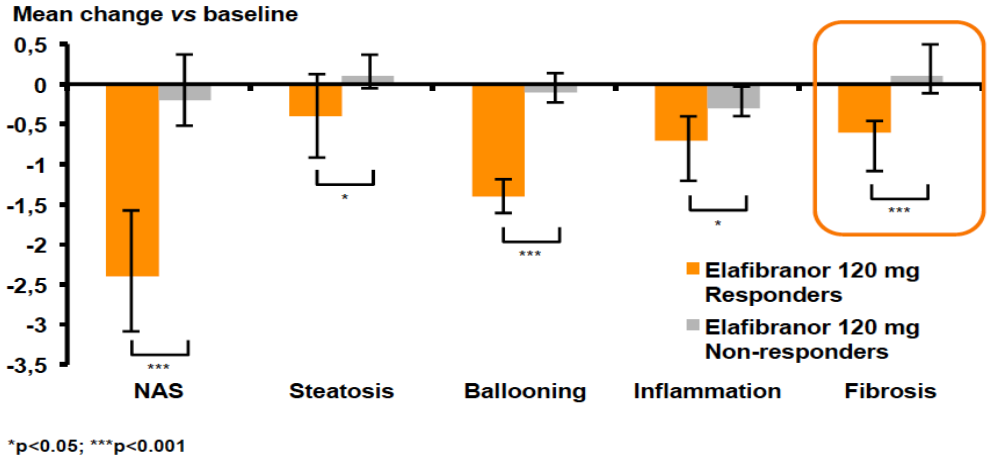
Source: Musso G et al, Hepatology 2017

PPARγ activity can also be completed by PPARα and δ efficacy

- **PPARα/δ** activation by elafibranor 120mg/day **leads to significant improvement of ballooning and inflammation** as well as metabolic markers in NASH patients vs. placebo after 12 months of treatment
  - **NASH resolution in ITT: 19% vs 12%, p = 0.045**
    (elafibranor 120mg, n=89; placebo, n=92)

- In patients with bNAS≥4 and randomized in centers that included in each treatment arm
  % patients with decrease of at least 1 point (elafibranor 120mg, n=31; placebo, n=39)
  - Steatosis: 35% vs 18%, p = 0.10
  - **Inflammation: 55% vs 33%, p < 0.05**
  - **Ballooning: 45% vs 23%, p = 0.02**

- **Patients who resolved NASH showed significant reduction in liver fibrosis**
  while non-responders did not show any change from baseline
  (elafibranor 120mg, responders, n=17; non-responders, n=61)



Source: Ratziu V, et al. Gastroenterology 2016

Lanifibranor shows consistent improvements in metabolic parameters and histology while displaying anti-fibrotic activity

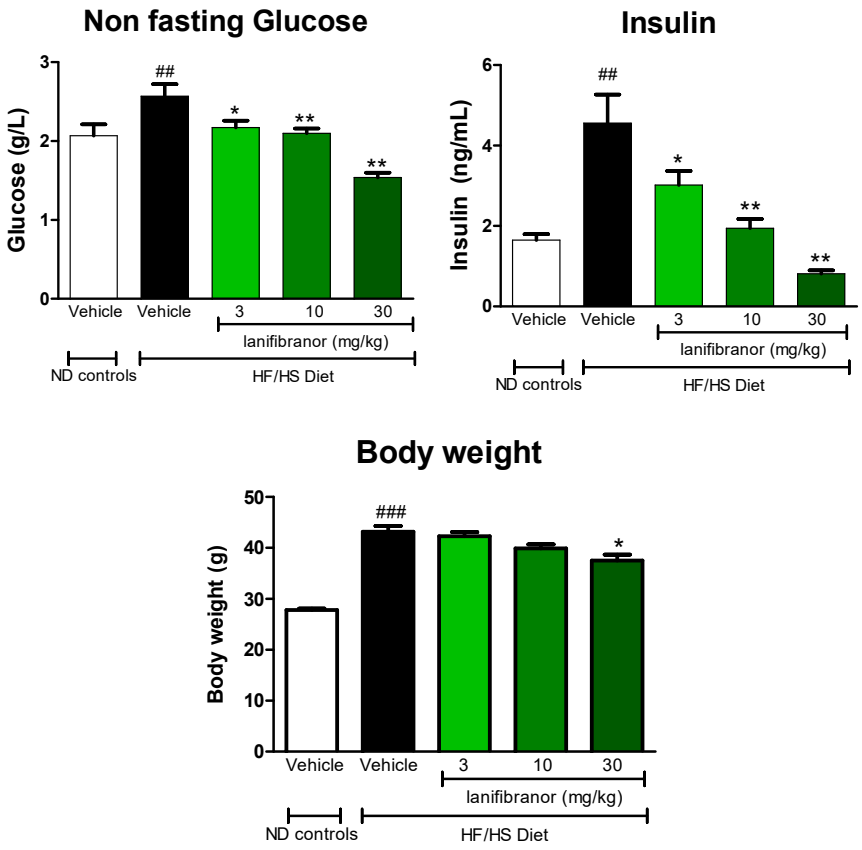
Metabolic models	NASH & NAFLD models	Fibrosis models	Cirrhosis models
Diet induced obesity high fat / high sucrose	Methionine Choline Deficient diet (MCD)	Carbon tetrachloride (CCL4)	Thiocetamide (TAA)
Foz / Foz			
	Choline-deficient amino-acid and high fat diet		
Hepatoma and muscle cells biology	Macrophages biology	HSC biology	
			Endothelial biology
Lanifibranor improves ▶ Insulin resistance ▶ Non fasting glucose ▶ Homa-IR ▶ Lipid profile Lanifibranor maintains body weight	Lanifibranor reduces ▶ Steatosis ▶ Inflammation ▶ Ballooning Lanifibranor improves NAS score	Lanifibranor reduces fibrosis Lanifibranor inhibits stellate cell activation Lanifibranor reverses NASH	Lanifibranor reduces ▶ Portal pressure ▶ Established fibrosis

In Vivo

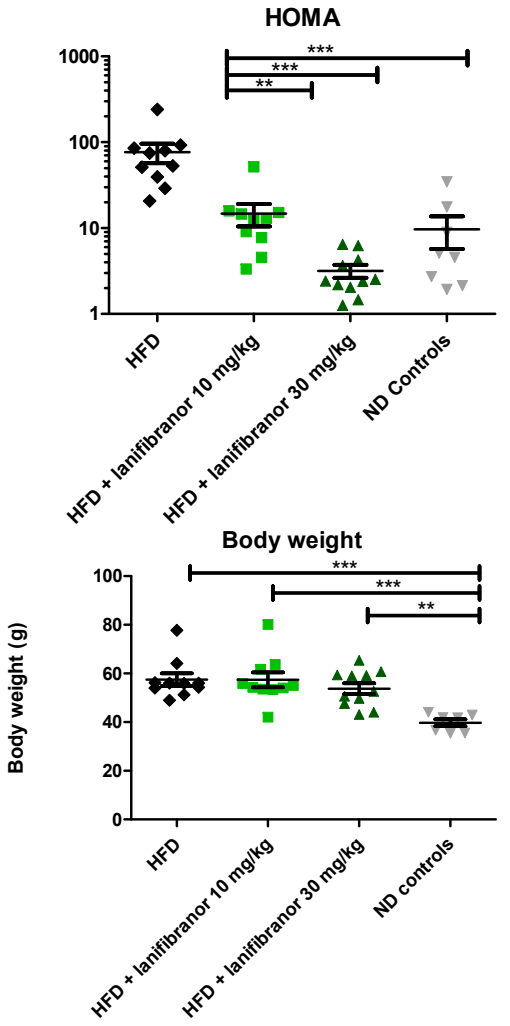
In Vitro

Lanifibranor significantly improves insulin sensitivity without increasing body weight gain in preclinical models of NASH

DIO mice model (HF/HS)



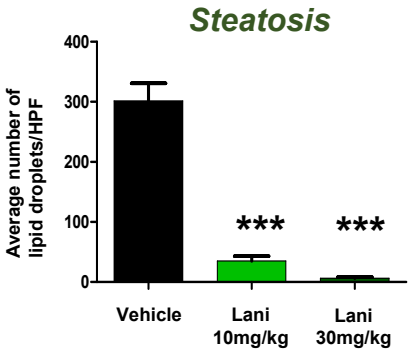
Foz/foz mice model

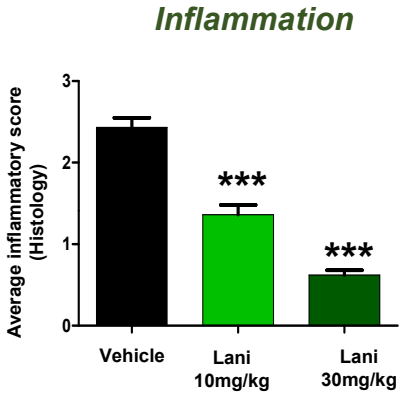


##, ###: vs ctrl vehicle p<0,01 or p<0,001 respectively
***, **, ***: vs HF:HS or HFD P<0,05, P<0,01 or P<0,001 respectively**

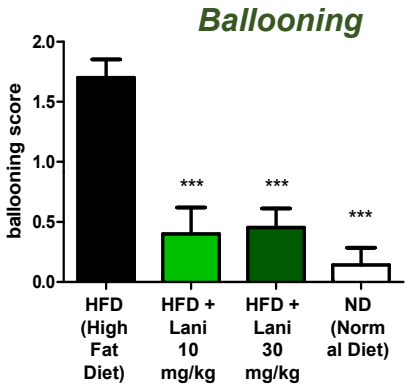
Lanifibranor significantly reduces steatosis, inflammation, ballooning and fibrosis in preclinical models of NASH

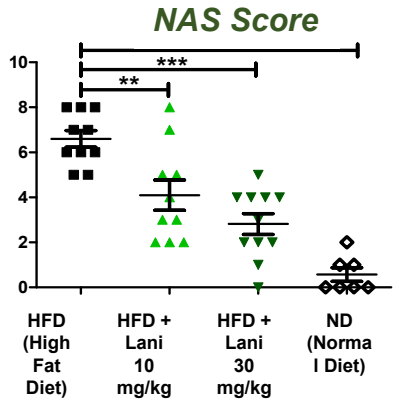
Lanifibranor inhibits steatosis and inflammation in the mice MCD model



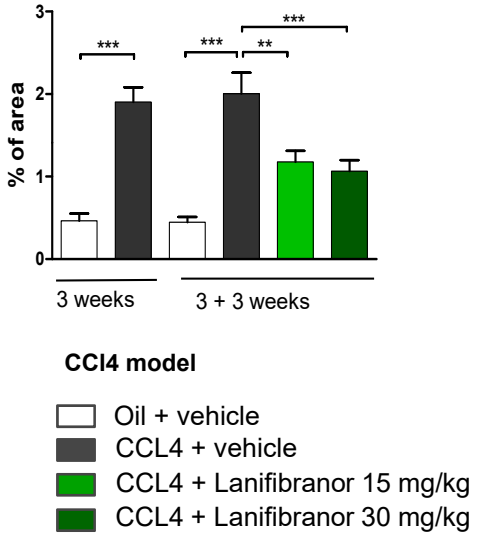


Lanifibranor significantly reduces ballooning and the NAS score in the foz/foz model





Lanifibranor reverses established liver fibrosis in mice CCL4 model

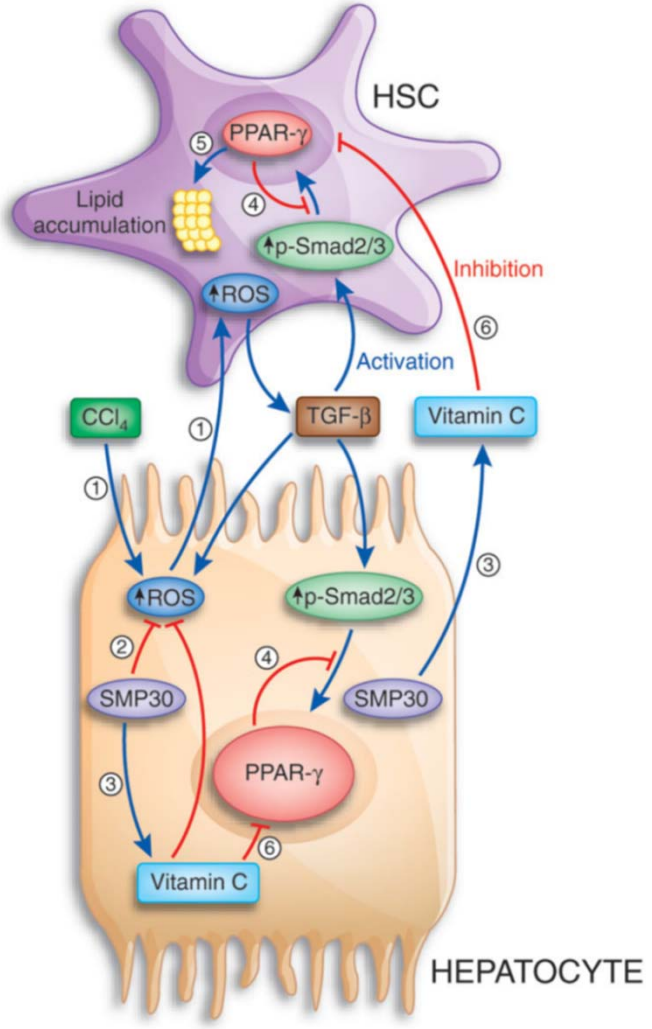


Lanifibranor associated with beneficial effects on all NASH-relevant liver features

Source: Company data; The new-generation Pan-Peroxisome Proliferator-Activated Receptor Agonist IVA337 Protects the Liver From Metabolic Disorders and Fibrosis; Hepatology Communications, June 2017

HSCs, the ultimate effectors of fibrogenesis in the liver, are regulated by PPARγ

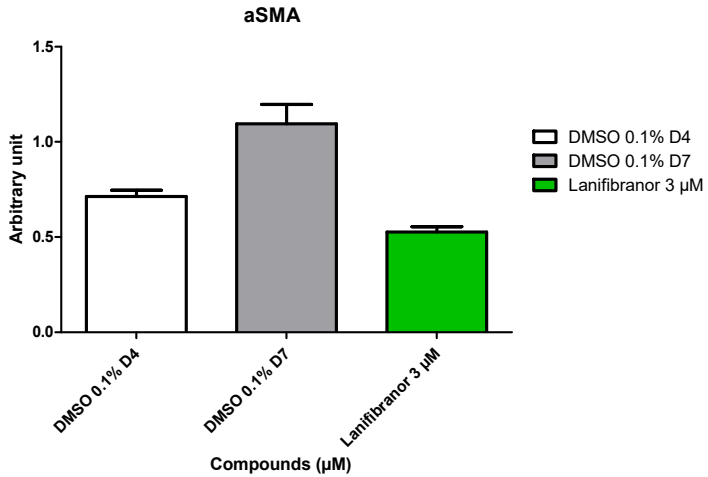
- **Large literature describing PPARγ as a key modulator of human HSC fate**
- **Activation or high expression of PPARγ maintains human HSC in a quiescent state**
- **Inhibition or decreased expression of PPARγ leads to human HSC activation (myofibroblasts)**
- **The transition from one state to another could be modulated by PPARγ alone and is reversible**
- **Some authors described that PPARγ inhibits HSC activation by reducing phosphoSMAD3** (*Park et al. hepatology 2010 and Zhao et al. Biochem Biophys Res Commun 2006*)
- **PPARα is not expressed in human HSC**



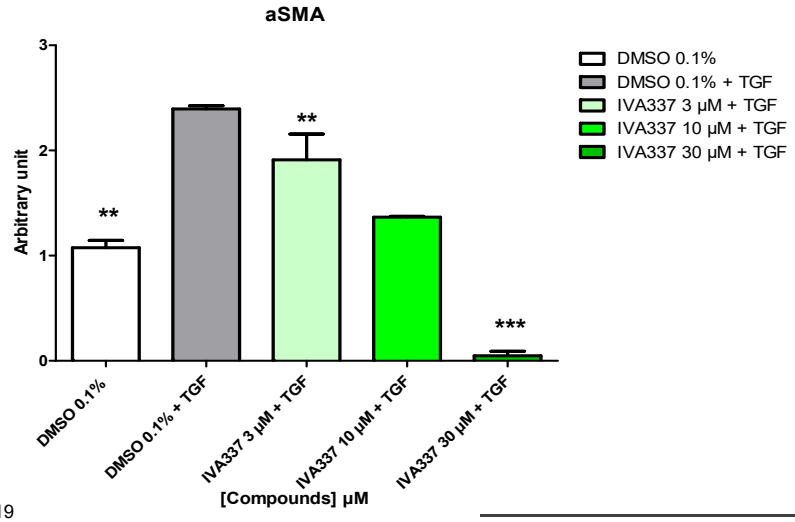
Park et al hepatology 2010

Lanifibranor significantly inhibits human HSC activation in preventive and curative settings

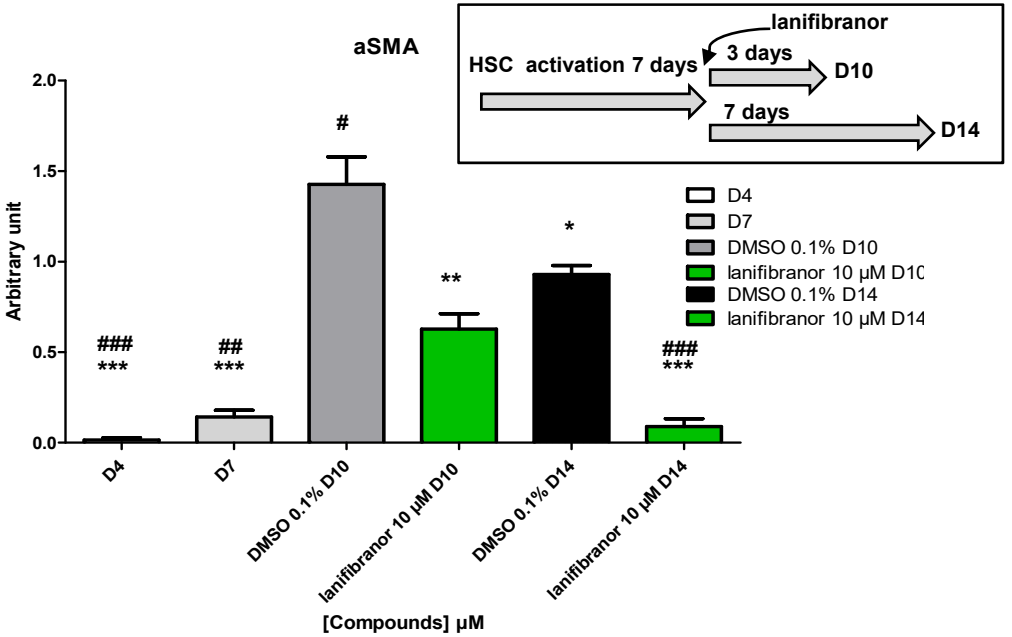
Stiffness-induced HSC activation
(7 days) concomitant



TGF-β1-induced HSC activation
(48 h) concomitant

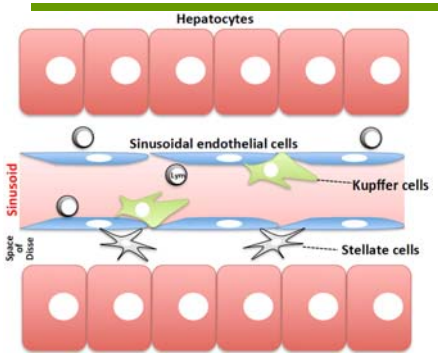


Stiffness-induced HSC activation
(7 days of stiffness + 3 or 7 days of stiffness and lanifibranor treatment) curative

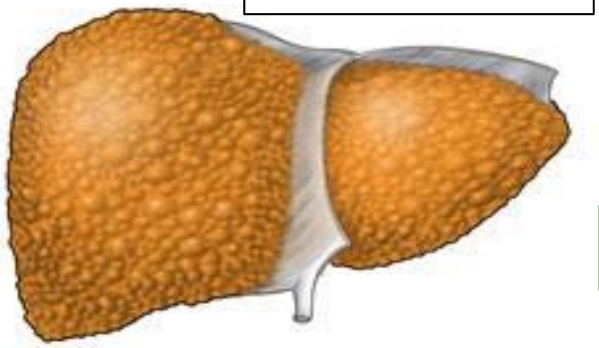


- **Lanifibranor inhibits HSC activation** (stiffness- or TGF-β1-induced) after concomitant or curative treatment
- **Fenofibrate (PPARα) has no effect** in preventing HSC activation
- **GW501516 (PPARδ) has a moderate effect** in preventing HSC activation but no effect in a curative mode
- **PPARγ agonists prevents HSC activation**

Dual PPARα and γ activation shows therapeutic efficacy in a preclinical model of chronic advanced liver disease



Liver fibrosis



Collagen deposition

PPARα/γ

Activated HSC

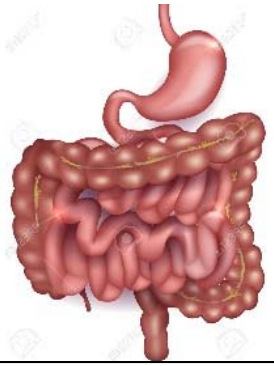
LSEC inflammation
LSEC capillarization
Endothelial dysfunction
Intrahepatic angiogenesis

HSC contractility

Portal pressure

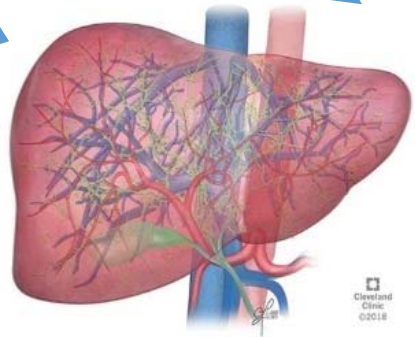
PPARα/γ

PPARα/γ



Intestinal hyperpermeability

Splanchnic inflammation and neoangiogenesis
Porto-systemic shunts

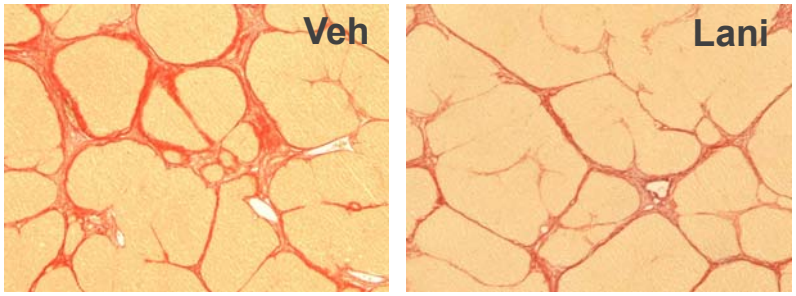


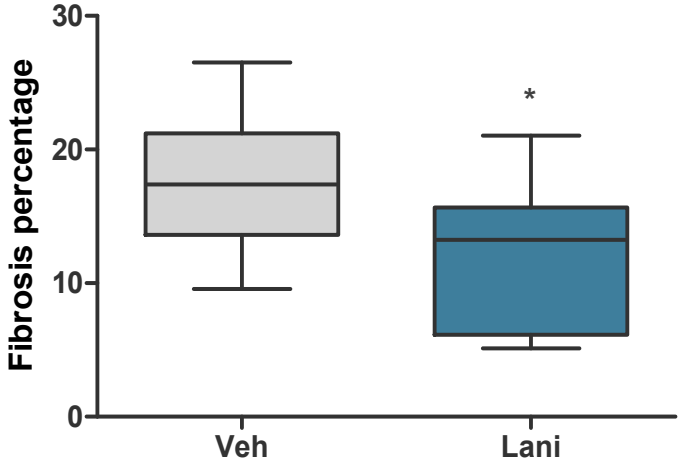
Extrahepatic complication

Intrahepatic vascular complication

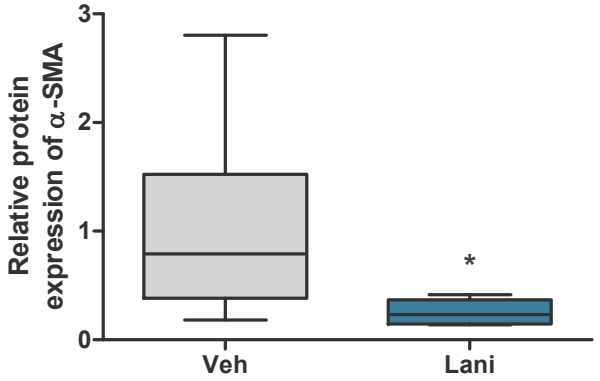
Lanifibranor significantly reverses HSC activation and liver fibrosis in a model of advanced chronic liver disease

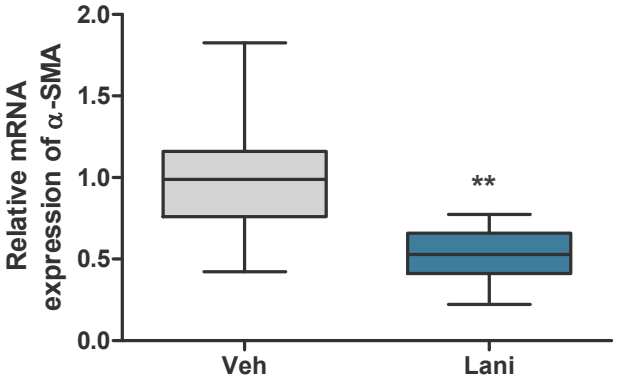
Lanifibranor reverses liver fibrosis





Lanifibranor reverses HSC activation

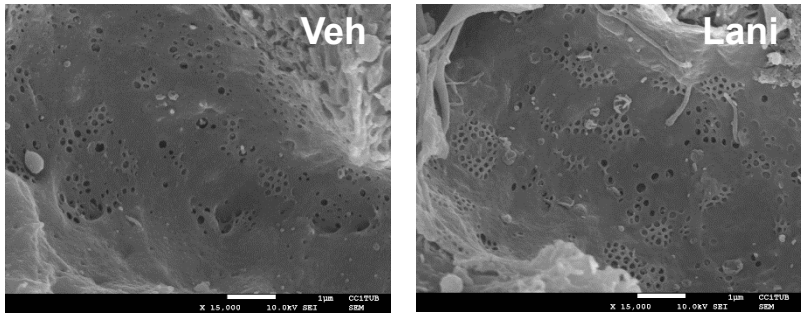


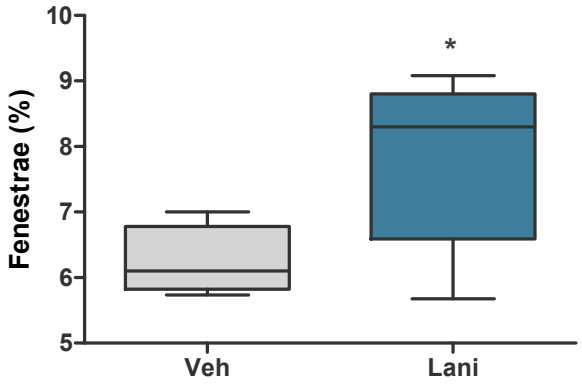


Source: "The pan-PPAR agonist lanifibranor improves portal hypertension and hepatic fibrosis in experimental advanced chronic liver disease", The Liver Meeting® 2019; **Methods.** Cirrhotic rats (due to 12-week TAA) randomly received lanifibranor (100mg/kg/day, po) or vehicle for 14 days (n=12 per group). In vivo systemic and hepatic hemodynamics (mean arterial pressure, MAP; portal pressure, PP; portal blood flow, PBF; and hepatic vascular resistance, HVR), serum AST, ascites degree (0-III), liver inflammation (IL-6 & IL-10), fibrosis (Sirius red staining, collagen I, MMPs & TIMPs), hepatic stellate cells activation (a-SMA, p-moesin and desmin) and liver sinusoidal endothelial cells de-differentiation (ICAM-1, VCAM-1, E-Sel, and sinusoidal porosity through scanning electron microscopy) were determined.

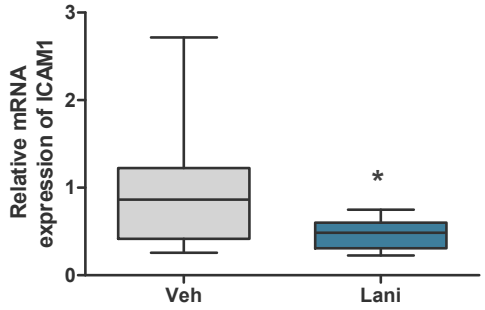
Lanifibranor significantly reverses LSEC capillarization in a model of advanced chronic liver disease

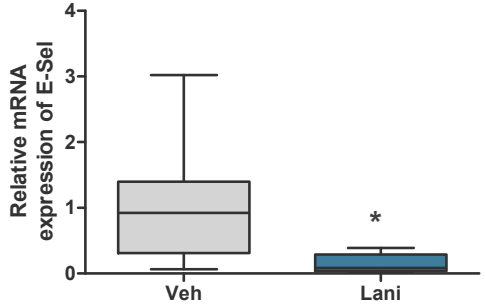
Lanifibranor increases LSEC porosity





Lanifibranor reverses LSEC inflammatory phenotype





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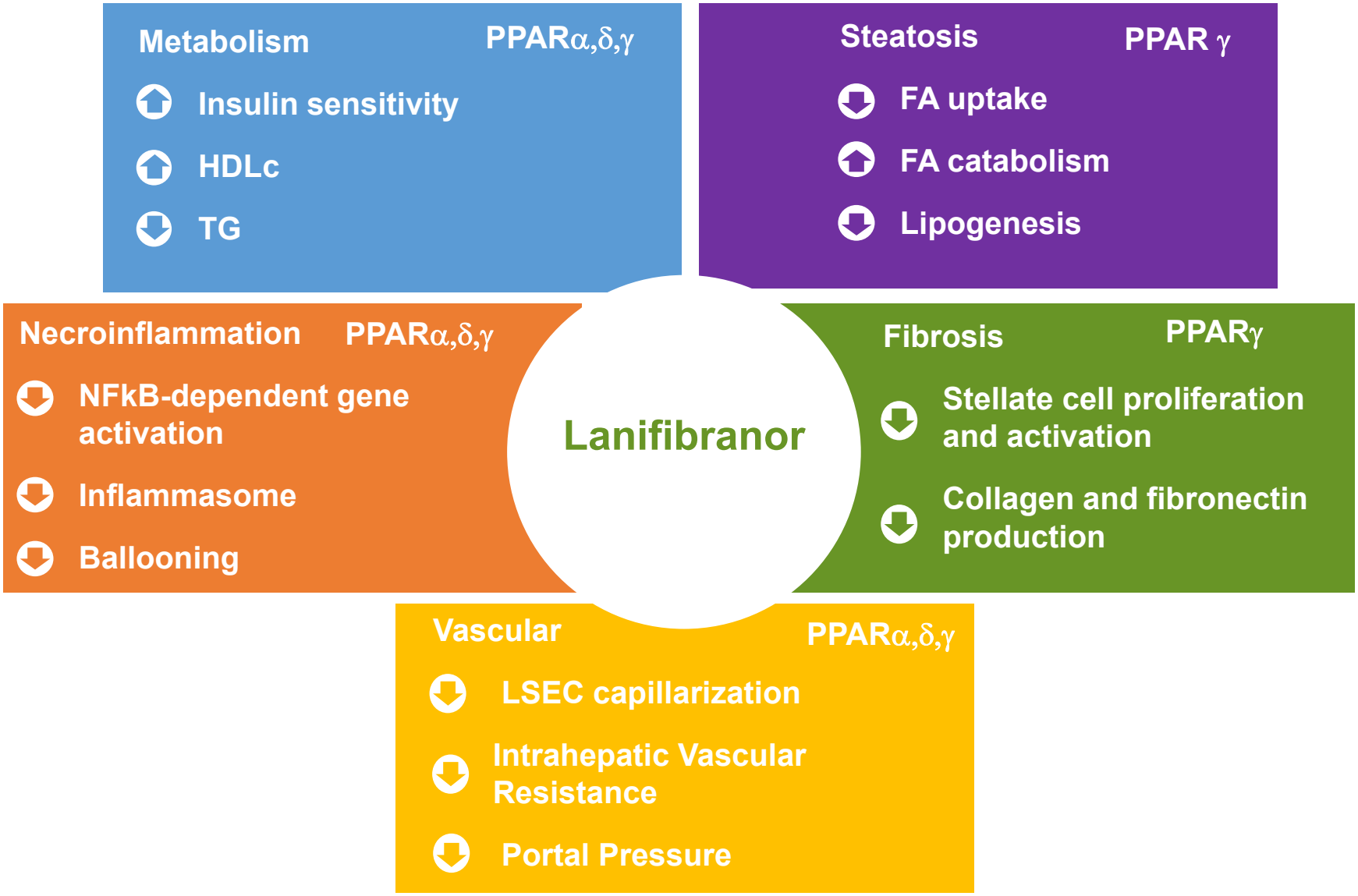
Lanifibranor significantly improves hepatic vascular resistance and portal pressure in a model of advanced chronic liver disease

	Vehicle (n=12)	Lanifibranor (n=12)	P-value
PP (mmHg)	13.1 ± 0.4	11.2 ± 0.5	P<0.01
PBF (mL/min)	19.0 ± 1.7	23.5 ± 2.1	NS (0.09)
IVR (mmHg.min/mL)	0.75 ± 0.1	0.53 ± 0.06	P<0.05
MAP (mmHg)	81 ± 3	84 ± 2	NS
AST (U/Ml)	155.8 ± 51.2	107.8 ± 15.6	P<0.01
N rats with ascites	8	2	P <0.05

Lanifibranor: a mechanism of action addressing all the key features of NASH



Lanifibranor shows a favorable safety profile

Safety package

- ☑ 6 month tox in rodents
- ☑ 6 month tox data in primates
- ☑ 12 month tox data in primates
- ☑ 2 year carcinogenicity studies in rats and mice
- ☑ 200+ healthy volunteers treated in Phase I trials
- ☑ 47 T2DM patients treated in Phase IIa study
- ☑ 97 SSc patients treated in a Phase IIb

Recently generated safety data

- ☑ **Fourth and last DSMB** for NATIVE trial in NASH recommending to continue the trial as planned based on safety data from **228 patients, including 139 patients treated for the whole study period**
- ☑ After review of carcinogenicity studies, **FDA has lifted PPAR class clinical hold and allowed long-term clinical studies in NASH with lanifibranor**

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NATIVE
NASH TRIAL TO VALIDATE IVA337 EFFICACY

Native Phase IIb study in NASH

Boston
November 2019

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NATIVE phase IIB trial in NASH

Trial design (clinicaltrials.gov identifier: NCT03008070)

Principal investigators

- Prof. Sven Francque (Antwerp University, Belgium)
- Prof. Manal Abdelmalek (Duke University, USA)

Randomisation

- 1/1/1, stratification on T2DM patients
- Study powered with 75 patients per group
- Central reading

Status

- ☑ Recruitment completed with 247 patients randomized
- ☑ 4 positive DSMB reviews recommending to continue the study without any changes

Inclusion criteria

- Liver biopsy
- Severe patients *i.e.* combined inflammation+ballooning score of 3 or 4
- Steatosis score ≥ 1 and fibrosis score < 4 (no cirrhosis)

Primary endpoint

- Decrease from baseline ≥ 2 points of the inflammation+ballooning score without worsening of fibrosis

Key secondary endpoints

- Decrease of ≥ 2 points in NAS
- Resolution of NASH (to NAFL: steatosis ± mild inflammation)
- Change in fibrosis score
- Change in liver enzymes, inflammatory markers, glucose metabolism parameters, plasma lipids parameters, adiponectin
- Safety

225 patients treated for 24 week + 4 week safety follow-up

Double blind, randomized, placebo-controlled

Screening
- Liver biopsy

Placebo, 75 patients

Lanifibranor, 800 mg once daily, 75 patients

Lanifibranor, 1200 mg once daily, 75 patients

End of treatment
- Liver biopsy

More information on: http://www.native-trial.com/

Primary efficacy end-point

Primary end point

Decrease from baseline to week 24 of at least 2 points of the combined inflammation+ballooning score without worsening of fibrosis

- Main analysis: evaluation of treatment effect 1200mg vs. placebo and 800mg vs. placebo
- Analyses by sub-groups
  - Diabetic vs. non-diabetics
  - BMI at baseline (obese vs. non-obese)
  - Metabolic syndrome at baseline
  - Biopsy length at baseline
  - Fibrosis at baseline (F0-F1, F2-F3)
- Evaluation of dose effect: 1200mg vs. 800mg
- Evaluation of country- and site-effect

Secondary end-points

Key secondary end points

- NASH improvers
  - Decrease from baseline to week 24 of ≥ 2 points of the NAS CRN score with no worsening of fibrosis
- Resolution of NASH with no worsening of fibrosis
- Improvement of fibrosis by ≥ 1 stage without worsening of NASH

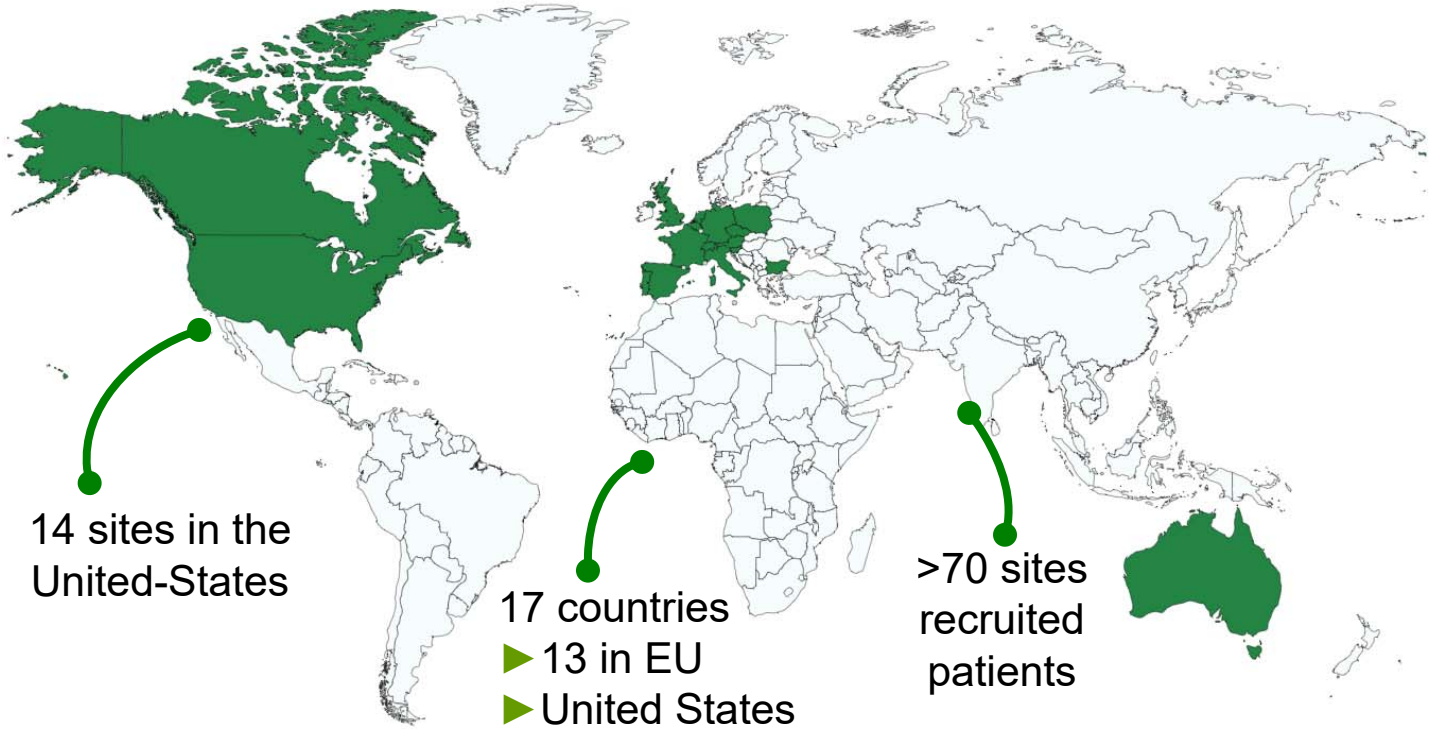
Other secondary end points

- Change in ISHAK-F: improvement / no worsening
- Change in parameters of glucose metabolism (fasting glucose, insulin, HOMA index, HbA1c…)
- Change in liver tests (ALT, AST, GGT, Alkaline Phosphatase, Total Bilirubin)
- Change in main plasma lipid parameters (TC, HDL-C, calculated LDL-C, TG…)
- Change in markers of inflammation (fibrinogen, hs-CRP, alpha2 macroglobulin, haptoglobin…)
- Change in fibrosis markers (TIMP-1, TIMP-2, Hyaluronic acid, P3NP, NFS, FIB-4 score, ELF score, Pro-C3…)
- Change in other relevant biochemistry markers (Plasma Iron, Transferrin, Ferritin)
- Change in adiponectin

NATIVE trial in NASH patients fully recruited

NATIVE
NASH TRIAL TO VALIDATE IVA337 EFFICACY

247 patients randomized, exceeding the initial target of 225 patients



Country	Patients randomized
Europe	183 (74%)
US	36 (15%)
Australia	13 (5%)
Canada	8 (3%)
Mauritius	7 (3%)
Total	247 (100%)

- **Patients with moderate/severe NASH recruited**: ~72% with NAS ≥ 6 and ~76% F2 or F3
- **~40% have type 2 diabetes** allowing to conduct the planned sub-analyses
- **167 patients(1) had already completed the six-month study** confirming that the treatment is well tolerated
- **Results expected first-half 2020**

(1) Database extraction October 8

NATIVE trial: baseline characteristics

Parameters		Patients without diabetes (N = 148 ; 60%)	Patients with diabetes (N = 99 ; 40%)	Total (N = 247 ; 100%)
Gender	Female	57%	60%	58%
	Male	43%	40%	42%
Age	Mean ± SD	51.8 ± 13.5	56.3 ± 10.4	53.6 ± 12.5
	Median	54.0	57.0	55.0
	Min ; Max	20 ; 76	28 ; 77	20 ; 77
Weight (kg)	Mean ± SD	93.5 ± 19.0	92.8 ± 18.8	93.2 ± 18.9
	Median	91.0	90.0	91.0
	Min ; Max	51 ; 142	55 ; 145	51 ; 145
BMI (kg/m²)	Mean ± SD	32.8 ± 5.5	33.0 ± 5.3	32.9 ± 5.4
	Median	32.2	32.9	32.4
	Min ; Max	21 ; 45	23 ; 44	21 ; 45
Male waist circumference (cm)	Mean ± SD	109.6 ± 12.6	112.2 ± 12.2	110.6 ± 12.4
	Median	108.0	110.0	110.0
	Min ; Max	88 ; 134	89 ; 142	88 ; 142
Female waist circumference (cm)	Mean ± SD	104.8 ± 13.5	105.7 ± 12.0	105.2 ± 12.9
	Median	106.0	106.0	106.0
	Min ; Max	76 ; 139	75 ; 138	75 ; 139
Fibrosis Score (%)	F0 – F1	27%	20%	24%
	F2	44%	36%	41%
	F3	29%	43%	35%

NATIVE trial: lanifibranor is well tolerated and safe as confirmed by 4 positive DSMB meetings

Parameters	DSMB # 1	DSMB # 2	DSMB # 3	DSMB # 4
Date of DSMB meeting	June 2018	October 2018	March 2019	September 2019
# patients reviewed / % of total patients treated	52 / 21%	94 / 38%	156 / 63%	227 / 92%
# patients having finished the study / % of total patients treated	18 / 7%	36 / 15%	86 / 35%	139 / 57%
DSMB conclusion: continue study as planned	✓	✓	✓	✓

Lanifibranor Development in NASH

Dr. Ken Cusi Slides

November 9, 2019

IVA
LISTED
EURONEXT

Treatment of NASH: Role of PPARs

1. The diagnosis gap:

- **ADA's 2019 "call to action":** NAFLD as a public health problem
- **Looking back:** Analogies to diabetic nephropathy

2. Treatment of NAFLD:

- **Current landscape:**
  - Vitamin E, GLP-1RA? and pioglitazone
- **The future:**
  - Brief overview of novel agents
  - **PPARs:** Targeting NASH + "cardiometabolic" risk (T2DM, CVD)

T2DM, type 2 diaberes mellitus; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist.

RR89
MOU6

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2019*

Diabetes Care 2019;42(Suppl. 1):S34–S45 | https://doi.org/10.2337/dc19-S004

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(page S40)

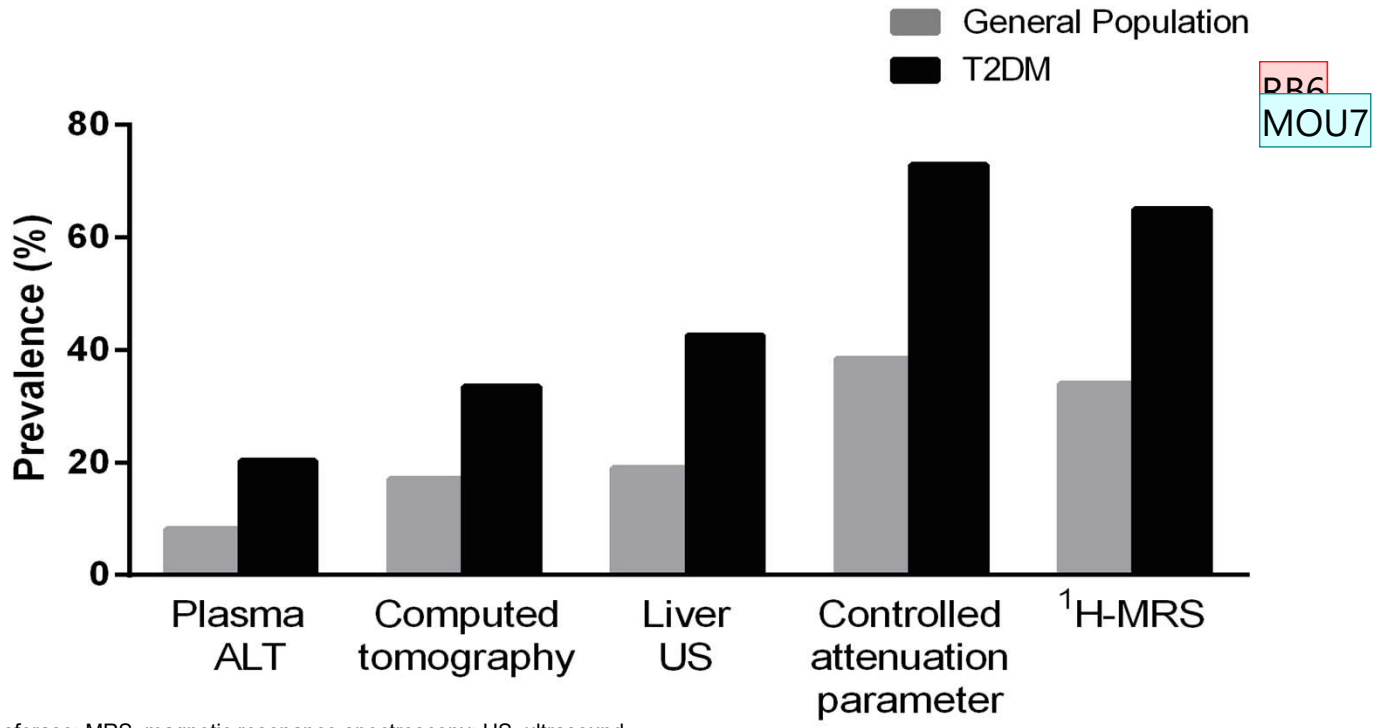
Recommendation

4.14 Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

ADA. *Diabetes Care* 2019;42 (Suppl 1):S34–45

Management of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Call to Action

Diabetes Care 2017;40:419–430 | DOI: 10.2337/dc16-1787



ALT, alanine aminotransferase; MRS, magnetic resonance spectroscopy; US, ultrasound.

Bril and Cusi. *Diabetes Care* 2017;40:419–30

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NASH: A "new" public health problem

	DM nephropathy in the 80's	Osteoporosis in the 90's	NASH in 2019
Long natural history	Yes	Yes	Yes
High prevalence?	Yes	Yes	Yes
Major cause of morbidity?	Yes	Yes	Cirrhosis, HCC, CVD
Increased mortality?	Yes	Yes	Yes
Diagnosis	Microalbuminuria	BMD	No great test yet
Any treatments?	Not initially, but yes today	Not initially, but yes today	None FDA-approved RB90 Weight loss, vitamin E MOU9 pioglitazone, GLP-1RA

BMD, bone mineral density; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HCC, hepatocellular carcinoma.

(Cusi, 2019 - unpublished)

Treatment of NAFLD: A Call to Action

1. The diagnosis gap:

- **ADA 2019:** a call to action: NAFLD as a public health problem
- **Looking back:** Analogies to diabetic nephropathy

2. Treatment of NAFLD:

- Current landscape:
  - Vitamin E, GLP-1RA? and pioglitazone

CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist.

The Diagnosis and Management of NAFLD:

Practice Guidance From the American Association for the Study of Liver Diseases (AASLD) 2018

Guidance statements – Weight Loss and Exercise

- **Weight loss (#21):** 3%-5% needed to improve steatosis, but 7%-10% minimal need to improve the majority of the histopathological features of NASH, including fibrosis.

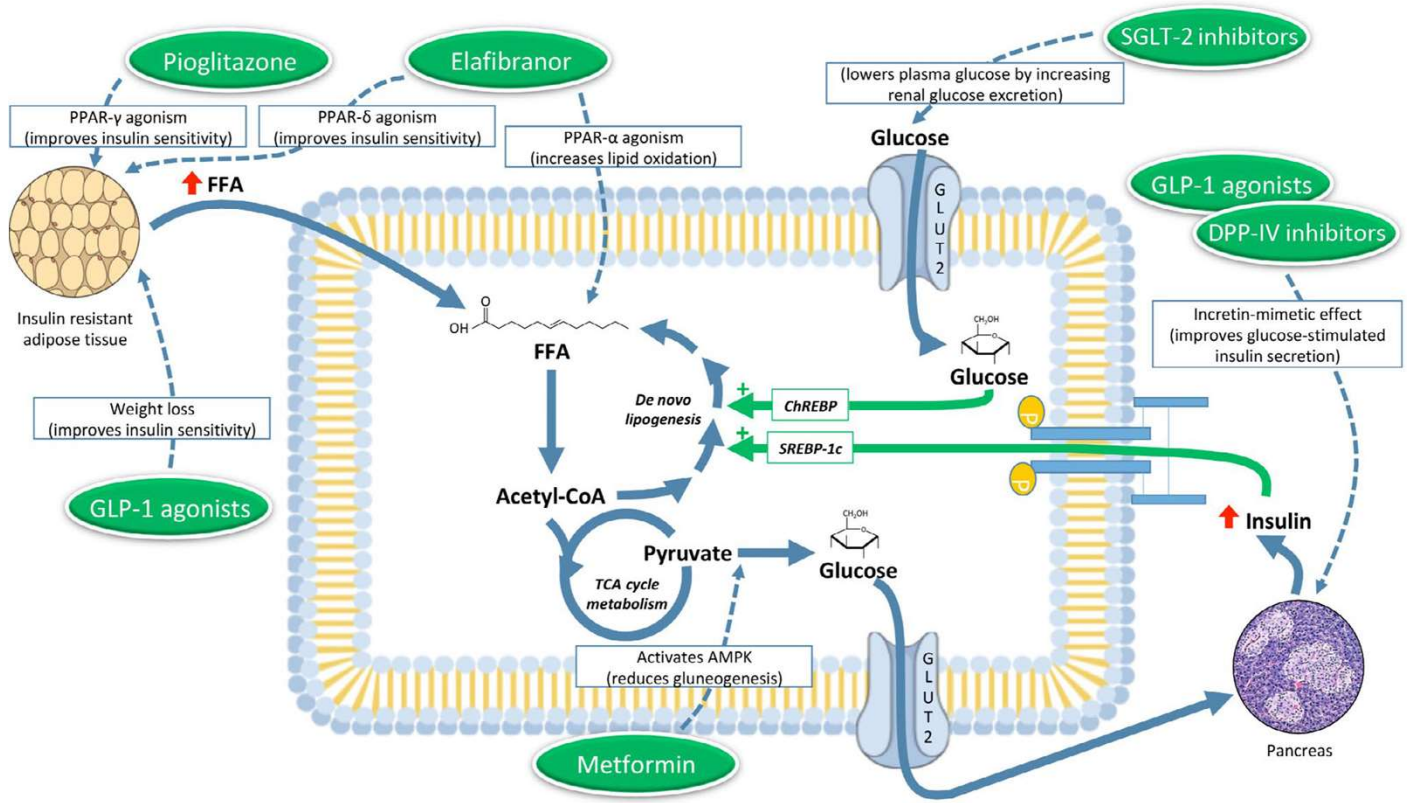
- **Exercise (#22):** Exercise alone may prevent or reduce steatosis, but its ability to improve other aspects of liver histology remains unknown

- **Bariatric surgery (#29-31):**
  - Can be considered in otherwise eligible obese individuals with NAFLD or NASH
  - Premature to consider bariatric surgery as an established option to treat NASH
  - The type, safety, and efficacy of bariatric surgery are not established in obese individuals with cirrhosis from NAFLD
  - In patients with compensated NASH or cryptogenic cirrhosis, bariatric surgery may be considered on a case-by-case basis

CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Chalasani et al, Hepatology 2018;67:328–57

Potential Targets of Agents that Reduce Insulin Resistance



(page S40)

Khan, Bril, Cusi, Newsome. *Hepatology 2019*

Effect of Liraglutide in Patients with T2DM

Table 2. Effect of liraglutide in NAFLD

Author †	n	Duration (weeks)	Comparator	Main study results: Weight	ALT	Liver fat
Open label studies						
Ohki et al, Sci World J 2012	82	74	Sitagliptin, pioglitazone	↓	↓	n/a
Eguchi, Hepatol Res 2015	19	24	Lifestyle	↓	↓	↓*
Tang et al, 2015	35	12	Insulin	↓	unchanged	unchanged
Feng et al, 2017	87	24	Gliclazide, metformin	↓	↓	↓**
Bouchi et al, 2017§	17	24	Insulin alone	↓	↓	↓
Petit et al, 2017	68	24	Insulin alone	↓	↓	↓
Matikainen et al, 2018	22	16	Lifestyle	↓	not reported	↓
RCTs						
Smits et al, 2016	18	12	Sitagliptin or placebo	unchanged	unchanged	unchanged
Armstrong et al, 2016	52	48	placebo	↓	↓	↓***
Vanderheiden et al, 2016 §	71	24	Insulin alone	↓	↓	↓
Frossing et al, 2018	72	26	placebo	↓	↓	↓

Statistically significant changes vs. comparison(s) indicated by arrows

*10 of 19 had a repeat liver biopsy; NAS score improved in 6. ** Reduced more vs gliclazide but not metformin. *** Improvement on histology (NAS score) greater with liraglutide on paired liver biopsies. §Liraglutide plus insulin vs insulin alone.

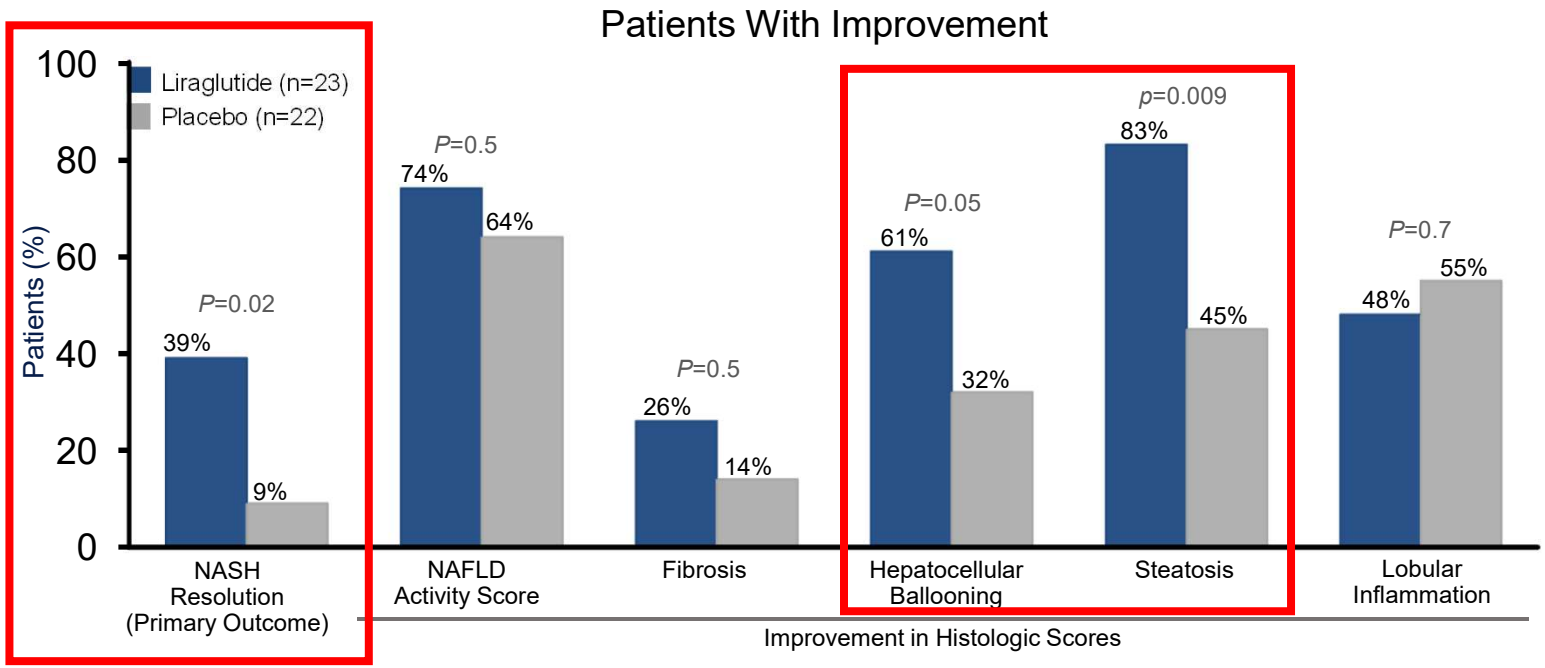
Cusi. *Hepatology* 2019;69:2318–22

Liraglutide is not approved for treatment of NAFLD or NASH. .

RR31

MOU19

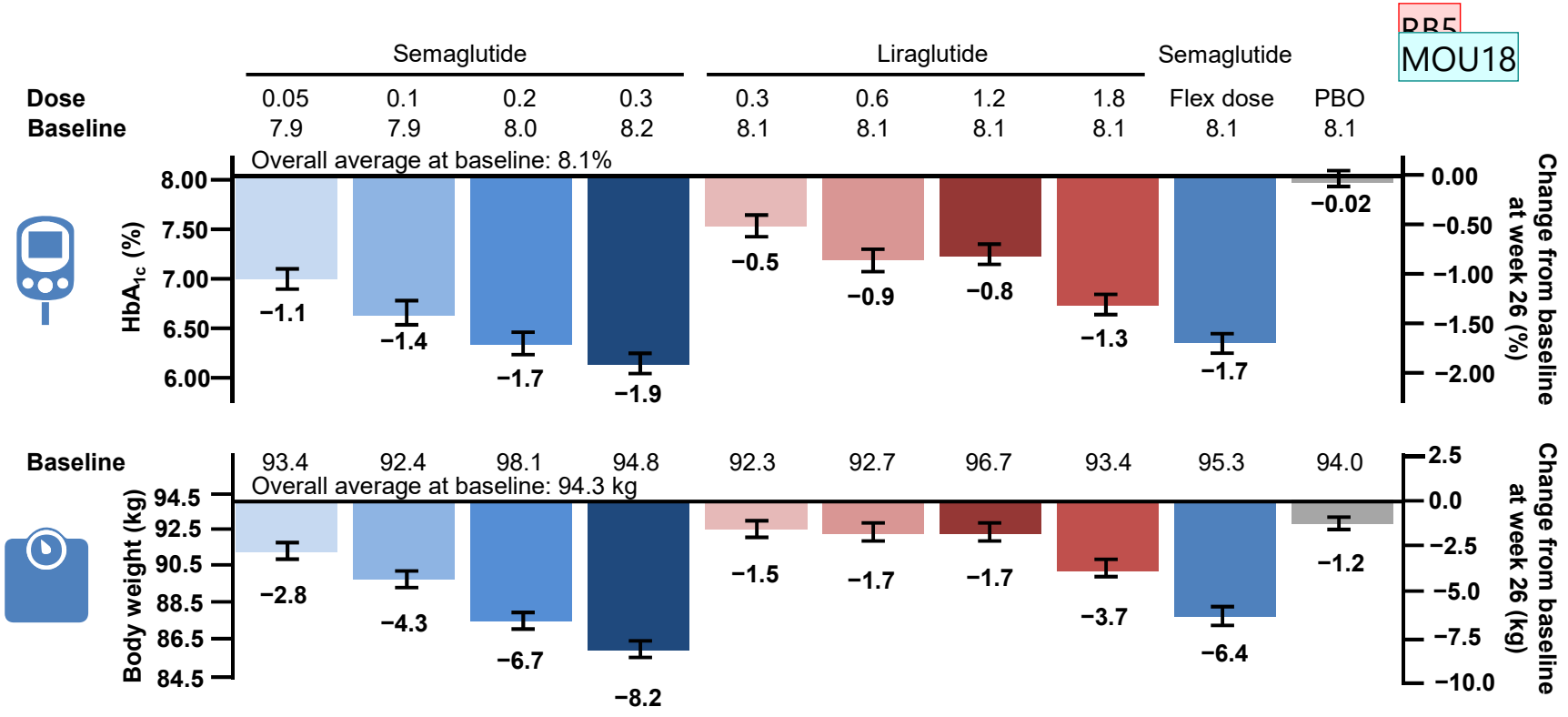
LEAN Study: Changes in Histologic Features at Week 48



LEAN: Liraglutide Efficacy and Action in NASH.

Armstrong et al. *Lancet* 2016;387:679–690

Semaglutide vs. Liraglutide



PBO, placebo.

Lingay et al, *Diabetes Care* 2018;41:1926–37

Treatment of NAFLD: A Call to Action

1. The diagnosis gap:

   - **ADA 2019:** a call to action: NAFLD as a public health problem
   - **Looking back:** Analogies to diabetic nephropathy

2. Treatment of NAFLD:

   - Current landscape:
     - Limited: Vitamin E, GLP-1RA? and pioglitazone
   - The future:
     - New agents: which? Which combination therapy?

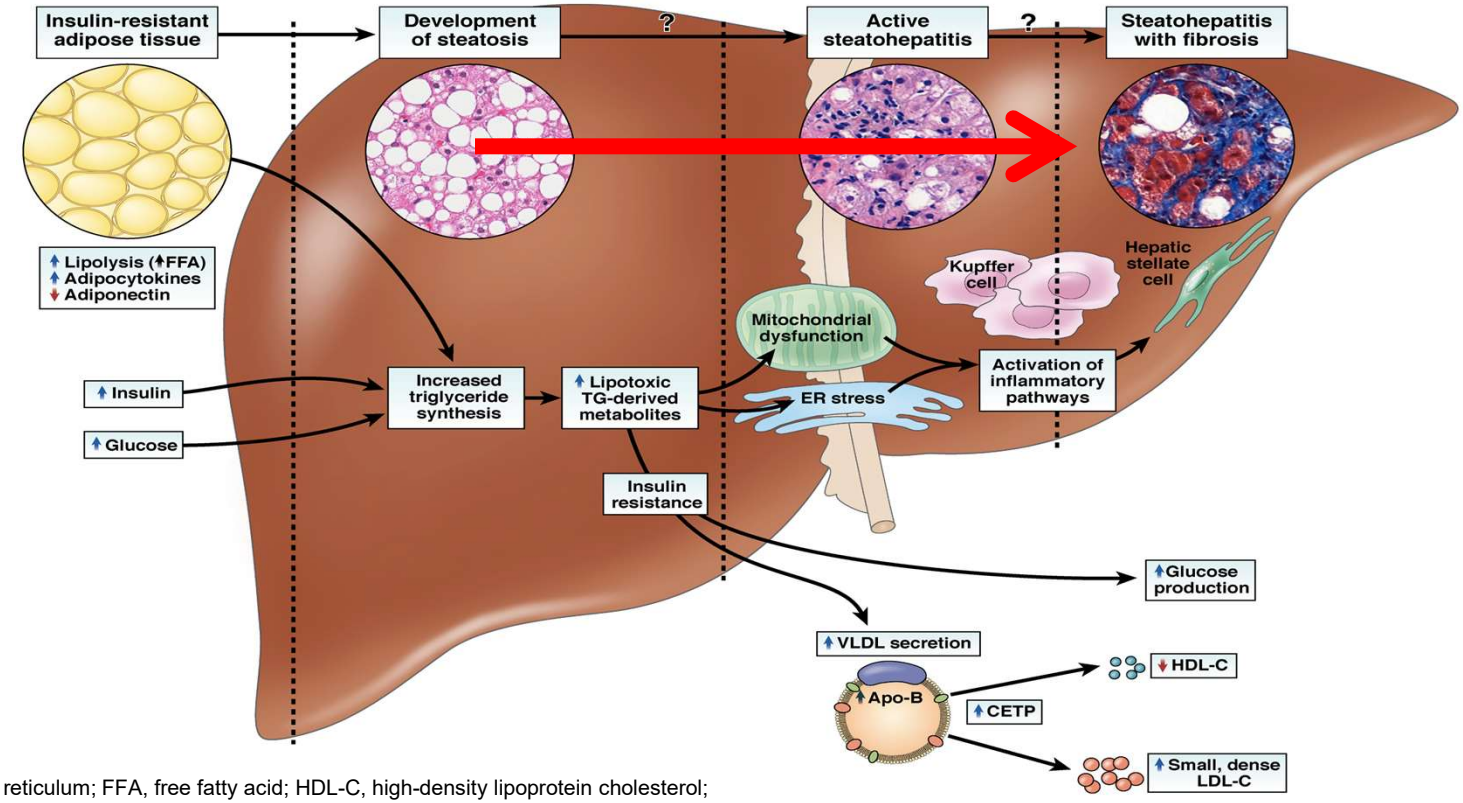
CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist.

NASH agents in clinical development

Elafibranor	Lipotoxicity/ oxidative stress (PPARα/δ agonist)	GOLDEN-505 (n=276, fibrosis stage 0–3) • Reversal of NASH without worsening of fibrosis
Cenicriviroc	Inflammation/ immune activation (CCR2/5 antagonist)	CENTAUR (n=289, fibrosis stage 1–3) • Improvement in NAS by ≥2 points and ≥1-point decrease in lobular inflammation or hepatocellular ballooning without worsening of fibrosis at Year 1
Selonsertib	Apoptosis/necrosis (ASK1 inhibitor)	STELLAR-4 (n=883, compensated cirrhosis) • Fibrosis improvement ≥1 stage without NASH worsening • Event-free survival STELLAR-3 (n=808, fibrosis stage 3) • Fibrosis improvement ≥1 stage without NASH worsening • Event-free survival
Pegbelfermin	Metabolic (rFGF21)	Phase 2 study (n=74, fibrosis stage 1–3) • Change in hepatic fat fraction
Resmetirom (MGL-3196)	Lipotoxicity (TRß agonist)	Phase 2 study (n=125, fibrosis stage 1–3) • NASH resolution without worsening of fibrosis
Obeticholic acid	Lipotoxicity/oxidative stress (FXR agonist)	REGENERATE (n=2370, fibrosis stage 1–3) • Fibrosis improvement ≥1 stage without NASH worsening FLINT (n=283, fibrosis stage 0–3) • Decrease in NAS of ≥2 without worsening of fibrosis from baseline
VK2809	TRß agonist	Phase 2 study (n=59) • Change in LDL-C
GS-0976	Acetyl coenzyme A carboxylase inhibitor	Phase 2 study (n=127) • Percentage of participants experiencing treatment-emergent adverse events
IONIS-DGAT2Rx	Antisense drug	Phase 2 study (n=44) • Incidence and severity of adverse events related to treatment with IONIS-DGATRx2 • Absolute change in liver fat percentage

ASK, apoptosis signal-regulating kinase; CCR, CC chemokine receptor; PPAR, peroxisome proliferator-activated receptor; FXR, farnesoid X receptor; TR, thyroid hormone.
ClinicalTrials.gov NCT01694849; ClinicalTrials.gov NCT02217475; ClinicalTrials.gov NCT03053050; ClinicalTrials.gov NCT03053063; ClinicalTrials.gov NCT02413372; ClinicalTrials.gov NCT02912260; ClinicalTrials.gov NCT02548351; ClinicalTrials.gov NCT01265498; ClinicalTrials.gov NCT01265498, NCT02784444; ClinicalTrials.gov, NCT02462967; ClinicalTrials.gov, NCT02279524.

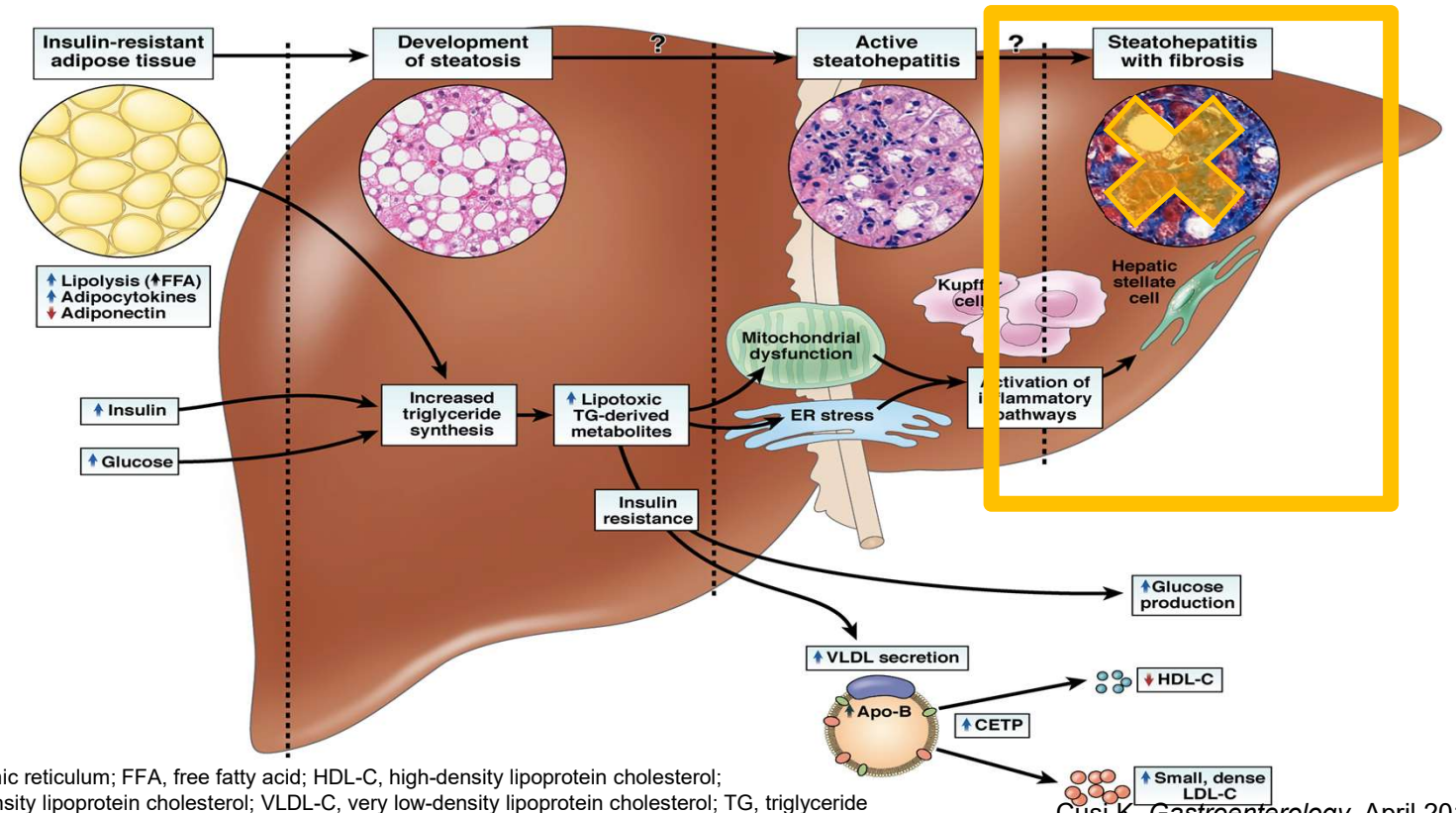
From Obesity to Lipotoxicity (NASH)



ER, endoplasmic reticulum; FFA, free fatty acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; TG, triglyceride

Cusi K, *Gastroenterology*, April 2012, 142:711-725

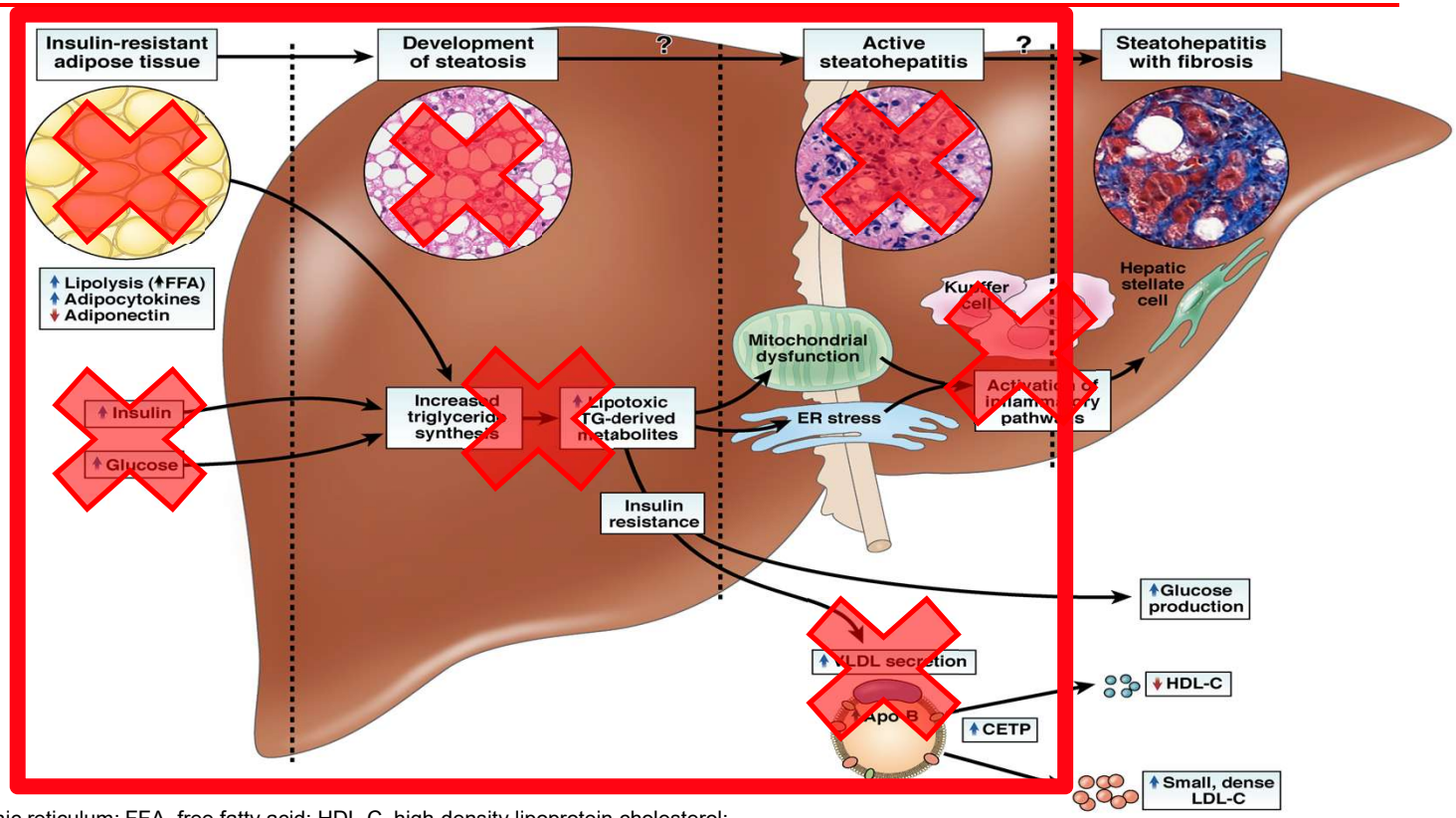
Downstream approach to NASH: The "Antifibrotic Approach"



ER, endoplasmic reticulum; FFA, free fatty acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; TG, triglyceride

Cusi K, *Gastroenterology*, April 2012, 142:711-725

Upstream approach to NASH: The “Insulin-Sensitizer Approach”



ER, endoplasmic reticulum; FFA, free fatty acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; TG, triglyceride

Cusi K, *Gastroenterology*, April 2012, 142:711-725

Treatment of NASH: Role of PPARs

UF UNIVERSITY of FLORIDA College of Medicine

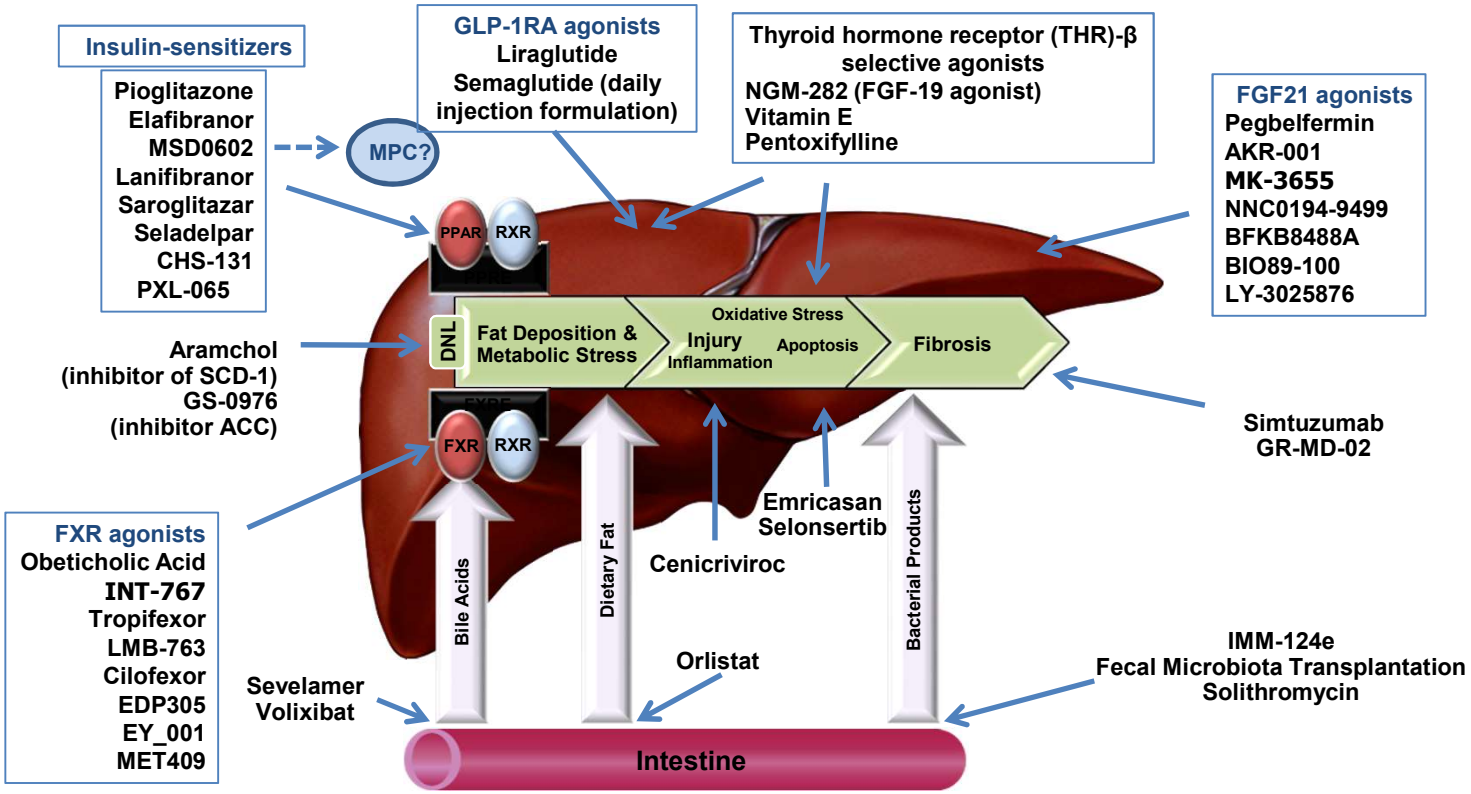
1. What is the role of the diabetologist?

   - A call to action: NAFLD as a public health problem
   - Looking back: Analogies to diabetic nephropathy or osteoporosis

2. Treatment of NAFLD:

   - Current options:
     - Weight loss, vitamin E, GLP-1RA and pioglitazone
   - The future:
     - New agents? Combination therapy?

Current and Potential Therapeutic Targets in NASH



ACC, acetyl-CoA carboxylase; DNL, *de novo* lipogenesis.

Adapted from Rotman et al. *Gut.* 2017;66:180–190

FXR Agents under Development

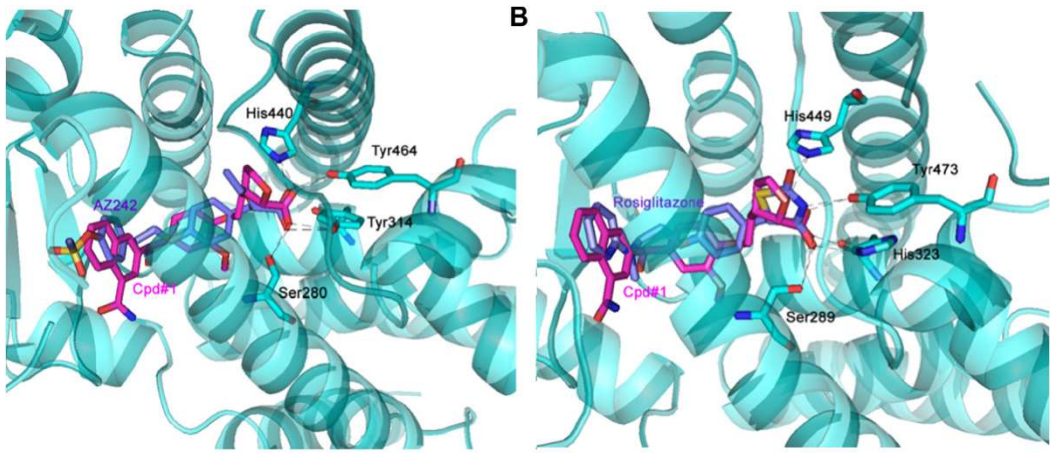
Company	Compound	Development phase	Dosing frequency	Current patient type	Notes
Intercept	OCA	Phase 3	QD	F2–F3 (+ high-risk F1); F4	Bile acid derivative
Novartis	Tropifexor	Phase 2b, 48-week recruiting	QD	F2–F3	Non-bile acid
Gilead	Cilofexor	Phase 2, 48-week recruiting	QD	F3–F4	Non-bile acid, gut targeted
Novartis	LMB-763	Phase 2, 12-week recruiting	QD	F1–F4c	Non-bile acid
Enanta	EDP-305	Phase 2, 12-week	QD	F1–F3	Bile acid isostere
Enyo	EYP001	Phase 2a, 12-week	QD	F2–F3	Non-bile acid
Intercept	INT-767	Phase 1	n.a.	n.a.	Bile acid derivative, dual FXR/TGR5
Metacrine	MET409	Phase 1	n.a.	n.a.	Non-bile acid

OCA, obeticholic acid; QD, once-daily.

FGF21 Agents under Development

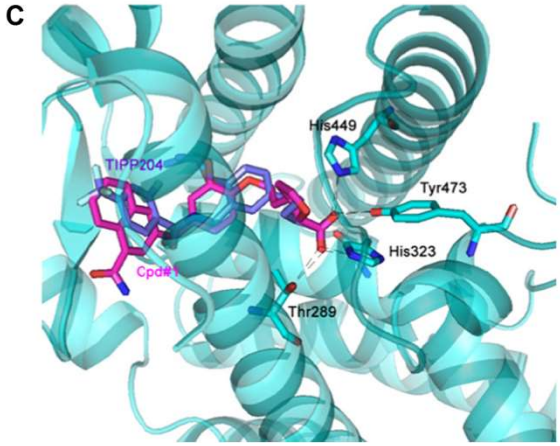
Name	Company	Description	Focus	Status
Pegbelfermin	BMS	PEG-FGF21	NASH	Ph2b
AKR-001 (AMG876)	Akero (formerly Amgen)	Fc-FGF21 fusion	NASH	Ph2 planned (Ph1 data in T2DM)
MK-3655 (NGM313)	NGM Bio / Merck	KLB / FGFR1c agonist mAb	NASH	Ph2 planned
NNC0194-9499	Novo Nordisk	FGF21 analog	Obesity	Ph1 (PCD Apr 2019)
BFKB8488A/ RG7992	Genentech	KLB / FGFR1c agonist mAb	T2DM	Ph1 (PCD June 2019)
BIO89-100/ TEV47948	89Bio	GlycoPEG-FGF21	NASH	Ph1 underway
LY-3025876	Lilly	Engineered FGF21 variant	T2DM	Ph1 completed 2014

PPARα

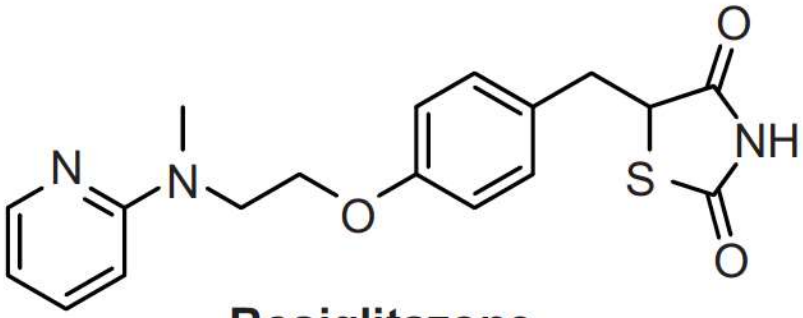


PPARγ

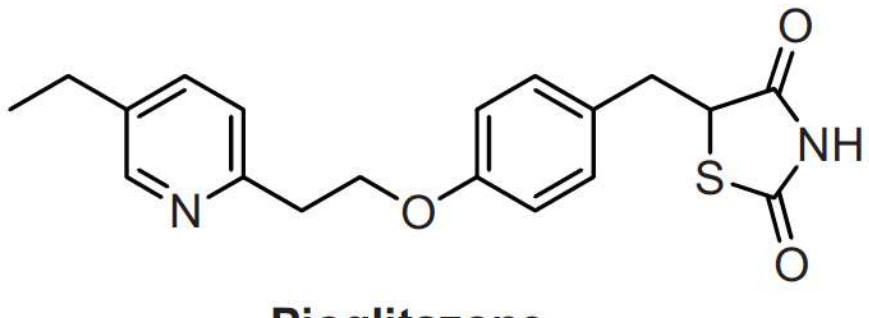
PPARδ



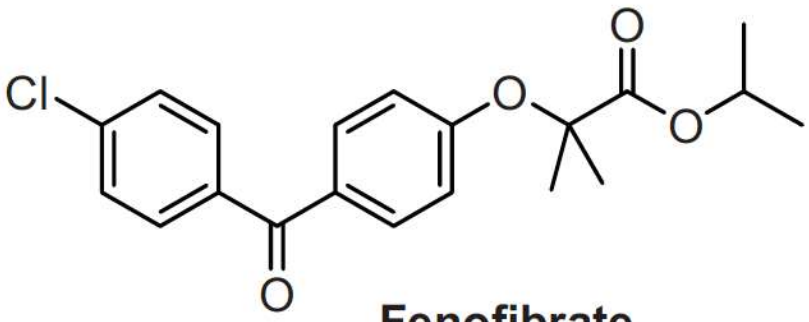
Wang et al, Drug Design, Development and Therapy 2014:8 2255–2262



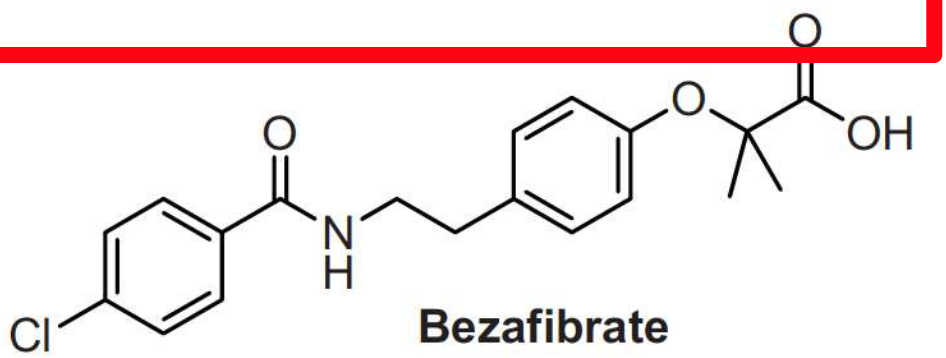
Rosiglitazone



Pioglitazone



Fenofibrate



Bezafibrate

Wang et al, Drug Design, Development and Therapy 2014:8 2255–2262

The NEW ENGLAND JOURNAL of MEDICINE
NEJM 2006, 355, 2297-2307

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Pioglitazo
in Subjects with Nonalcoholic Steatohepa

The NEW ENGLAND JOURNAL of MEDICINE
NEJM 2010;362:1675–1685

ORIGINAL ARTICLE

tazone, Vitamin E, or Placebo
Nonalcoholic Steatohepatitis

M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D.,
, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D.,
euschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D.,
Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S.,
e Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D.,
E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D.,
ricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

Annals of Internal Medicine

ORIGINAL RESEARCH

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus

A Randomized, Controlled Trial

Kenneth Cusi, MD; Beverly Orsak, RN; Fernando Bril, MD; Romina Lomonaco, MD; Joan Hecht, RN; Carolina Ortiz-Lopez, MD; Fermin Tio, MD; Jean Hardies, PhD; Celia Darland, RD; Nicolas Musi, MD; Amy Webb, MD; and Paola Portillo-Sanchez, MD

Background: The metabolic defects of nonalcoholic steatohepatitis (NASH) and prediabetes or type 2 diabetes mellitus (T2DM) seem to be specifically targeted by pioglitazone. However, information about its long-term use in this population is limited.

Objective: To determine the efficacy and safety of long-term pioglitazone treatment in patients with NASH and prediabetes or T2DM.

Design: Randomized, double-blind, placebo-controlled trial. (ClinicalTrials.gov: NCT00994

Setting: University hospital.

Participants: Patients (n = 10
biopsy-proven NASH were re
tion and outpatient clinics.

Intervention: All patients we
(500-kcal/d deficit from weig
then randomly assigned to pio
18 months, followed by an
pioglitazone treatment.

Measurements: The primary
least 2 points in the nonalcoho
(NAS) (in 2 histologic categor
Secondary outcomes include
patic triglyceride content mea
proton spectroscopy, and me

Results: Among patients randomly assigned to pioglitazone, 58% achieved the primary outcome (treatment difference, 41 percentage points [95% CI, 23 to 59 percentage points]) and 51% had resolution of NASH (treatment difference, 32 percentage points [CI, 13 to 51 percentage points]) ($P < 0.001$ for each). Pioglitazone treatment also was associated with improvement in individual histologic scores, including the fibrosis score (treatment difference, −0.5 [CI, −0.9 to 0.0]; $P = 0.039$); reduced hepatic triglyceride content from 19% to 7% (treatment difference, −7 percentage points [CI, −10 to −4 percentage points]; $P <$

Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes: A Randomized Controlled Trial

Fernando Bril,[1] Diane M. Biernacki,[1] Srilaxmi Kalavalapalli,[1] Romina Lomonaco,[1] Sreevidya K. Subbarayan,[1] Jinping Lai,[2] Fermin Tio,[3] Amitabh Suman,[4] Beverly K. Orsak,[5] Joan Hecht,[6] and Kenneth Cusi[1,7]

Diabetes Care 2019;42:1–8 | https://doi.org/10.2337/dc19-0167

RB36
MOU27

Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes: A Randomized Controlled Trial

Fernando Bril,[1] Diane M. Biernacki,[1] Srilaxmi Kalavalapalli,[1] Romina Lomonaco,[1] Sreevidya K. Subbarayan,[1] Jinping Lai,[2] Fermin Tio,[3] Amitabh Suman,[4] Beverly K. Orsak,[5] Joan Hecht,[6] and Kenneth Cusi[1,7]

Diabetes Care 2019;42:1–8 | https://doi.org/10.2337/dc19-0167

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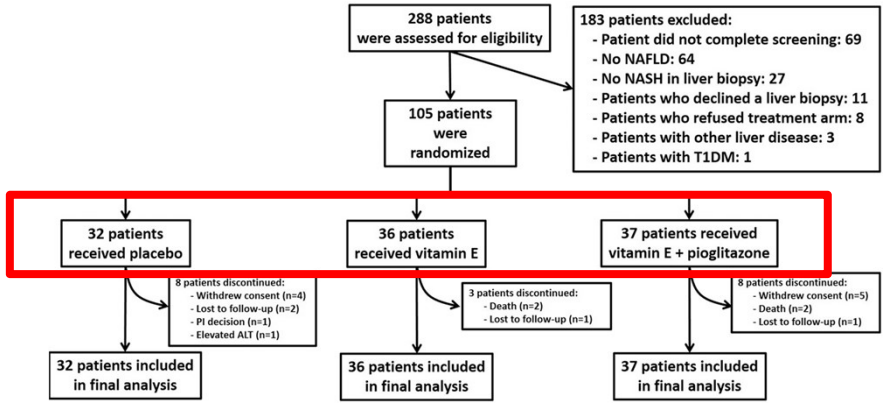


Table 2—Primary and secondary histological outcomes

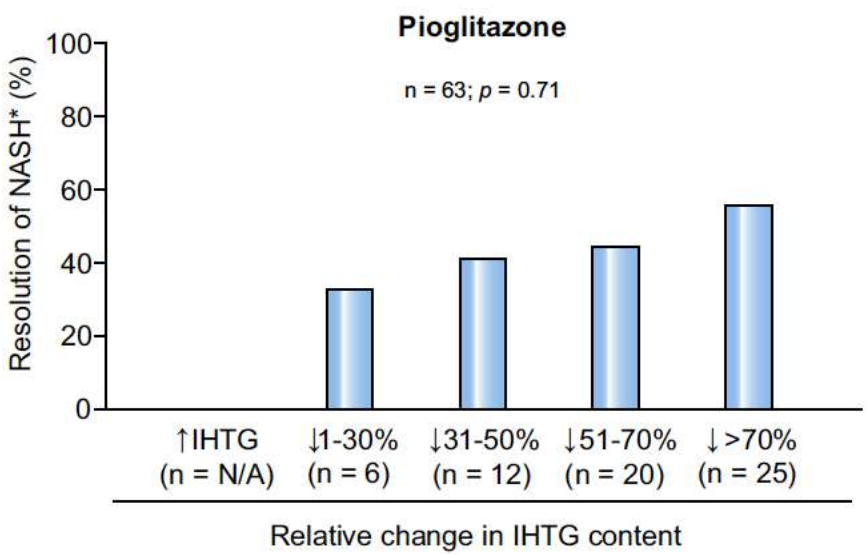
	Placebo (n = 32)	Vitamin E (n = 36)	P value vs. placebo	Vitamin E + pioglitazone (n = 37)	P value vs. placebo
Primary outcome: reduction of ≥2 points in NAS (from two different parameters), without worsening of fibrosis					
Prespecified analysis (noncompleters considered as failures)	6 (19)	11 (31)	0.26	20 (54)	0.003
Multiple imputation of missing data	7 (22)	13 (36)	0.18	24 (65)	<0.001
Resolution of NASH without worsening of fibrosis					
Prespecified analysis (noncompleters considered as failures)	4 (12)	12 (33)	0.04	16 (43)	0.005
Multiple imputation of missing data	5 (17)	14 (40)	0.04	20 (54)	0.002

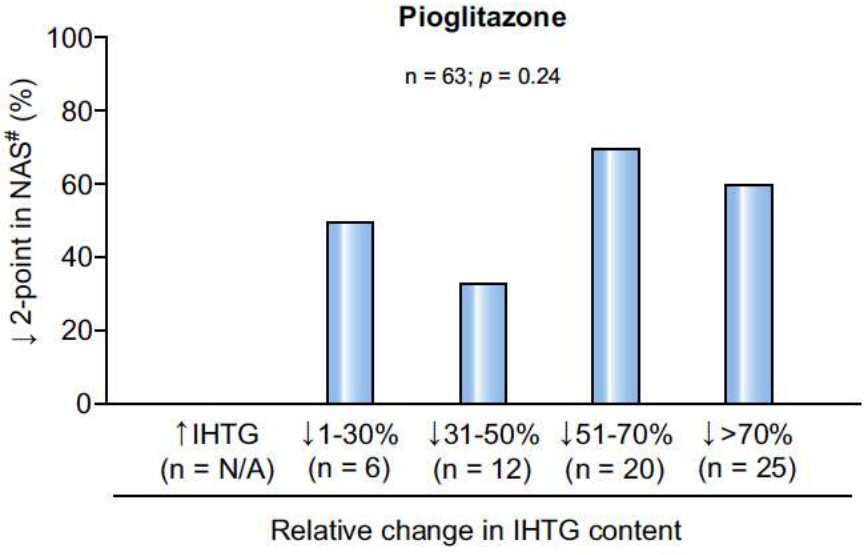
Name	Target	Major Clinical Effects	Effects in NASH	Cardiovascular
Pioglitazone	PPARγ/α – MPC	Glucose/lipids, inflammation	++++	+++*
Rosiglitazone	PPARγ	Glucose/HDL-C, inflammation	+ (steatosis)	- **
Elafibranor	PPARα/δ	Glucose/lipids, inflammation	Phase 2/3	+?
MSD0609	PPARγ – MPC	Glucose/lipids	Phase 2	?
Lanifibranor	PPARα/δ/γ	Glucose/lipids	Phase 2	?
Seladelpar	PPARδ	Lipids	Phase 2	?
Saroglitazar	PPARα/γ	Glucose/lipids	Phase 2	+?
CHS-131	PPARγ – other?	Glucose	Phase 2	?
PXL-065	PPARγ/α – MPC?	?	Phase 1	?

* PROACTIVE (Lancet 2006); CHICAGO (JAMA 2007); PERISCOPE (JAMA 2008); IRIS Study (NEJM 2016; Circulation 2017; JAMA 2019).
** Final conclusion indicated neutral effect on CVD from RCTs by FDA in 2014.

Cusi K, unpublished 2019

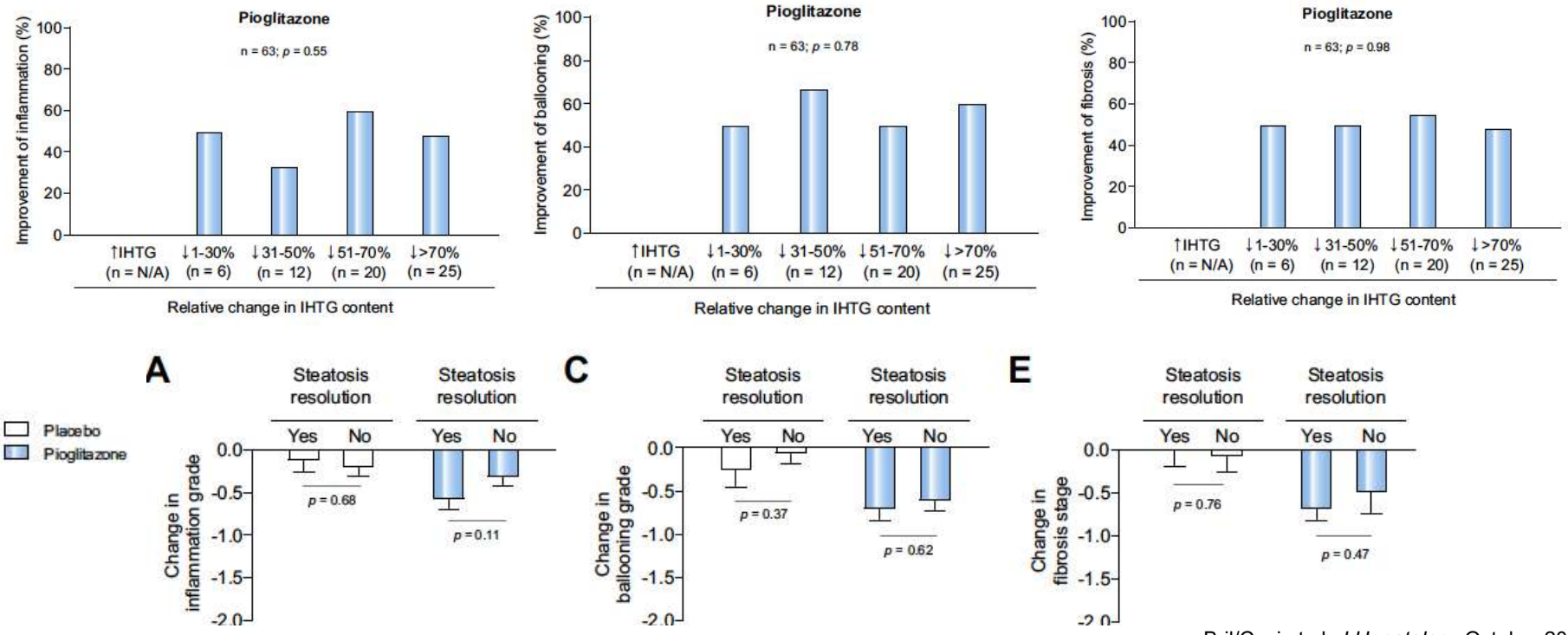
Change in hepatic fat content measured by MRI does not predict treatment-induced histological improvement of steatohepatitis with pioglitazone





Bril/Cusi et al. *J Hepatology* October 2019

Change in hepatic fat content measured by MRI does not predict treatment-induced histological improvement of steatohepatitis with pioglitazone



Bril/Cusi et al. *J Hepatology* October 2019

Treatment of NASH: Role of PPARs

1. What is the role of the diabetologist?

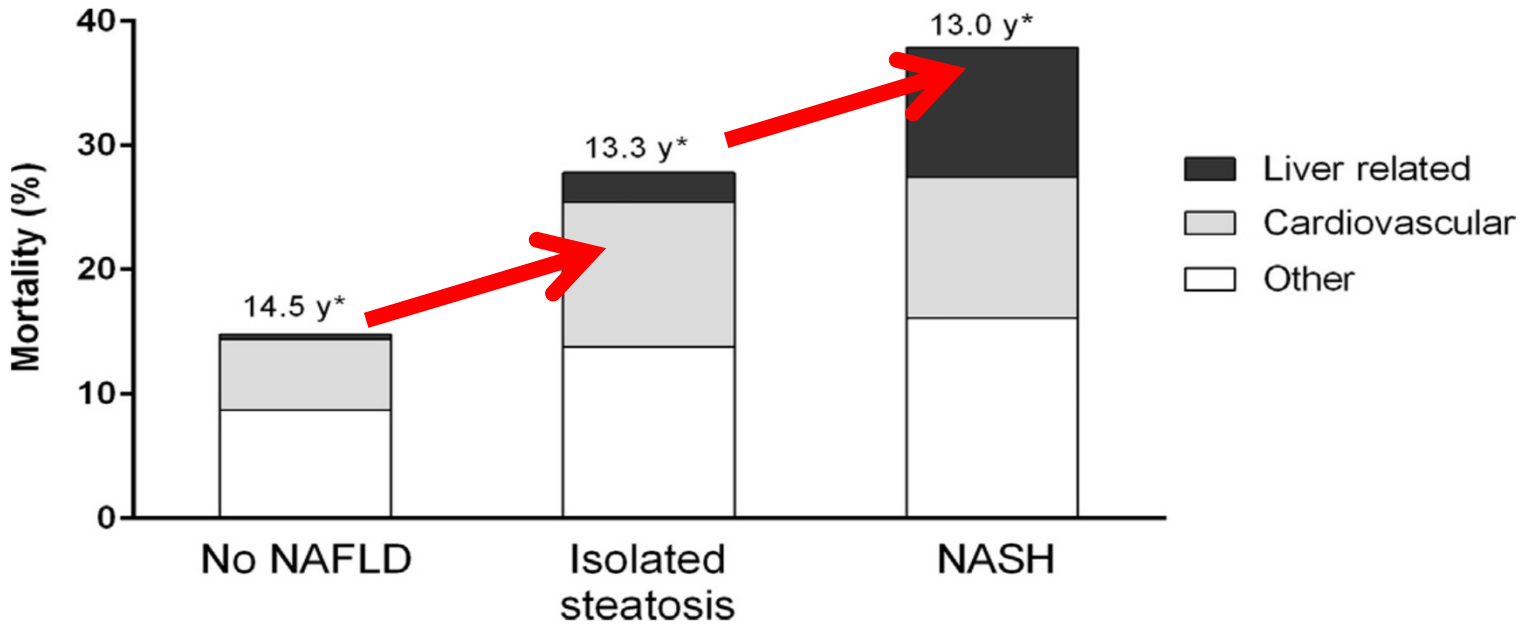
- A call to action: NAFLD as a public health problem
- Looking back: Analogies to diabetic nephropathy or osteoporosis

2. Treatment of NAFLD:

- Current options:
  - Weight loss, vitamin E, GLP-1RA and pioglitazone
- The future:
  - New agents and combination therapy
  - **PPARs:** Targeting NAFLD + “cardiometabolic” risk (T2DM, CVD)

CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Mortality in Isolated Steatosis versus NASH:
Cardiovascular disease as the major cause of death



Bril and Cusi. Endocrinol Metab Clin North Am 2016;45:765–81

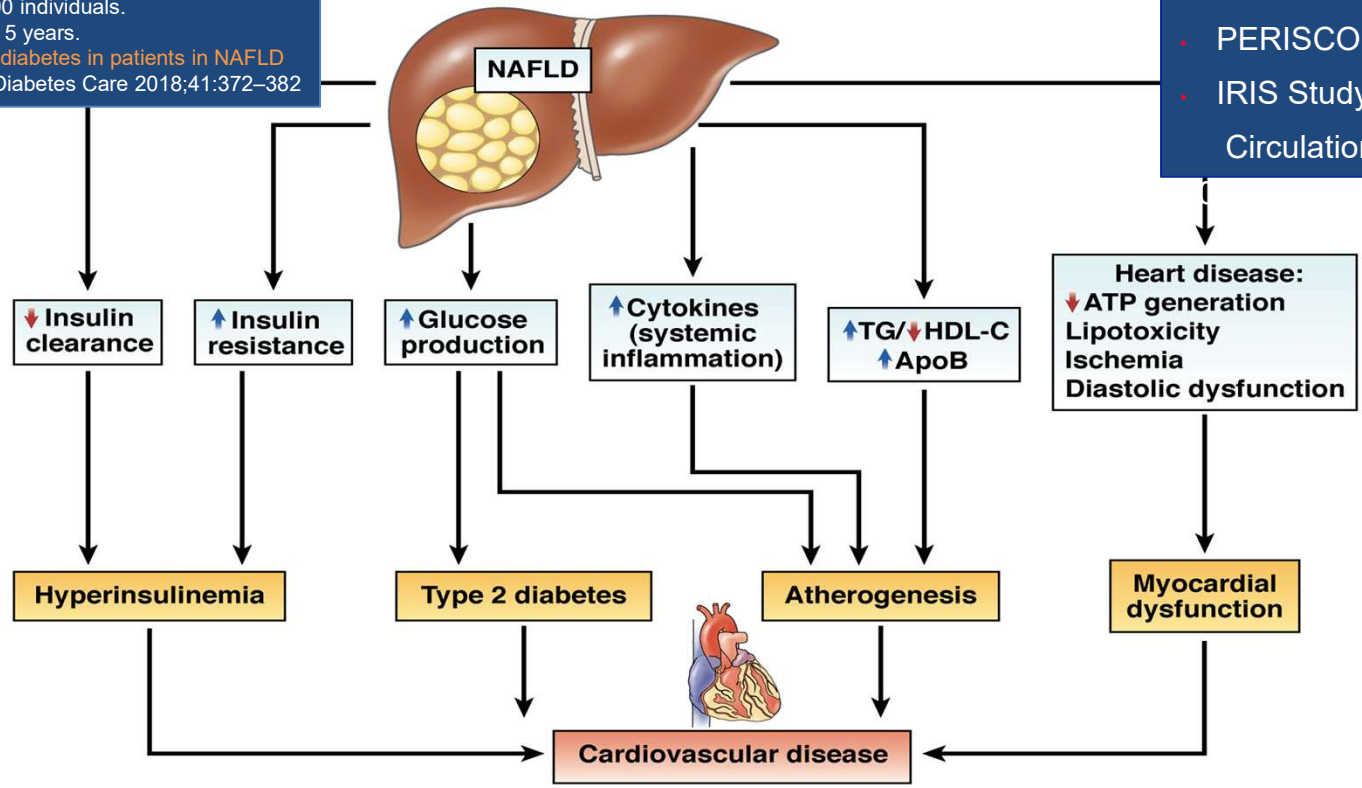
Cardiovascular Consequences of NAFLD

- Confirmed in meta-analysis of 19 observational studies with ~300,000 individuals.
- Follow-up median of 5 years.
- 2-fold greater risk of diabetes in patients in NAFLD

Mantovani et al, Diabetes Care 2018;41:372–382

Pioglitazone and CVD risk reduction:

- PROACTIVE (Lancet 2006)
- CHICAGO (JAMA 2007)
- PERISCOPE (JAMA 2008)
- IRIS Study (NEJM 2016; Circulation 2017; JAMA



ATP, adenosine triphosphate; HDL-C, high-density lipoprotein; TG, triglycerides.

Cusi K *Gastroenterology* 2012;142:711–25

JAMA Neurology | Original Investigation

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Pioglitazone Therapy in Patients With Stroke and Prediabetes

A Post Hoc Analysis of the IRIS Randomized Clinical Trial

J. David Spence, MD; Catherine M. Viscoli, PhD; Silvio E. Inzucchi, MD; Jennifer Dearborn-Tomazos, MD; Gary A. Ford, MB, Bchir; Mark Gorman, MD; Karen L. Furie, MD; Anne M. Lovejoy, PA-C; Lawrence H. Young, MD; Walter N. Kernan, MD; for the IRIS Investigators

Table 2. Hazard Ratios in Cox Regression for On-Treatment and Intention-to-Treat Analyses

Variable	Hazard Ratio (95% CI)	*P* Value	NNT
Adherence ≥80%			
Stroke/MI	0.57 (0.39-0.84)	.004	24
Stroke	0.64 (0.42-0.99)	.04	39
Acute coronary syndrome	0.47 (0.26-0.85)	.01	40
Stroke/MI/HF hospitalization	0.61 (0.42-0.88)	.008	26
New-onset diabetes	0.18 (0.10-0.33)	<.001	12
Intention to treat			
Stroke/MI	0.70 (0.56-0.88)	.002	28
Stroke	0.72 (0.56-0.93)	.01	39
Acute coronary syndrome	0.72 (0.52-1.00)	.052	62
Stroke/MI/HF hospitalization	0.78 (0.63-0.96)	.02	34
New-onset diabetes	0.46 (0.35-0.61)	<.001	19

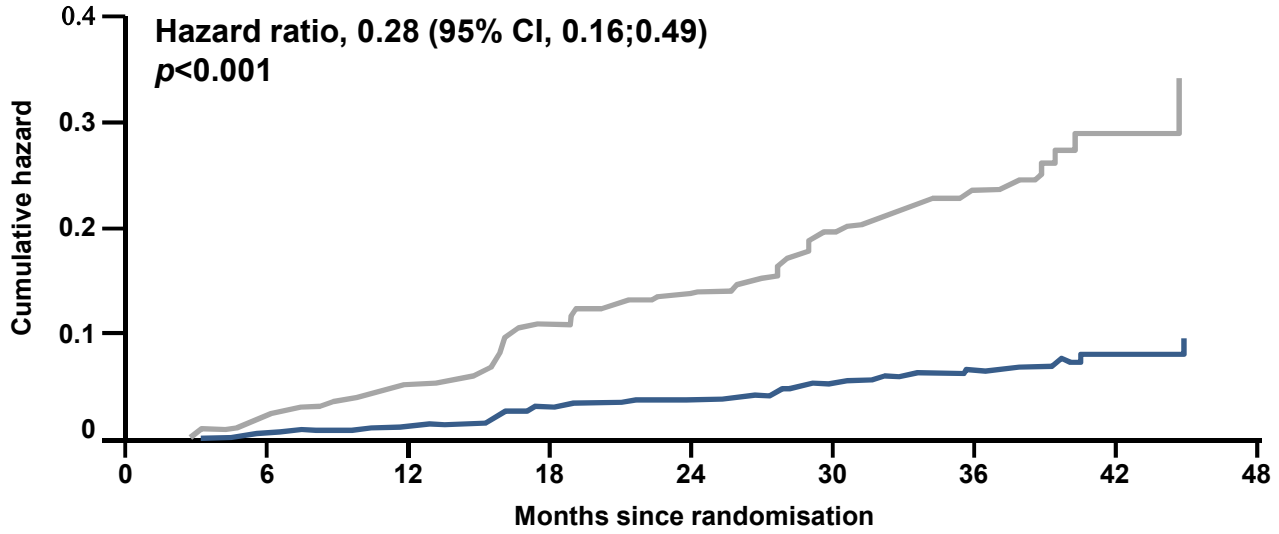
CONCLUSIONS AND RELEVANCE Pioglitazone may be effective for secondary prevention in patients with stroke/transient ischemic attack and with prediabetes, particularly in those with good adherence.

CI, confidence interval; HF, heart failure; MI, myocardial infarction; NNT, number needed to treat.

Spence et al. *JAMA Neurol* 2019;76:526–35

ACT NOW: prevention of T2DM

Time to development of diabetes



No. at risk								
Placebo	299	259	228	204	191	134	83	17
Pioglitazone	303	262	244	228	218	140	87	24

CI, confidence interval.

DeFronzo et al. *N Engl J Med* 2011;364:1104-11, 2011

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PPARs to Address the Unmet Medical Need in NASH

1. Role of the PCP and endocrinologist expanding

- We are at the dawn of incorporating NASH in the risk assessment of obesity and T2DM
- ADA: asking for routine early diagnosis and treatment

2. Treatment

- Many new agents in the pipeline
- PPARs offer a great opportunity to tackle a major driving force in NASH (IR, lipotoxicity) while significantly ameliorating cardiometabolic risk
- Combination therapy will be the standard of care in the future (PPARs + ?)
- Best combination unclear (“upstream” + “downstream” combo?)

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