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

April 5 th, 2018

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NASH and Type 2 Diabetes

Nonalcoholic fatty liver disease (NAFLD) develops in ~70% of patients with type 2 diabetes mellitus (T2DM):

- Diabetes becomes more difficult to control and often needs more medication
- About 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

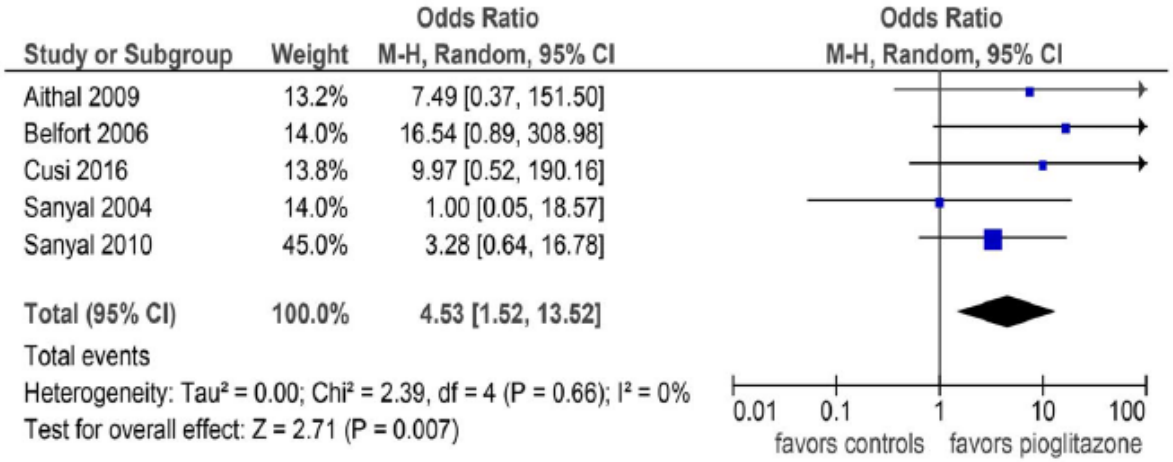
Coexistence of T2DM and NAFLD leads to worse insulin resistance at multiple levels:

- In adipose tissue, insulin resistance increases the flux of fatty acids to the liver with severe hepatic steatosis and hepatocyte « lipotoxicity »
- 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

Clinical proof of concept of efficacy of PPAR γ and α/δ agonists 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	6 mo (Belfort et al, 2006)	18 mo (Cusi et al, 2016)
Steatosis (% patients improved)	65% vs 38%, p < 0.001	71% vs 26%, p < 0.001
Inflammation (% patients improved)	65% vs 29%, p < 0.001	49% vs 22%, p < 0.001
Ballooning (% patients improved)	54% vs 24%, p < 0.001	51% vs 24%, p < 0.001
NASH resolution (% patients)	NA	51% vs 19%, p < 0.001



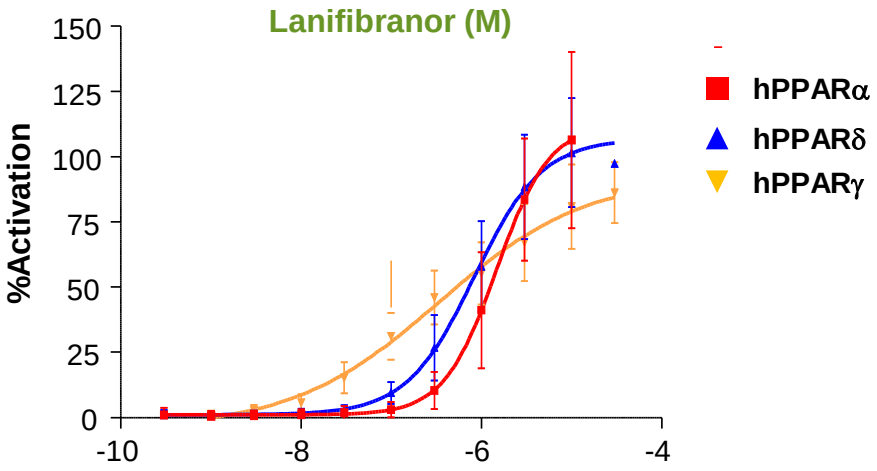
- **Pioglitazone: improvement of advanced fibrosis (stage F3-F4) in patients with biopsy-proven NASH, defined as the number of NASH patients whose fibrosis stage changed from F3-F4 to F0-F2 at the End Of T**

Musso G et al, Hepatology 2017

- **PPARα/δ activation by elafibranor leads to significant improvement of ballooning and inflammation as well as metabolic markers in NASH patients after 12 months of treatment (Ratziu et al, Gastroenterology, 2016)**

Lanifibranor: a next generation panPPAR with moderate and well balanced activity on the 3 PPAR isoforms

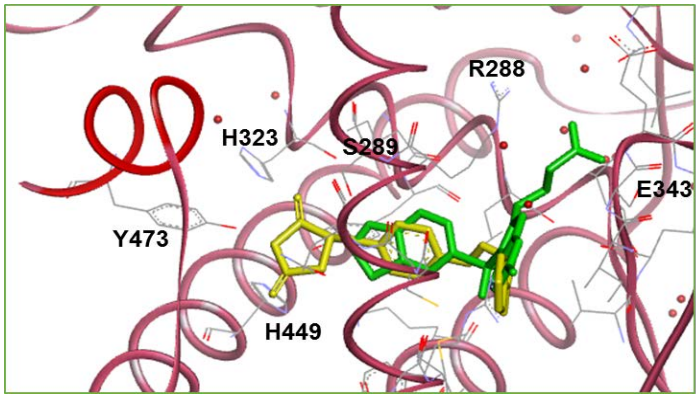
Lanifibranor DRCs and EC50s for hPPARs (nM)



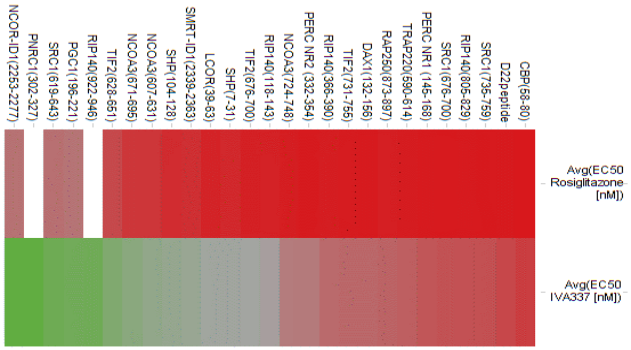
Lanifibranor presents a similar profile for the 3 rodent PPAR isoforms

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 coactivators recruitment



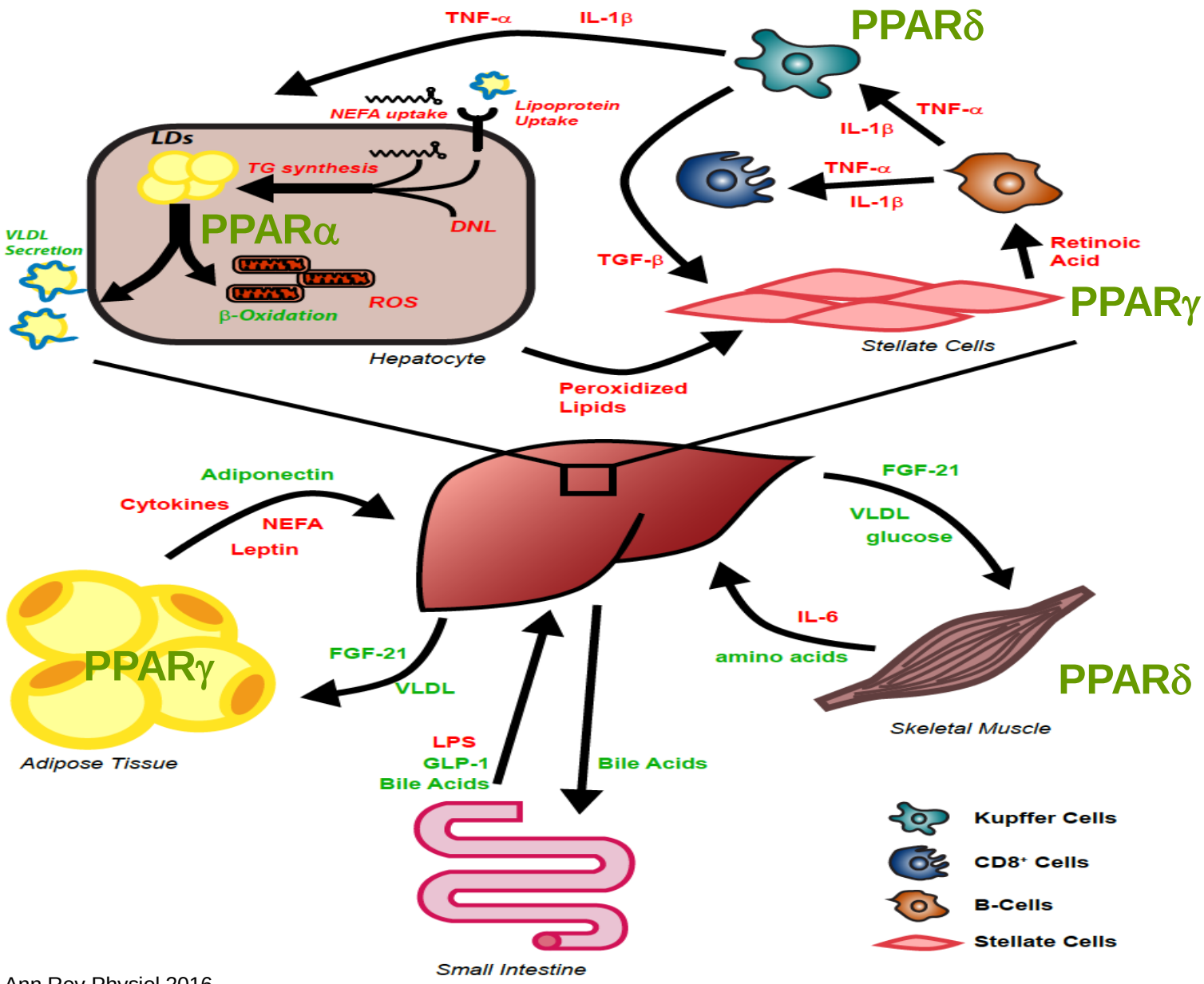
J Med Chem. 2018 Feb 15. doi: 10.1021/acs.jmedchem.7b01285



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

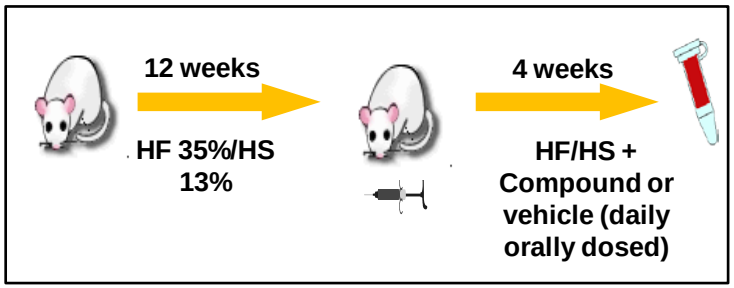
Coordinated activation of PPARs for NASH and fibrosis resolution



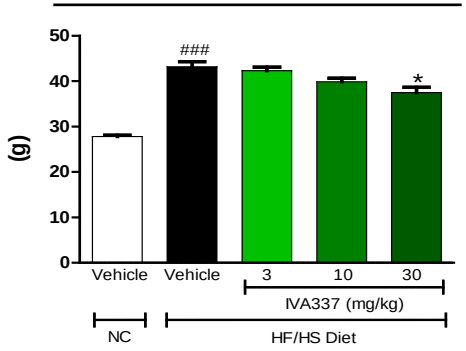
Haas, Francque & Staels. Ann Rev Physiol 2016

Lanifibranor improves NASH relevant metabolic markers in a model of diet-induced obesity and insulin-resistance

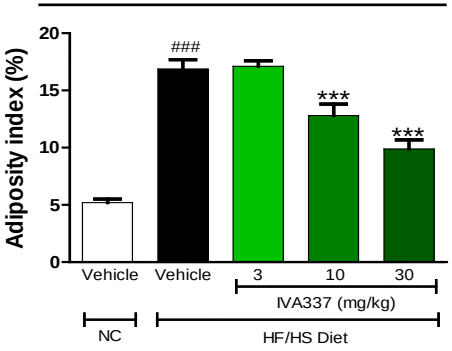
Diet-induced obesity model



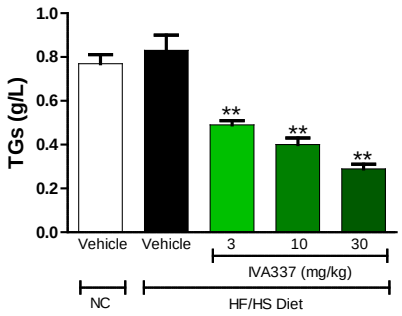
Body Weight



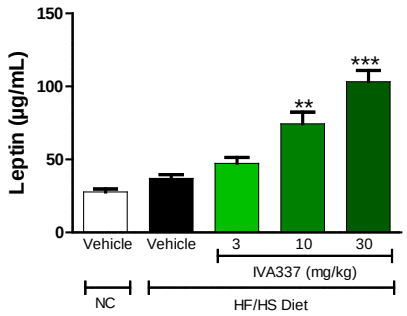
Adiposity index



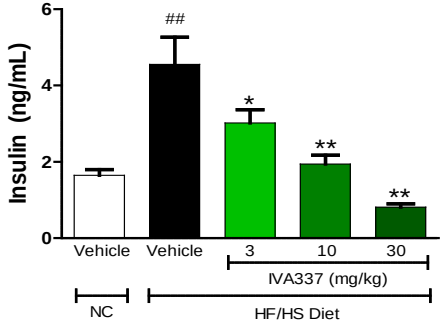
Triglycerides



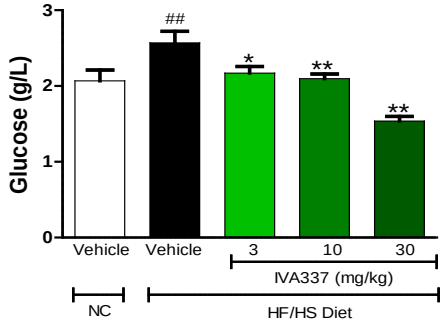
Adiponectin



Insulin



Non Fasting Glucose



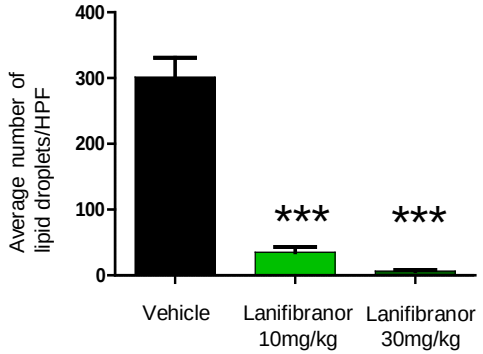
Lanifibranor reduced significantly body weight, adiposity index, non fasting glucose and insulin in a dose-dependent manner compared to HF/HS treated with vehicle, indicating an improvement of insulin sensitivity

Source: Company data

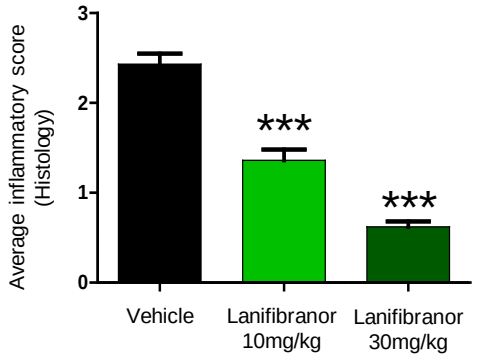
Lanifibranor significantly reduces steatosis, inflammation, ballooning and fibrosis in NASH preclinical models

Lanifibranor inhibits steatosis and inflammation in the MCD model

Steatosis

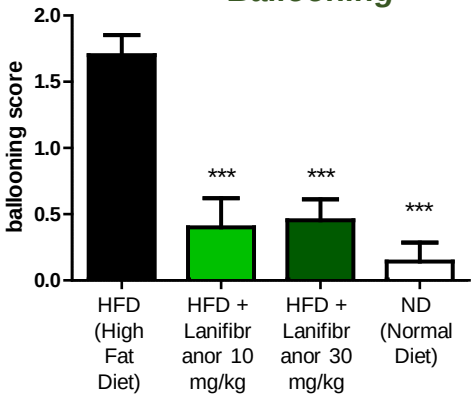


Inflammation

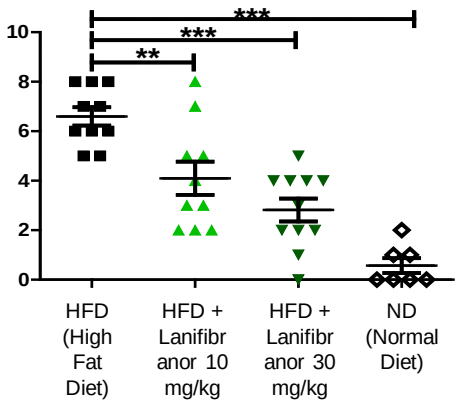


Lanifibranor significantly reduces ballooning and the NAS score in the foz/foz model

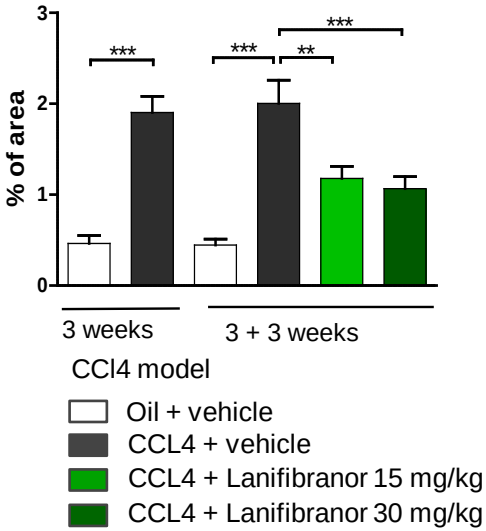
Ballooning



NAS Score



Lanifibranor reverses established liver fibrosis



Lanifibranor positively impacts all NASH-relevant liver lesions

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

Lanifibranor: 4-week PK/PD phase IIa study in Type 2 Diabetes

Trial design

Population

- TD2M patients stable on metformin
- HbA1c ≥ 7% but < 10%

Randomisation

- N=56
- 14 patients randomized/group

Study objectives

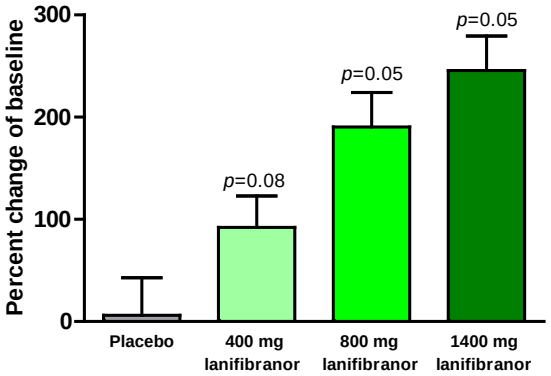
- Safety (ankle foot volume, ankle circumference, body weight, AEs, BNP, albumin, hematocrit, hemoglobin, troponin I, CK, creatinine, cystatin C, ALT, AST, Hcys, bone markers (osteocalcin and B-Crosslaps), SBP/DBP, ECG)
- Pharmacodynamics effects
- PK in patients
- Choice of dose range for phase IIb in NASH

56 patients
4 week treatment
Double blind randomized placebo controlled

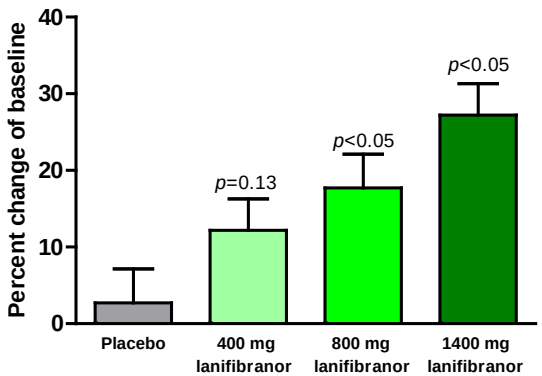
Phase IIa clinical study results confirmed lanifibranor safety and efficacy on key metabolic markers

- Improves insulin sensitivity (HOMA-IR, adiponectin)
- Improves dyslipidemia (increase in HDL-C, reduction of TG)

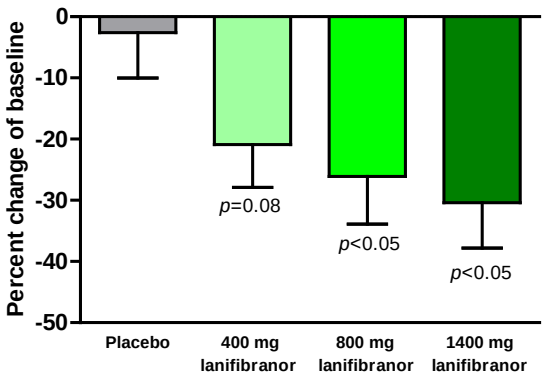
Adiponectin (PPARγ)



HDL Cholesterol (PPARα/δ)



Triglycerides (PPARα)



Clinical findings underline the excellent tolerability of lanifibranor

- Good overall tolerance and no major safety findings
- No increases of creatinine, LFTs, or CPK
- No changes in blood pressure
- No signal of fluid overload or hemodilution
- No weight gain
- 800 and 1200 mg doses investigated in Phase 2b trials

NATIVE Phase IIb in NASH

Trial design

Status

- Trial enrolling

Randomisation

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

Clinicaltrials.gov identifier:

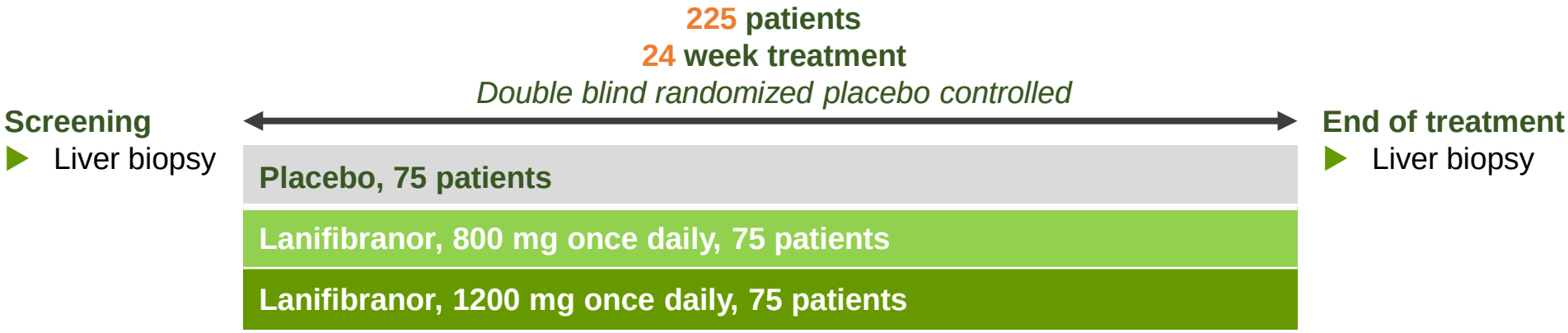
- NCT03008070

Inclusion criteria

- Liver biopsy
- Moderate to severe patients with a inflammation and 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 and ballooning score without worsening of fibrosis
- Central reading for pre- (before randomization) and post treatment biopsy



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

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

Main inclusion criteria

- Type 2 d**iabetes with a fasting plasma glucose (FPG) ≥ 100 mg/dL but ≤ 250 mg/dL and HbA1c ≥ 7.0% but ≤ 9.5%, on diet alone, or on metformin (≥1,000 mg/day), and/or sulfonylurea and/or DPP-IV/SGLT2 therapies. These medicines will be continued at stable doses during the entire study.**
- **Hepatic steatosis (IHTG) > 10 % determined by ^{1}H-MRS.**
- **Stable weight**

Main procedures performed in the study

- **^{1}H-MRS, 2D-MRE, T_1 MRI mapping, Fibroscan**
- Determination of hepatic insulin sensitivity, gluconeogenesis, and 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)
- Hepatic insulin sensitivity
- Hepatic glucose production
- Gluconeogenesis and de-novo lipogenesis
- Advanced lipid testing, biomarkers of liver fibrosis, genetic markers

Trial design and endpoints

Principal investigator

- Pr. Ken Cusi (University of Florida)

Design

- 24-week treatment period
- Two arm (placebo, lanifibranor 800 mg/day)
- Randomized (1:1), double-blind, placebo-controlled
- There is in addition a non-obese subject control group for the metabolic and imaging procedures

Sample size

- N= 64 calculated assuming a 35% relative reduction of IHGT

Primary endpoint

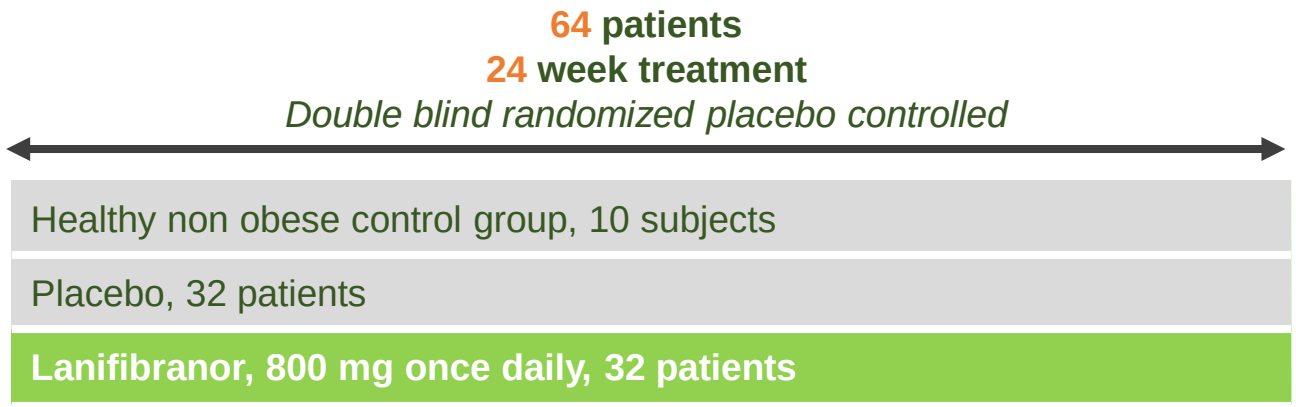
- Change from baseline to week 24 in IHTG

Key secondary endpoints

- Proportion of responders (IHTG, NAFLD resolution)
- Change in hepatic fibrosis (MRE, biomarkers)
- Change in metabolic outcomes (Iinsulin sensitivity, DNL, glycemic control, lipids)
- Safety

Clinicaltrials.gov identifier:

- NCT03459079



Conclusion

The trial's objective is to evaluate the efficacy of lanifibranor on intrahepatic triglycerides and hepatic insulin sensitivity in type 2 diabetic patients with nonalcoholic fatty liver disease (NAFLD)

- Ken Cusi, M.D., F.A.C.P. (University of Florida) as principal investigator
- Change from baseline to week 24 in IHTG as primary endpoint

Lanifibranor selection for this study was motivated by its unique mechanism of action that can potentially address all key features of NAFLD and NASH:

- Insulin-sensitivity improvement
- Steatosis reduction
- Anti-inflammatory activity
- Anti-fibrotic activity

A positive result would further reinforce lanifibranor as the ideal drug for NAFLD and NASH patients with type 2 diabetes

The trial should begin in Q2/Q3 2018 pending FDA approval of lanifibranor IND filing

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