Lanifibranor (IVA337) in Patients with Type 2 Diabetes (T2D) and Nonalcoholic Fatty Liver Disease (NAFLD)

Topline Results Presentation
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These statements include, but are not limited to, forecasts and estimates with respect to Inventiva’s pre-clinical programs and clinical trials, including design, duration, timing, recruitment, costs, screening and enrolment for those trials, including the LEGEND trial for the treatment of NAFLD, the NATiV3 Phase III clinical trial with lanifibranor in NASH, the investigator-initiated Phase II trial withof lanifibranor in patients with NAFLD and T2D, and the expected Phase IIb clinical trial of cedirogant led by AbbVie, potential development of odiparcil including potential trial design and regulatory pathway, clinical trial data releases and publications, the information, insights and impacts that may be gathered from clinical trials, the potential therapeutic benefits of lanifibranor generally and in combination with empagliflozin, including reduction in liver fat, steatosis resolution, improvement in glycemic control, in hepatic and muscular insulin sensitivity, and in lipid metabolism, of Inventiva’s product candidates, including lanifibranor, , the potential therapeutic benefits of odiparcil, the design of trials and any potential amendments to trial design and the anticipated benefits related thereto, the Company’s agreement with Sino Biopharm, including expectations with respect to enrollment of patients in Greater China in the NATiV3 trial, pipeline and preclinical and clinical development plans, milestone payments, royalties and product sales, potential proceeds under the Company’s financing arrangements, future activities, expectations, plans, growth and, business prospects, competitive advantages and opportunities, including pipeline product development of Inventiva and the sufficiency of Inventiva’s cash resources and cash runway. 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Please refer to the Universal Registration Document for the year ended December 31, 20212 filed with the Autorité des Marchés Financiers on March 1130, 20232, and the Annual Report on Form 20-F for the year ended December 31, 20212 filed with the Securities and Exchange Commission on March 1130, 20232 and the financial report for the first half of 2022 filed Securities and Exchange Commission for other additional information in relation to such factors, risks and uncertainties affecting Inventiva, including those described from time to time under the caption “Risk Factors”. Other risks and uncertainties of which Inventiva is not currently aware may also affect its forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated..

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Why it is important to treat insulin resistance in patients with NASH?

- Insulin resistance has been implicated in the pathogenesis of NAFLD and its comorbidities, including the development of metabolic syndrome, T2D and cardiovascular disease (CVD).

- Patients with worse insulin resistance, whether lean or obese, have more severe NASH and are prone to disease progression (i.e., advanced fibrosis and cirrhosis).

- Hepatic and muscle insulin resistance are known to be a primary feature of patients with steatohepatitis, and their reversal with lifestyle modification causing weight loss or pharmacotherapy improves NASH and reverses or delays progression of hepatic fibrosis.

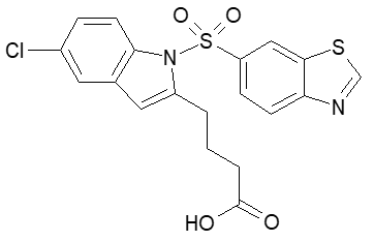
- Dysfunctional/insulin resistant adipose tissue and low adiponectin levels are a major risk factor for developing worse steatohepatitis, as well as for T2D and CVD. Its normalization by PPARγ agonists is associated with improved liver histology in NASH.

Khan R et al. Heepatology. 2019;70:711-724 Gastaldelli A & Cusi K. JHEP Rep. 2019;1:312-328; Francque S et al, Nat Rev Gastroenterol Hepatol 2021:18, 24–39; Bril F, Sanyal A, Cusi K. Clin Liver Dis. 2023;27:187-210; Kalvalaplli et al, JCEM 2023;108:1192-1201.

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

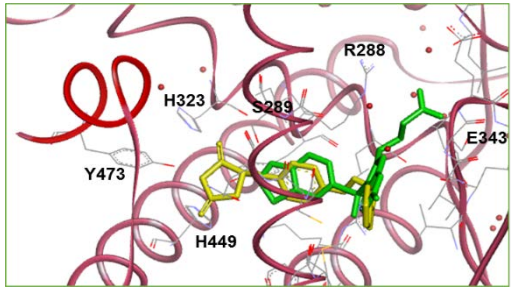
LANIFIBRANOR

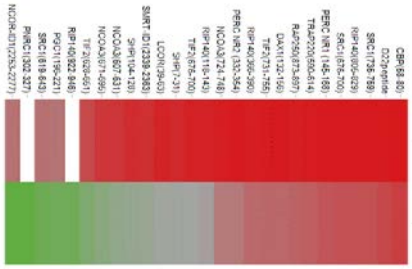
Differentiated oral small molecule …



- 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)

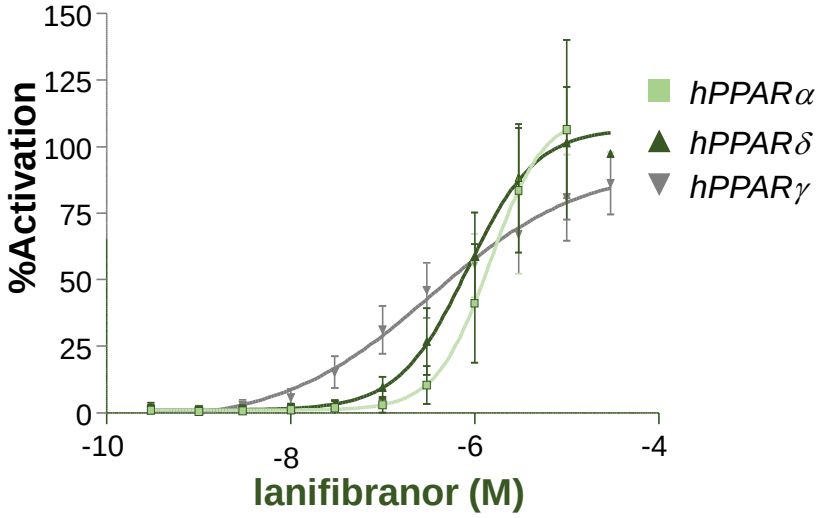
… that binds differently than glitazone to PPARγ





- Induces different coactivator recruitment^^

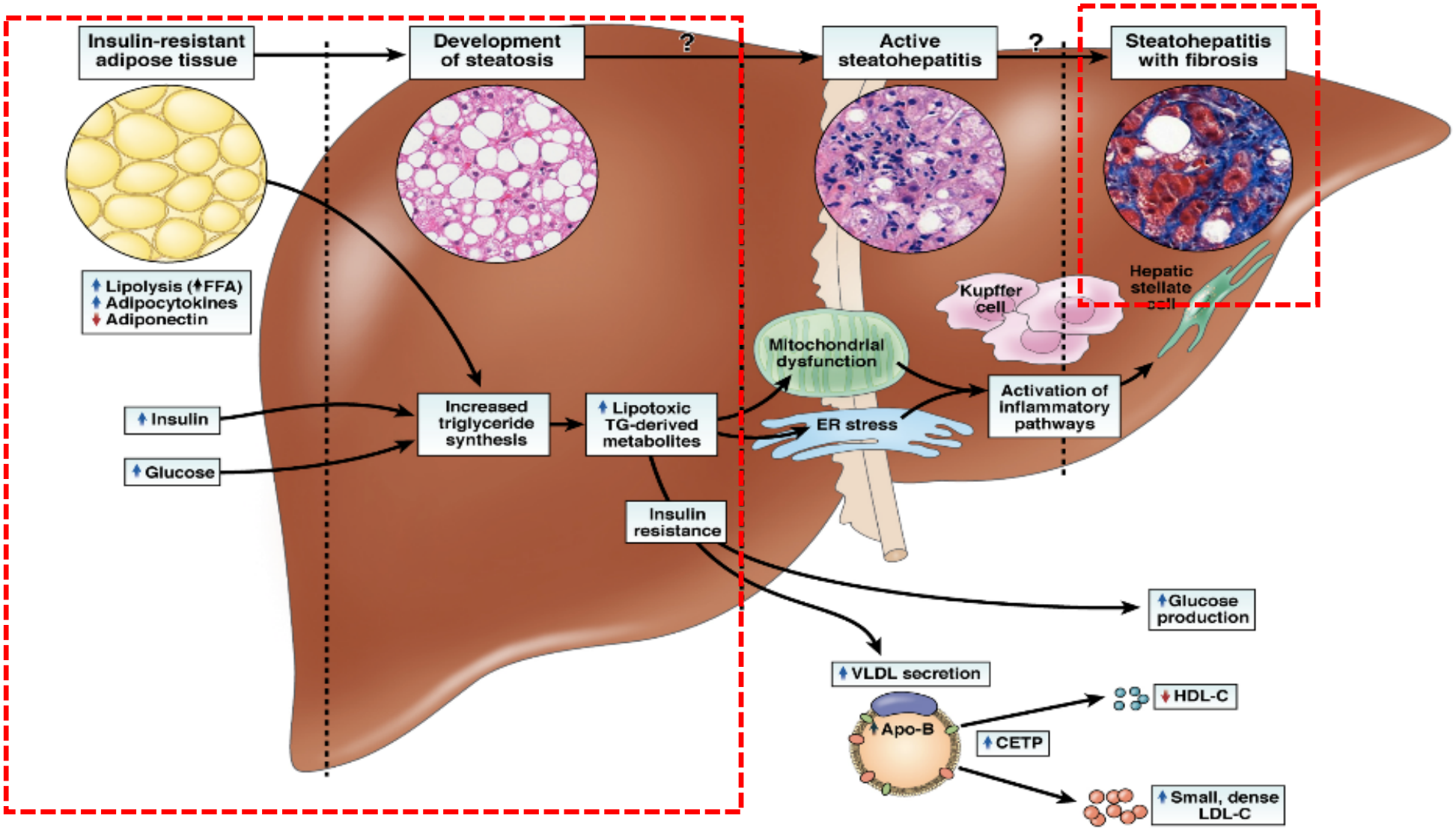
Moderate and balanced pan-PPAR agonist activity



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*	*-*

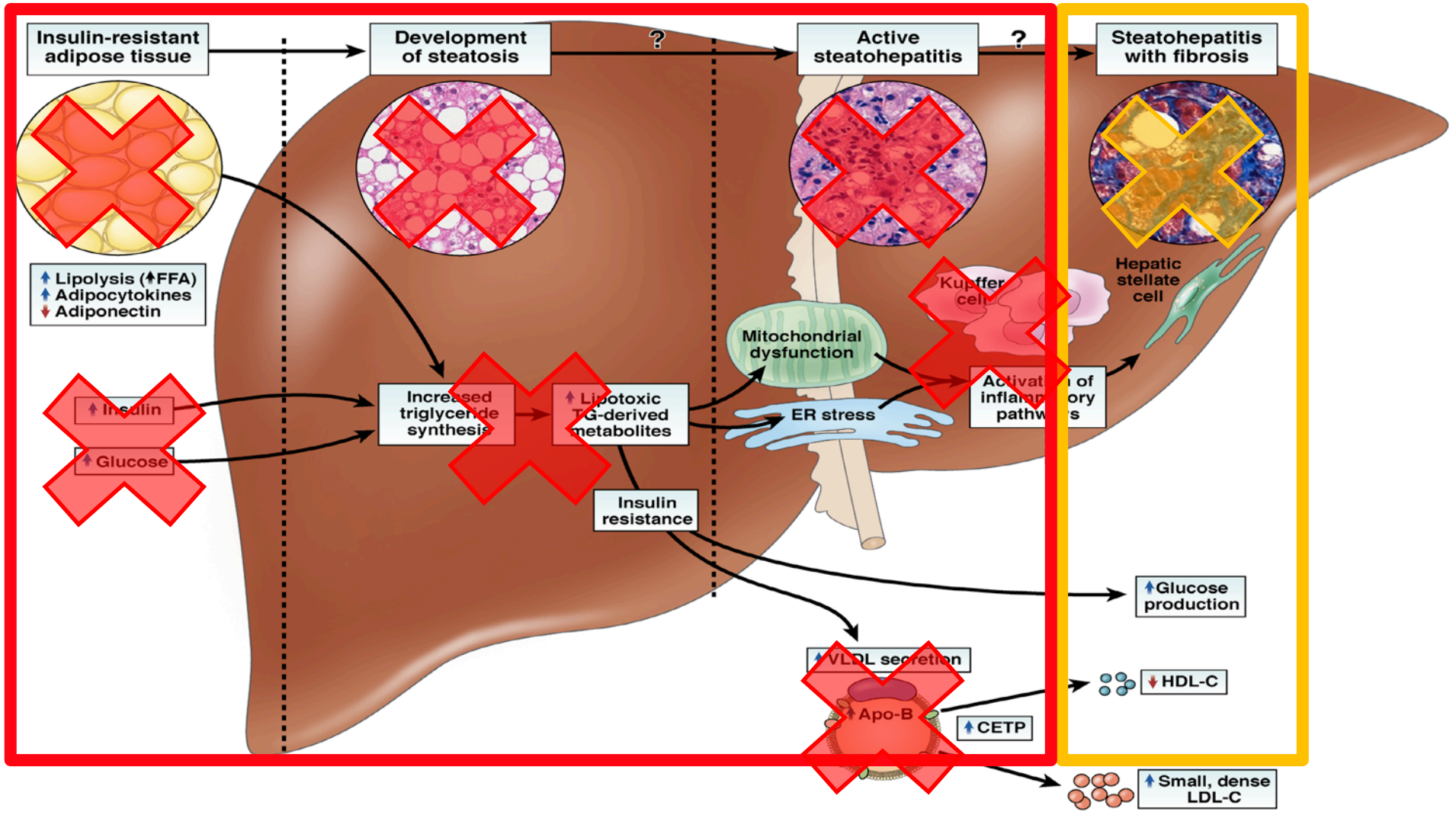
Source: * Company data ** Hanf R et al, Diabetes & Vascular Dis Res 2014 ^ Cymabay company presentation ^^ J Med Chem. 2018 Feb 15. doi: 10.1021/acs.jmedchem.7b01285

The Natural History of NAFLD: From steatosis to cirrhosis



Adapted from Cusi K, Gastroenterology, April 2012, 142:711-725

PanPPAR stimulation: targeting insulin resistance to reverse steatohepatitis and fibrosis in NASH



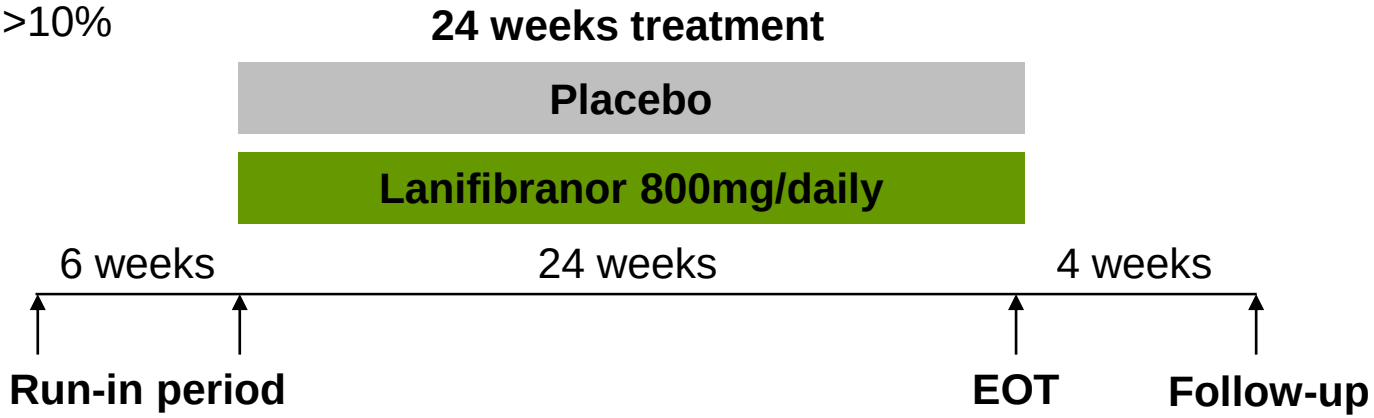
Adapted from Cusi K, Gastroenterology, April 2012, 142:711-725

Study design and objectives

Objective of investigator-initiated trial: Establish safety, efficacy and mechanism of action of lanifibranor in patients with T2D and NAFLD. Specifically determine if lanifibranor decreases IHTG(1), improves hepatic insulin sensitivity, endogenous (hepatic) glucose production, gluconeogenesis and DNL(2).

Patients with NAFLD and T2D

- **Fasting plasma glucose**: 100mg - 250mg/dL
- **HbA1c**: 6.0% to 9.5%
- **Hepatic steatosis:** >10%



Primary endpoint: change in Intrahepatic triglycerides (IHTG)

Secondary endpoints:

- Proportion of responders reaching a decrease in IHTG from baseline ≥ 30% quantified by proton magnetic resonance spectroscopy (^{1}H-MRS)
- Proportion of patients with NAFLD resolution (patients with IHTG ≤ 5%) quantified by ^{1}H-MRS
- Change in hepatic and muscle insulin sensitivity and lipid metabolism
- Safety

(1) Intrahepatic triglycerides (2) De-novo lipogenesis

Patient disposition

38 patients randomised and treated

Full Analysis Set (FAS) - All patients who were randomized and received at least one dose of study drug

Safety Set - All subjects who received at least one dose of study drug

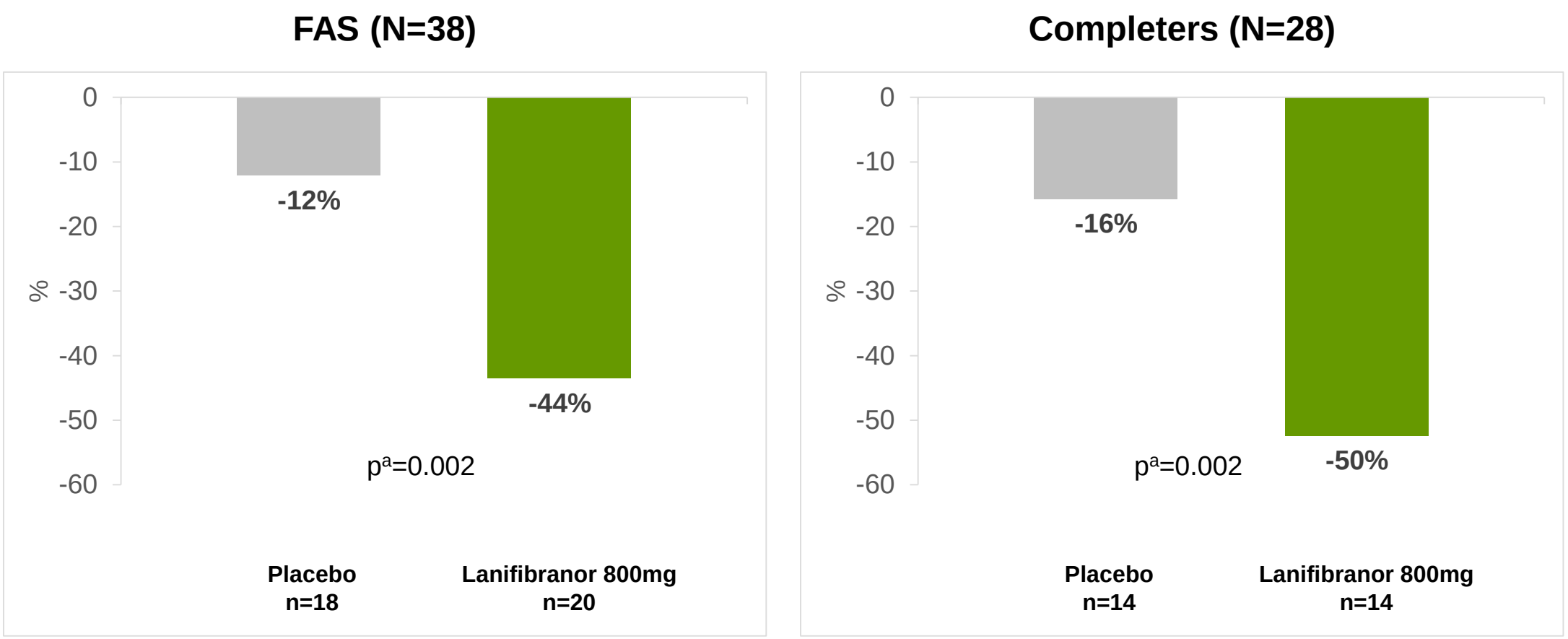
Placebo N = 18	Lanifibranor 800 mg/day N = 20
14 (78%) patients completed the 24-week treatment	14 (70%) patients completed the 24-week treatment
4 (22%) patients prematurely withdrawn: - Adverse events (n=2) - Consent withdrawal (n=2)	6 (30%) patients prematurely withdrawn: - Adverse events (n=4) - Consent withdrawal (n=2)

Baseline patients characteristics

	Placebo (n=18)	Lanifibranor (n=20)
Age, years	58	61
Gender (male/female), %	28/72	45/55
Weight, kg	99	96
BMI, kg/m^2	34.3	33.8
Hemoglobin, g/dL	13.6	13.7
Fasting plasma glucose, mg/dL	123	131
HbA1c, %	7	6.8
Fasting plasma insulin, µU/ml (-180 min)	14	16
Muscle insulin-stimulated glucose disposal, mg/kg LBM/min	5.5	4.4
HIRI	49	51
Liver fat (intrahepatic triglycerides), %	17	21
Triglycerides, mg/dL	180	162
Cholesterol	173	158
HDL-C, mg/dL	44	41
AST, U/L	24	30
ALT, U/L	30	28

24-week treatment with lanifibranor significanty reduce liver fat measured by proton magnetic resonance spectroscopy (^{1}H-MRS)

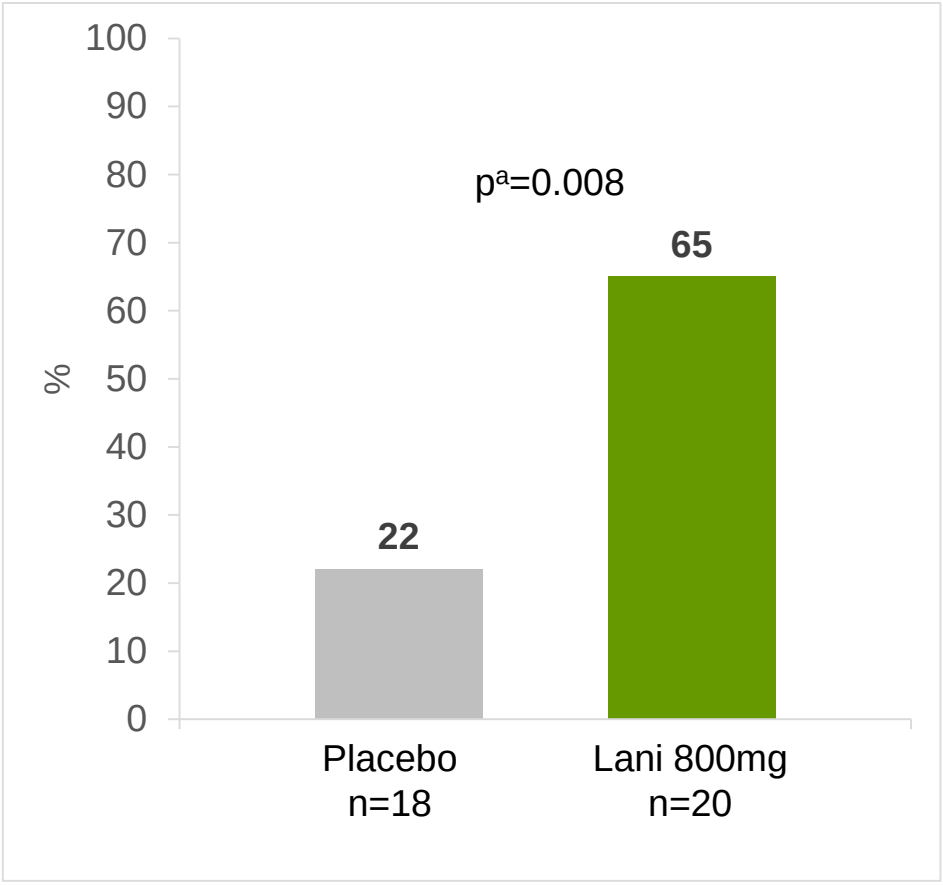
LS Means Relative Percent Change From Baseline in Liver Fat (IHTG) at Week 24



[a] P-value from an Analysis of Covariance (ANCOVA) using the relative change from baseline to week 24 as the response, the treatment as covariate as well as the baseline of IHTG. In the FAS, missing data at Week 24 were imputed by baseline data.

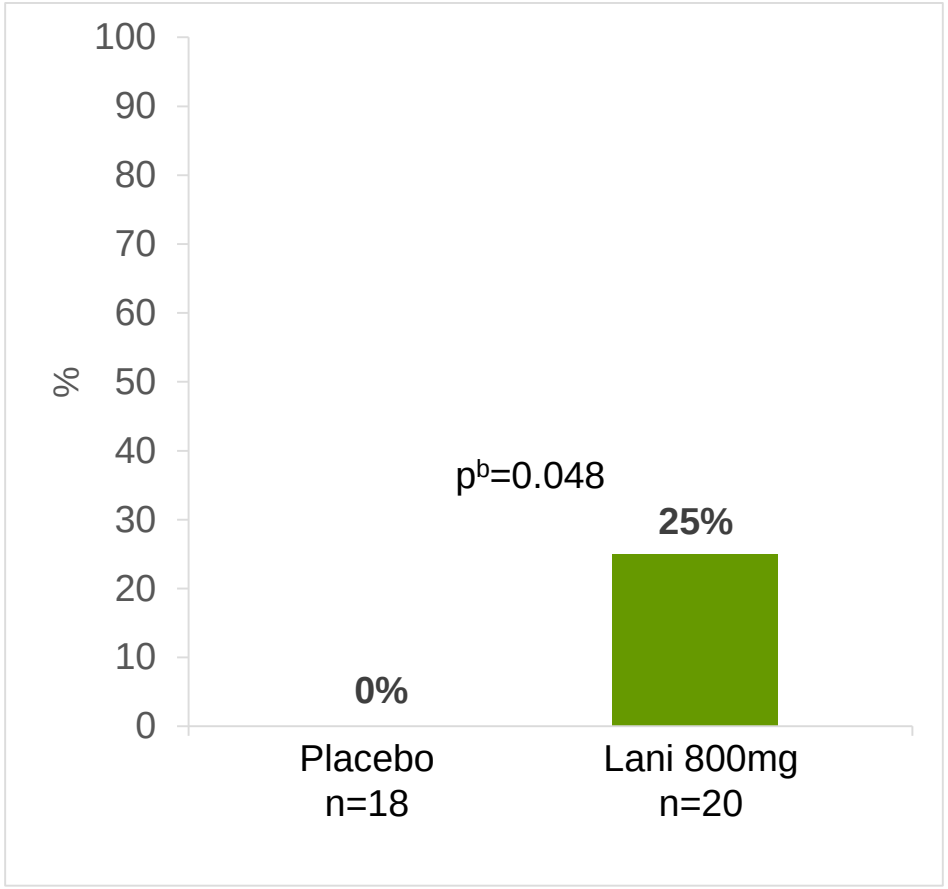
Significantly higher proportion of patients achieved ≥30% liver fat reduction and steatosis resolution with lanifibranor vs placebo

Percentage of patients achieving liver fat reduction ≥30% at week 24 FAS (N=38)



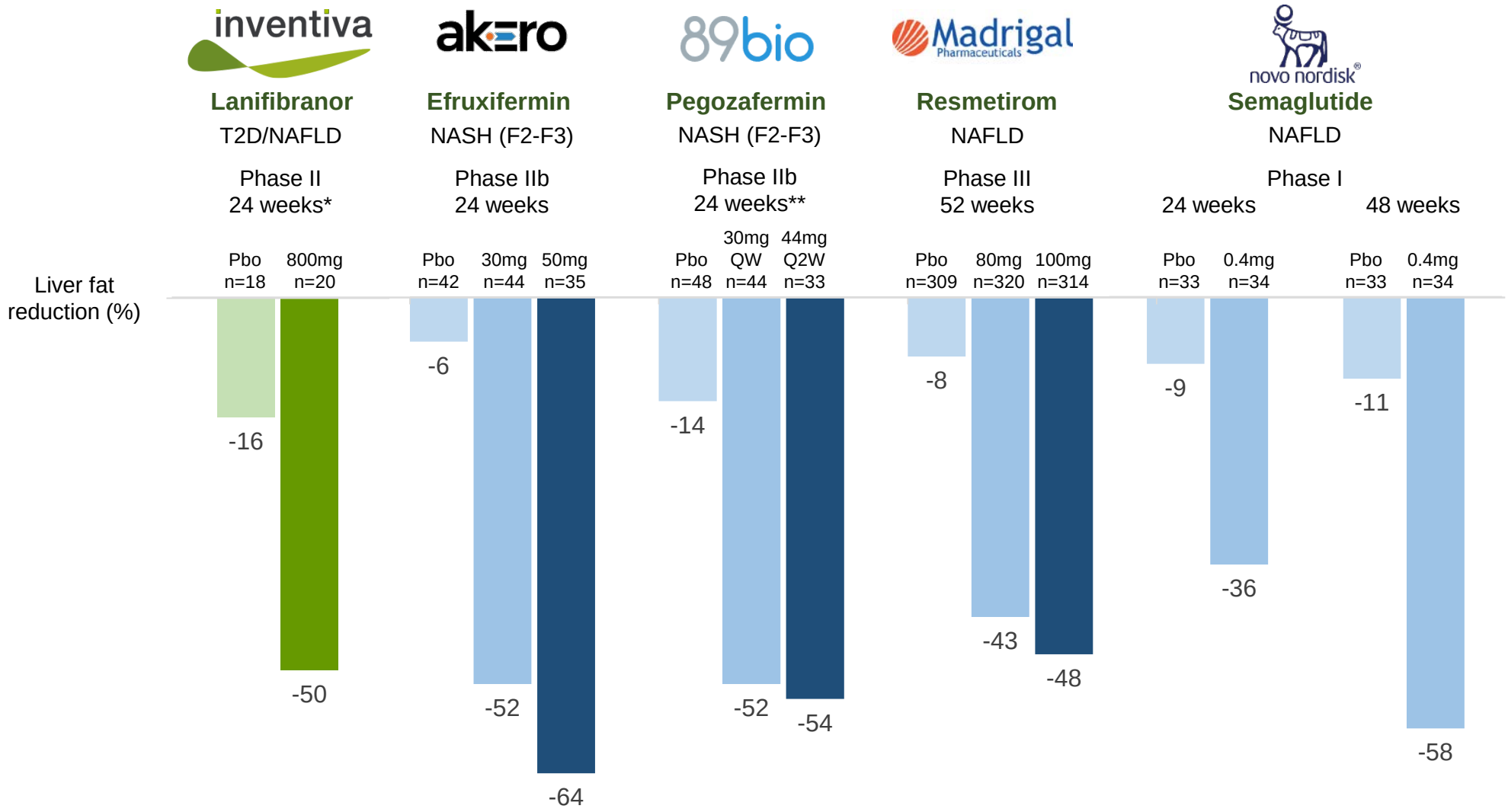
[a] Chi² test
In the FAS, missing data at Week 24 were imputed as non-achieving reduction.

Percentage of patients achieving NAFLD resolution at week 24 FAS (N=38)



[b] Fisher test
NAFLD resolution is defined as IHTG ≤ 5.5% at week 24.
In the FAS, missing data at Week 24 were imputed as non-responders

Treatments effects on liver fat reduction: competitive landscape



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.

*** Results reported among completers**

****Reductions reported only for subset of patients with liver fat content ≥10 at baseline**

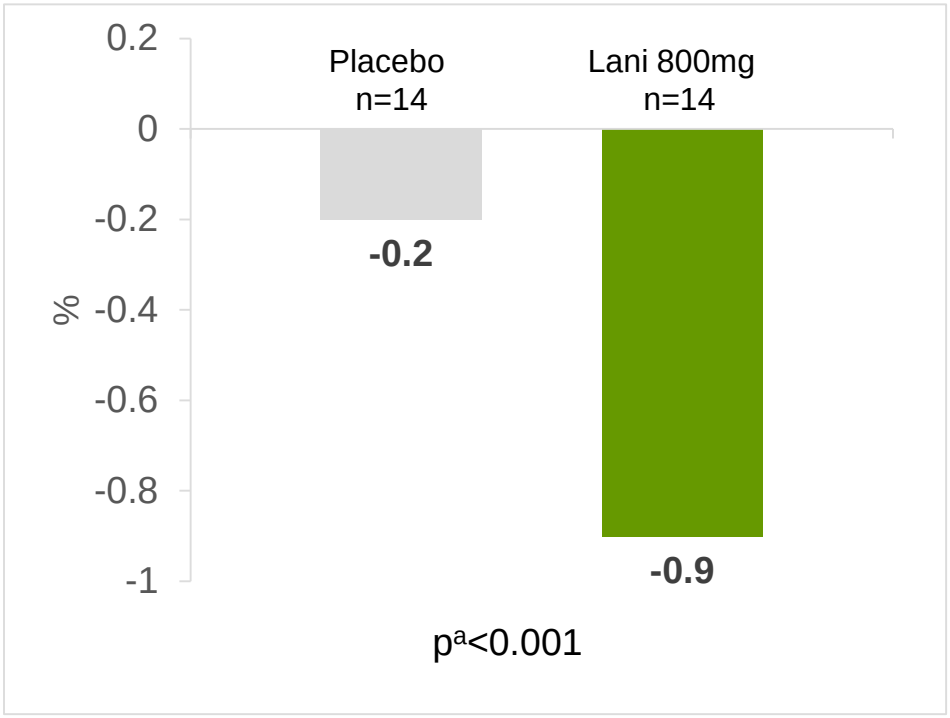
Efruxifermin – Akero's Phase 2b Harmony Study Results presentation (sept. 2022), Pegozafermin - 89Bio' Corporate Presentation (May 2023); Resmetirom – Madrigal's corporate presentation (May 2023); Semaglutide - Flint A, Andersen G, Hockings P, Johansson L, Morsing A, Sundby Palle M, Vogl T, Loomba R, Plum-Mörschel L. Randomised clinical trial: semaglutide versus placebo reduced liver steatosis but not liver stiffness in subjects with non-alcoholic fatty liver disease assessed by magnetic resonance imaging. Aliment Pharmacol Ther. 2021 Nov;54(9):1150-1161. doi: 10.1111/apt.16608. Epub 2021 Sep 27. PMID: 34570916; PMCID: PMC9292692.

Lanifibranor induces improvements in glycemic control

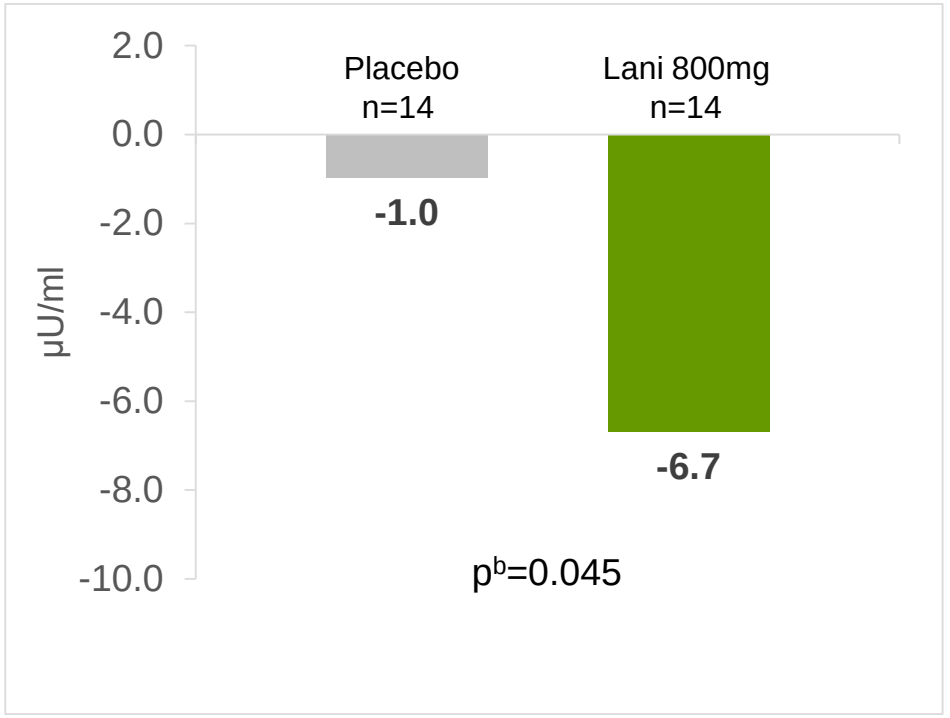
Completers (N=28)

LS Mean absolute change from baseline to week 24 in

HbA1c



Fasting Plasma Insulin



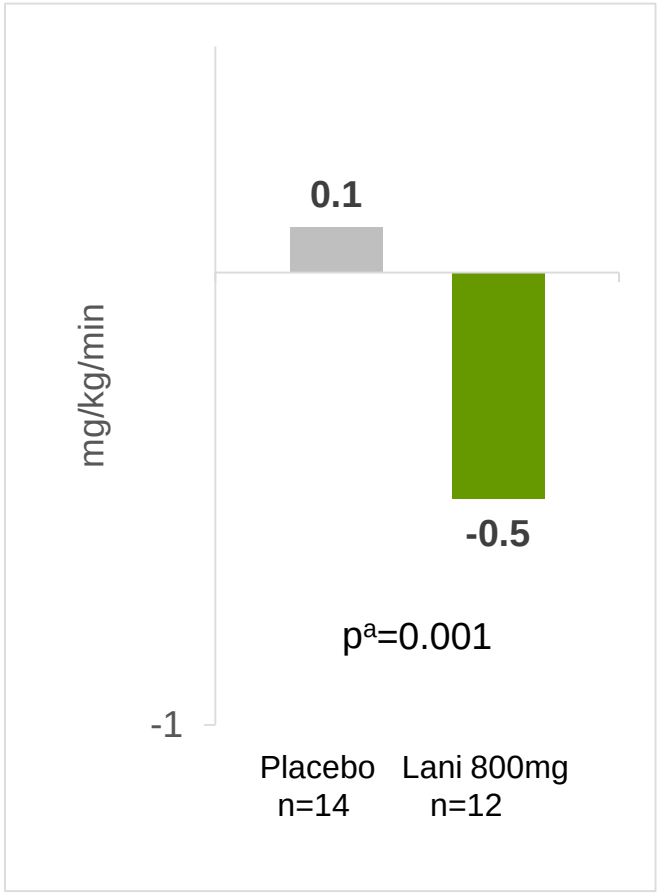
[a] Mixed Model Repeated Measures (MMRM)
[b] ANCOVA.

Lanifibranor leads to significant improvements in hepatic and muscular insulin sensitivity

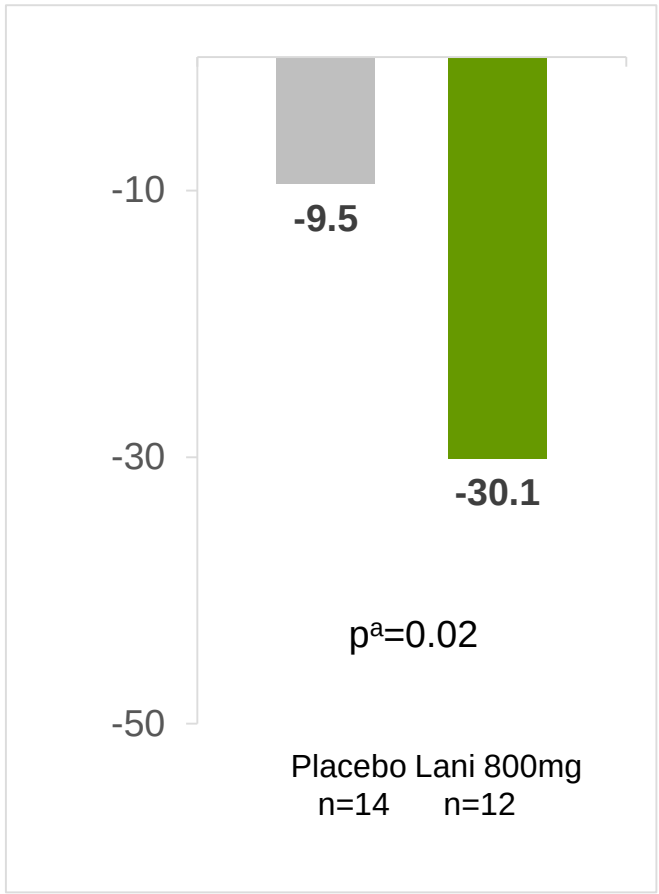
Completers (N=28)

LS Mean absolute change from baseline to week 24 in

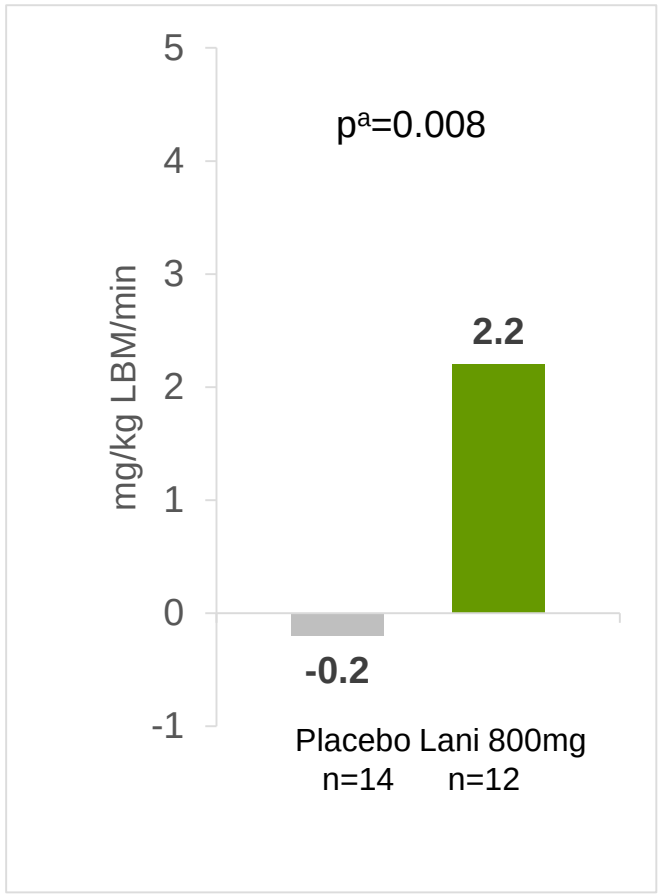
Endogenous glucose production



Hepatic insulin resistance index at week 24



Insulin-stimulated muscle glucose disposal



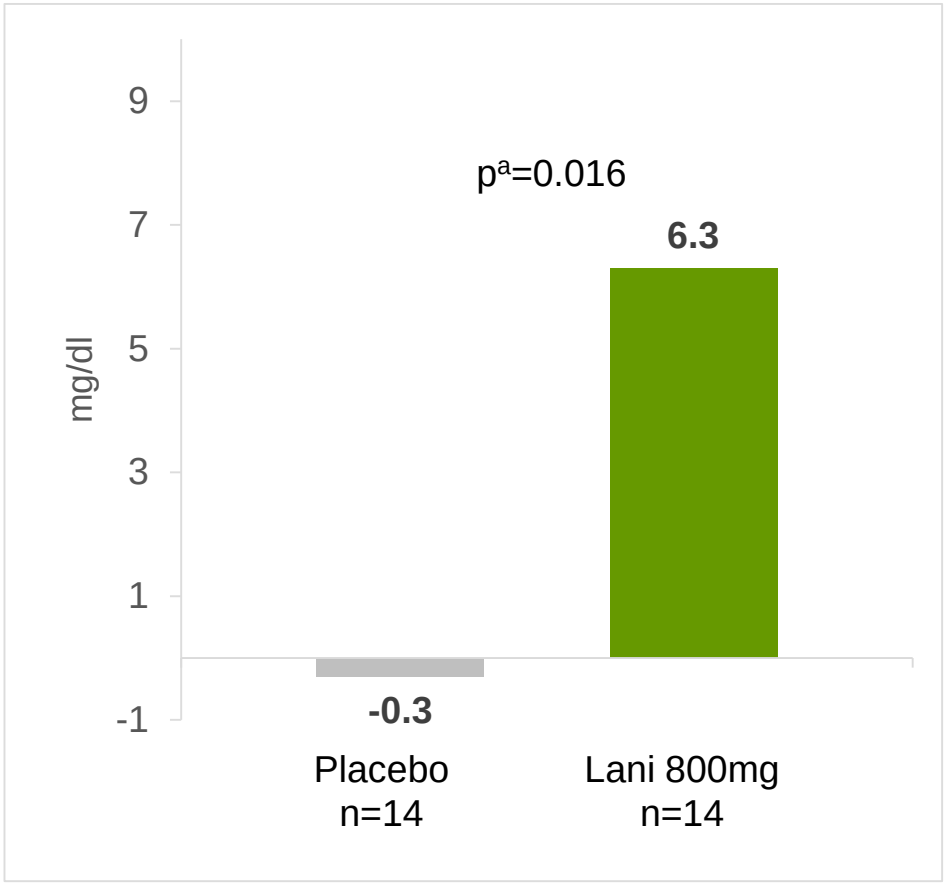
[a] ANCOVA.

Lanifibranor treatment increases HDL and adiponectin levels

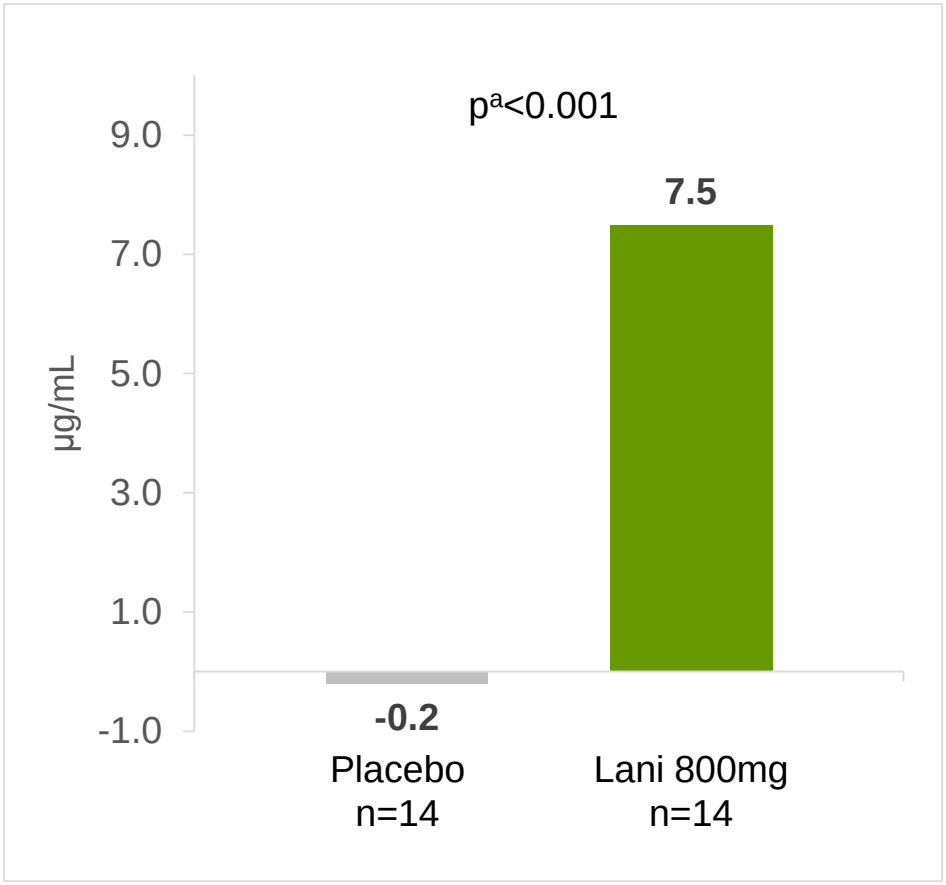
Completers (N=28)

LS Mean absolute change from baseline to week 24 in

HDL cholesterol



Adiponectin



[a] Mixed Model Repeated Measures (MMRM).

- **No change in LDL-cholesterol**

Treatment-emergent adverse events (TEAE): comparable profile accross treatment groups

Treatment-Emergent Adverse Event (TEAE)	Lanifibranor (n=20)	Placebo (n=18)
TEAE leading to death	0	0
Serious Adverse Event (SAE)	1*	0
Drug-Related SAE	0	0
TEAE leading to discontinuation	4	2
Drug-Related TEAE leading to discontinuation	3	2

Most frequent (>15%) related TEAE by SOC	Lanifibranor (n=20)	Placebo (n=18)
Investigations	4 (25.0%)	4 (22.2%)
Blood disorders	4 (20.0%)	3 (16.7%)
Gastrointestinal disorders	5 (25.0%)	1 (5.6%)

** pneumonia and pulmonary embolism due to Covid 19*

SOC: System Organ Class

Key take-aways

- **Lanifibranor met the primary efficacy endpoint by inducing a liver fat reduction of 44% in patients with T2D and NAFLD treated for 24 weeks.**
  - **65% of patients with T2D and NAFLD treated with lanifibranor achieved a greater than 30% liver triglyceride reduction and 25% achieved NAFLD resolution after 24 weeks.**
- **Lanifibranor has a potent therapeutic effect on insulin sensitivity, and corresponding metabolic markers in patients with T2D and NAFLD**
  - **Potent effect as insulin sensitizer on hepatic and muscular insulin sensitivity**
- **Lanifibranor significantly improved adiponectin, which is known to regulate glucose levels, lipid metabolism, and insulin sensitivity through its anti-inflammatory, anti-fibrotic, and antioxidant effects**
- **Study confirms the favorable safety and tolerability profile of lanifibranor**

Contacts

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