Paris NASH Meeting

International Think Tank

September 7 & 8, 2023
Institut Pasteur
9th edition

Inventiva: development of Lanifibranor for the treatment of patients with NASH/MASH

Pierre Broqua, co-founder and Chief Scientific Officer

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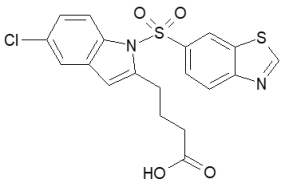
Conflict of interest disclosure

- Inventiva employee and shareholder

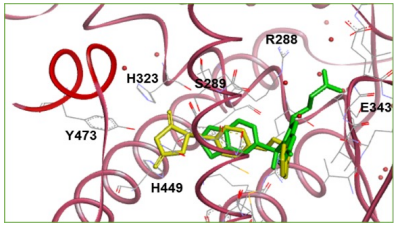
Lanifibranor is a differentiated pan-PPAR agonist with moderate and well balanced activity on the three PPAR isoforms

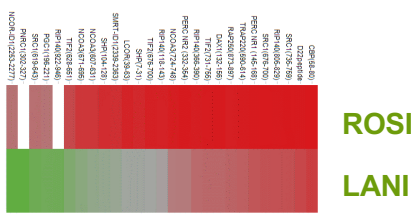
Differentiated oral small molecule …



- Small molecule that activates all three PPAR isoforms
- Differentiated chemical structure with once daily oral administration
- Offered in two dosage forms (800 mg, 1200 mg)

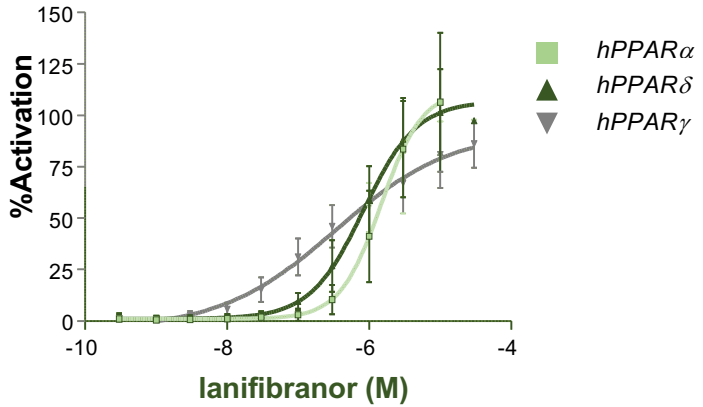
… that binds differently than glitazone to PPARγ





- Induces different coactivator recruitment^^

Moderate and balanced pan-PPAR agonist activity



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

Source: * Company data ** Hanf R et al, Diabetes & Vascular Dis Res 2014 ^ Cymabay company presentation ^^ J Med Chem. 2018 Feb 15. doi: 10.1021/acs.jmedchem.7b01285

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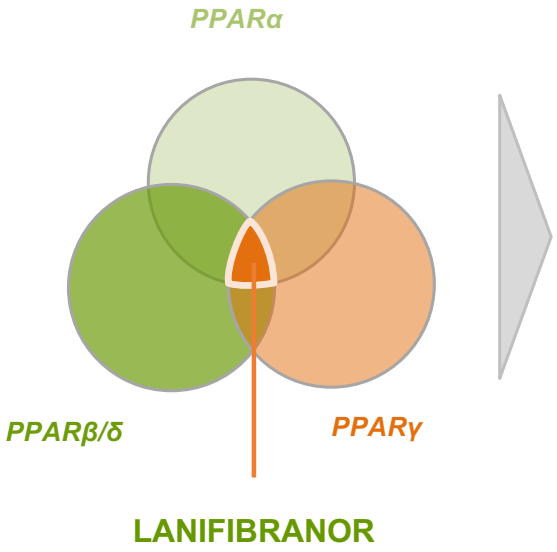
Lanifibranor's activation of the three PPAR isoforms addresses the key features of NASH/MASH

Pan-PPAR activity expected to ensure improved efficacy



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

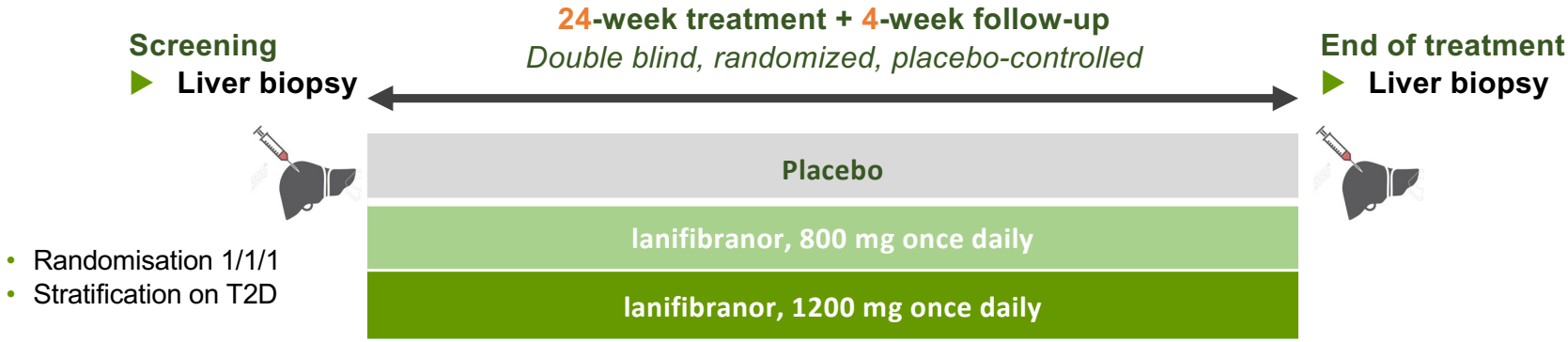
- ↓ Stellate cell proliferation and activation
- ↓ Collagen and fibronectin production

VASCULAR

PPARα PPARγ

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

The Phase IIb NATIVE trial evaluated 800 mg and 1200 mg once-daily lanifibranor versus placebo in 247 patients



Patient population	# patients	Definition
Safety / Intention-to-Treat (ITT)	247	Patients randomized having received at least one dose of lanifibranor/placebo
Per Protocol (PP)	194	Patients with paired biopsies and without deviation impacting efficacy results

- **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 in the New England Journal of Medicine**(1):

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

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(1) https://www.nejm.org/doi/full/10.1056/NEJMoa2036205

Lanifibranor: comprehensive impact on the histology and biology of NASH/MASH

HISTOLOGY AND MARKERS

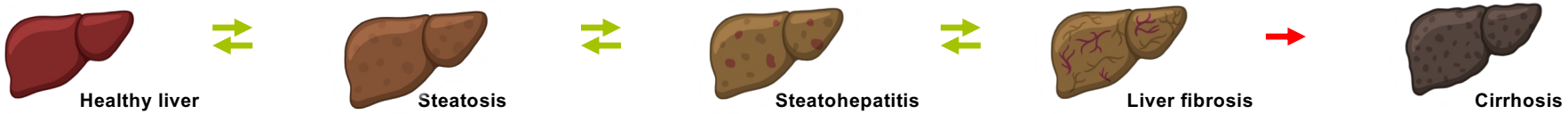
NATIVE
NASH TRIAL TO VALIDATE IVA337 EFFICACY

Lanifibranor: statistically significant effects after 24 weeks

Fibrosis Regression

NASH Resolution

Fibrosis Regression & NASH Resolution



- Steatosis measured by histological grading, CAP/Fibroscan; Intra-hepatic TG content by ^{1}H-MRS[(1)]; NAFLD resolution
- Biomarkers of inflammation (ferritin, CRP), tissue injury (ALT,AST) and apoptosis (CK18)
- Circulating biomarkers of fibrosis: Pro-C3, TIMP-1/MMP-2, MACK-3

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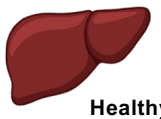
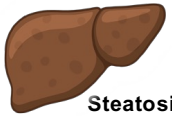
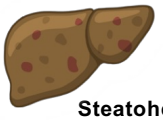


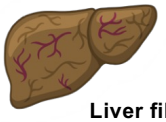
Healthy liver



Steatosis



Steatohepatitis



Liver fibrosis

Cirrhosis

- Steatosis measured by histological grading, CAP/Fibroscan; Intra-hepatic TG content by ^{1}H-MRS(1); NAFLD resolution
- Biomarkers of inflammation (ferritin, CRP), tissue injury (ALT,AST) and apoptosis (CK18)
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GLUCOSE METABOLISM MARKERS

Improves insulin resistance and glycemic control in patients with or without diabetes

- Fasting glucose
- Fasting insulin
- HbA1c
- HOMA-IR index
- Hepatic glucose production
- Insulin resistance
- Hepatic and muscle insulin resistance

CARDIOVASCULAR RISK MARKERS

Improves markers of cardiovascular risk and lipid metabolism

- HDL-C
- Triglycerides levels
- LDL-cholesterol level
- Hs-CRP
- APO-B
- APO-B/APO-A1
- APO-C3
- DBP
- Adiponectin

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(1) Proton magnetic resonance spectroscopy

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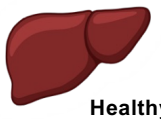

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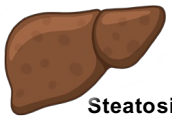
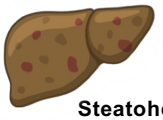


Steatosis



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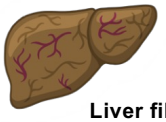

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  → LDL-cholesterol level
  ↓ Hs-CRP
- ↓ APO-B
  APO-B/APO-A1
  APO-C3
- ↓ DBP
  ↑ Adiponectin

Improves markers of cardiometabolic health independently of weight gain which has been shown to be metabolically healthy
Increases adiponectin known to regulate glucose levels, lipid metabolism and insulin sensitivity through its anti-inflammatory, anti-fibrotic and antioxidant effects

(1) Proton magnetic resonance spectroscopy

LEGEND Study Design - Lanifibranor in Combination with the SGLT2 Inhibitor empagliflozin in patients with NASH and Type 2 Diabetes

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)
- ClinicalTrials.gov Identifier: NCT05232071

Status

- Study to be conducted in ~40 sites in Belgium, France, Holland, UK and the US.
- IND accepted by FDA
- **First site activated:** H1 2022
- **Topline results**: Q1 2024

Inclusion criteria

- Adult patients with diabetes and NASH

Primary outcome measures

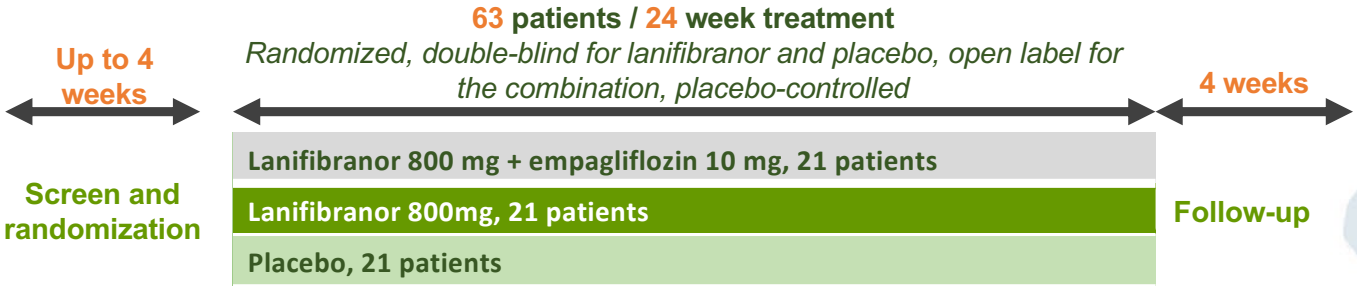
- HbA1c change

Secondary outcome measures

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

Other outcome measures (safety/exploratory)

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



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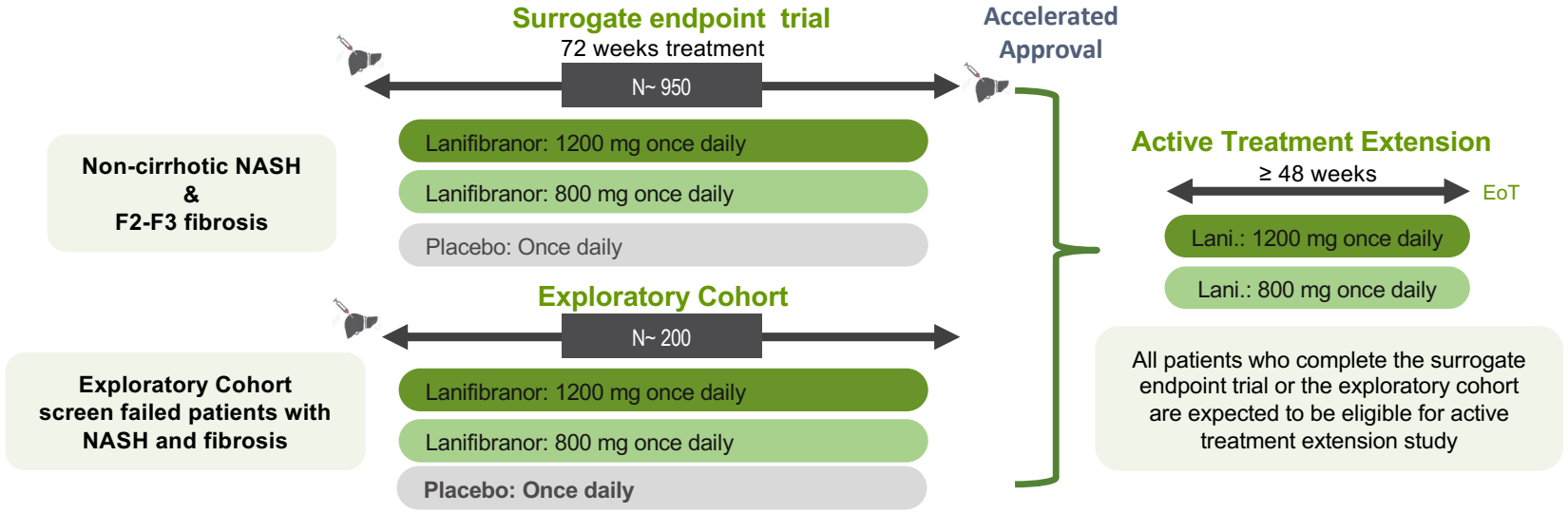
Phase III NATiV3 study design in patients with non-cirrhotic NASH

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



PRINCIPAL INVESTIGATORS: Dr. Sven Francque & Dr. Arun Sanyal

MAIN INCLUSION CRITERIA: aligned to NATIVE Phase IIb trial

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

OTHER INCLUSION CRITERIA: Patients under a stable dose of GLP1-RA for at least 3 months prior to screening

RANDOMISATION AND STRATIFICATION: Randomisation 1:1:1 with stratification on T2DM and fibrosis stage

STATISTICAL POWERING: 90% considered for sample size calculations

CENTRAL BIOPSY READING: done by three expert pathologists

PRIMARY ENDPOINT at week 72 on c.950 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
- Improvement of fibrosis and no worsening of NASH

SAFETY

- needs to demonstrate good safety and tolerability and favourable benefit-risk ratio

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CONCLUSION

- Lanifibranor is a well-balanced pan-PPAR agonist with activity on all three PPAR subtypes
  - And a distinct interaction with PPAR targets compared to other PPAR agonists

- Lanifibranor has demonstrated robust efficacy after 24 weeks of treatment in patients with non- cirrhotic NASH in the phase IIb NATIVE study addressing the spectrum of the disease:
  - Meeting both histological efficacy endpoints '**resolution of NASH**' AND '**improvement of hepatic fibrosis**'
  - Improving a broad panel of biomarkers of cardiometabolic health
    - Lipid and apolipoprotein profile
    - Glycemia control
    - Insulin resistance
    - Inflammation
    - Hepatic steatosis
  - With a favorable safety and tolerability profile

- Recent updated clinical development program
  - Pivotal phase III study NATiV3 of 72-week duration of therapy in patients with non-cirrhotic NASH (F2/F3)
  - Outcomes confirmation trial to be conducted in patients with NASH and cirrhosis