Lanifibranor Reverses Hepatic and Peripheral Insulin Resistance, Improves Lipid and Glucose Metabolism in Patients with Type 2 Diabetes (T2D) and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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INTRODUCTION

- Insulin resistance (IR) has a central role in the development and progression of steatohepatitis.[1,2]
- Liver-related mortality in NAFLD appears closely related to IR.[3]
- Insulin resistance is also central to the development of type 2 diabetes (T2D) and cardiovascular disease in people with MASLD.[1,2]
- Lanifibranor, a pan-PPAR agonist, improves steatohepatitis and fibrosis in patients with NASH (Phase 2b NATIVE trial)[4], but its effect on IR in different tissues is unclear and warrants further investigation.

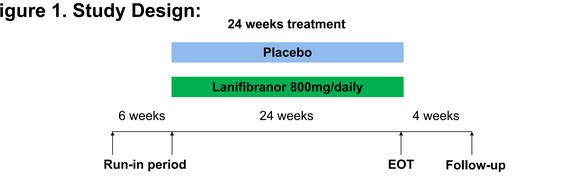
STUDY AIM

To assess the effect of lanifibranor on IR in liver, muscle and adipose tissue in relation to changes in intrahepatic triglyceride (IHTG) content.

METHODS

Participants: 38 adults with T2D on a background of metformin +/- a 2nd oral agent and MASLD (≥10% liver fat by ^{1}H-MRS) were randomized 1:1 to lanifibranor 800 mg or placebo daily for 24 weeks (NCT03459079).

Figure 1. Study Design:



Study Measures:

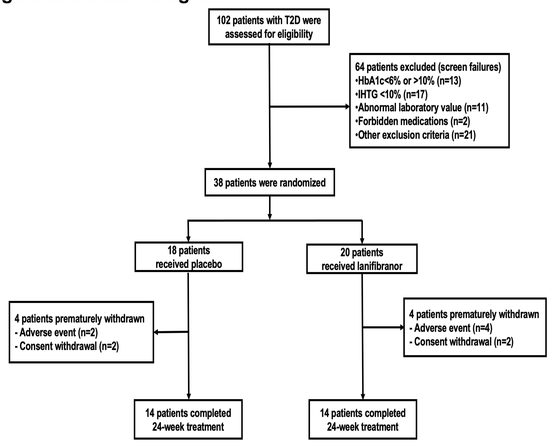
Primary efficacy endpoint:

Change in intrahepatic triglyceride (IHTG) change quantified by ^{1}H-MRS from baseline to end of treatment (EOT) at 24 weeks.

Secondary endpoints:

a) Change in hepatic, muscle and adipose tissue IR using the euglycemic insulin clamp with stable 6-6D_2-glucose and indirect calorimetry;
b) Proportion of patients with ≥ 30% decrease in IHTG
c) Proportion of patients with steatosis resolution (≤5.5% IHTG)
d) Changes in HbA1c and lipid profile.

Figure 2. Consort Diagram



RESULTS

Table 1. Baseline Clinical and Laboratory Characteristics

	Lanifibranor N=20	Placebo N=18
Age, years	61 ± 7	58 ± 11
Gender (male/female), %	45/55%	28/72%
Race		
White, n (%)	18 (90%)	15 (83%)
African American, n (%)	0 (0%)	2 (11%)
Asian, n (%)	0 (0%)	0 (0%)
More than one race, n (%)	1 (5%)	1 (6%)
Unknown, n (%)	1 (5%)	0 (0%)
Weight, kg	96 ± 14	99 ± 20
Body mass index, kg/m²	33.8 ± 5.1	34.3 ± 6.2
Fasting plasma glucose, mg/dl	126 ± 28	123 ± 23
HbA1c, % (mmol/mol)	6.8 ± 0.5	7.0 ± 0.8
Fasting plasma insulin, µU/ml	16.4 ± 8.6	18.2 ± 12.7
Free fatty acids (FFA), mmol/L	0.55 ± 0.23	0.47 ± 0.19
Total Cholesterol, mg/dl	159 ± 50	176 ± 40
Triglycerides, mg/dl	175 ± 95	196 ± 101
HDL-C, mg/dl	42 ± 9	43 ± 12
LDL-C, mg/dl	83 ± 42	89 ± 39
Adiponectin, µg/mL	4.5 ± 2.8	5.0 ± 3.7
Aspartate aminotransferase, U/L	31 ± 14	31 ± 19
Alanine aminotransferase, U/L	37 ± 20	35 ± 27
Cytokeratin-18 fragments, U/L	332 ± 260	285 ± 254
Baseline HOMA-IR, mg/dL x µU/mL	5.6 ± 3.2	5.4 ± 3.4
Baseline Adipo-IR, mmol/L x µU/mL	9.2 ± 6.1	8.7 ± 9.2
Baseline Liver fat/IHTG content (%)	21 ± 7	18 ± 7
Baseline corrected T1 mapping, ms	887 ± 72	924 ± 116
Baseline MRE, kPa	2.8 ± 0.8	2.5 ± 1.1
Baseline CAP, db/m	356 ± 36	352 ± 28
Baseline LSM, kPa	8.3 ± 4.6	8.2 ± 7.2

Data presented as mean ± SD; HDL= High Density Lipoprotein, LDL=Low Density Lipoprotein, IHTG=IntraHepatic TriGlyceride; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance, ADIPO-IR= Adipose Tissue Insulin Resistance,MRE=MR Elastography, CAP= Control Attenuation Parameter, LSM= Liver Stiffness Measurement.

Lanifibranor reverses insulin resistance, improves adiponectin and HDL-C

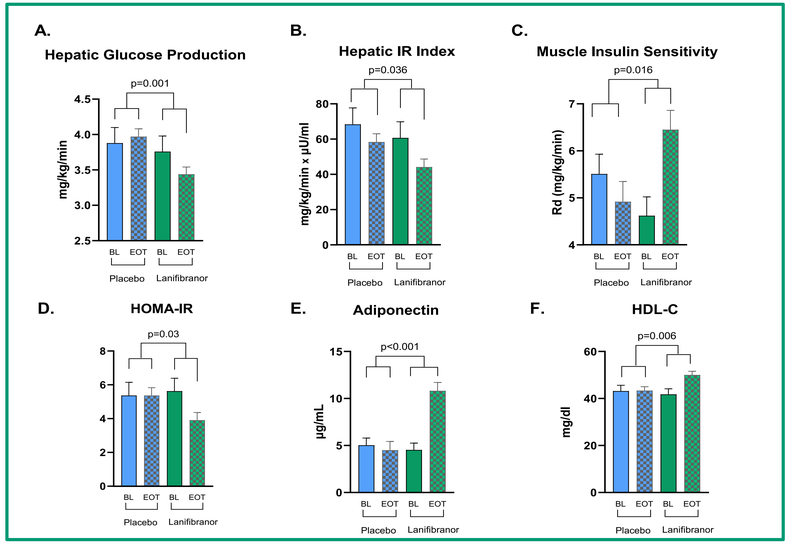


Figure 4. Data shown as adjusted mean + Standard Error in FAS, n=38; P-value from an ANCOVA or MMRM with treatment and baseline data as covariates. IR=Insulin Resistance. Rd=Insulin-stimulated glucose uptake.

Figure 4 (A-F): Lanifibranor significantly improved hepatic and peripheral insulin resistance, i.e., fasting hepatic glucose production (panel A), hepatic IR index (panel B), and muscle insulin sensitivity shown as insulin-stimulated glucose disposal (panel C); Lanifibranor significantly improved in secondary metabolic endpoints [adjusted LS mean difference]: fasting plasma insulin (-3.1 [-6.5;0.3], p=0.07), fasting glucose concentration (-19.6 [-34.5;-4.7], p=0.01), HbA1c (-0.6 [-1.0;-0.5], p<0.001) and HOMA-IR (-1.5 [-2.8;-0.2], p=0.03) in both FAS (Figure 4D) and completers (data not shown).

- In completers, lanifibranor also improved adipose tissue insulin resistance as measured by ADIPO-IR (-3.0 [-5.8;-0.20],p<0.05).
- Lanifibranor treatment resulted in more than 2-fold adiponectin increase (p<0.001) – Figure 4, panel E.
- Lanifibranor improved plasma HDL-C (Figure 4, panel F) with no change in plasma LDL-C (not shown).

Safety and Tolerability

- Drug-related TEAE leading to discontinuation were balanced between groups (3 on lanifibranor, 2 on placebo).
- More than 90% of adverse events were mild, with most common being gastrointestinal in nature and mild decrease in hemoglobin levels by week 24.
- None of the events of elevated lipase in lanifibranor group were associated with clinical symptoms.
- Compared to placebo, lanifibranor caused weight gain of +2.7% (+2.5 ± 3.1 kg vs -1.2 ± 2.6 kg in placebo, p=0.002) and in 1 patient mild edema.

Treatment-Emergent Adverse Event (TEAE) ≥15%	Lanifibranor (n=20)	Placebo (n=18)
Diarrhea	5 (25%)	3 (17%)
Elevated Lipase Level	5 (25%)	3 (17%)
Anemia	4 (20%)	2 (11%)
Leukopenia	3 (15%)	1 (6%)
Headache	3 (15%)	1 (6%)
Arthralgia	0 (0%)	3 (17%)

Lanifibranor significantly reduced IHTG

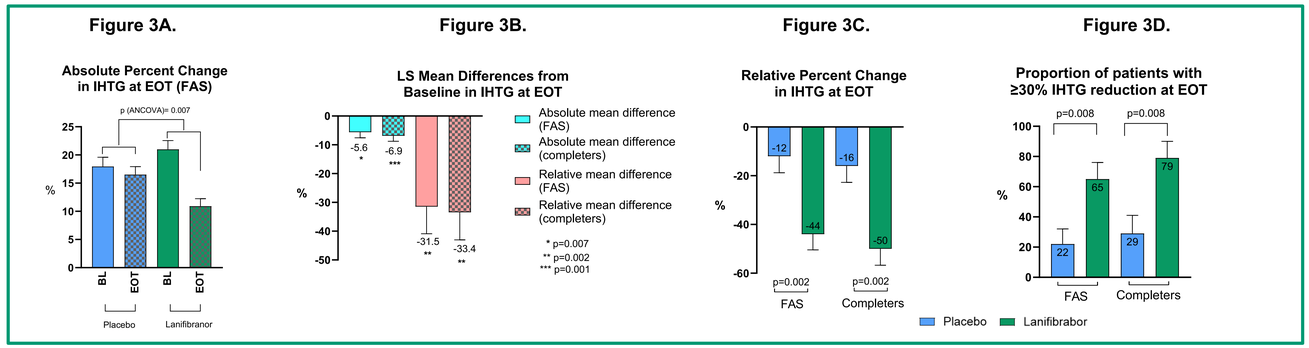


Figure 3: p-value from an ANCOVA with treatment and baseline data as covariates for continuous variables, or Chi² test for categorical variables. Missing continuous data were imputed using the last observation carried forward, missing categorical data were imputed as a failure. LS=Least Square, FAS=Full Analysis Set (n=38); Completers (n=28, 14 per group)

- **Figure 3:** Lanifibranor compared to placebo significantly lowered IHTG at EOT: in FAS the absolute change in IHTG as -10.1% in lanifibranor vs. -1.4% in placebo; least squares [LS] means difference -5.6%, [95% CI -9.6 to -1.7%], p=0.007; completers -12.4% vs. -2.4%; LS means difference -6.9%, [95% CI -10.8 to -2.9%], p=0.001 (Figure 3A and 3B).
- IHTG relative change in FAS was -44% with lanifibranor vs. -12% in placebo; LS means difference -31.5%, [95% CI -51 to -12%]; completers -50% vs. -16%; LS means difference -33.4%, [95% CI -53 to -14%]; both p<0.01 (Figure 3C and 3B).
- At EOT, more patients reached ≥30% IHTG reduction with lanifibranor compared to placebo (FAS 65% vs. 22%; completers 79% vs. 29%; both p<0.01) as shown in Figure 3D.
- At EOT more patients reached steatosis resolution (FAS 25% vs. 0%; p<0.05).

CONCLUSIONS

- Treatment of patients with T2D and MASLD with lanifibranor 800 mg/day for 24 weeks, led to:
  - Reduced IHTG content by 50%,
  - Improved hepatic and peripheral insulin sensitivity,
  - Improved adipose tissue biology, with more than two-fold increase in adiponectin levels,
  - Improved glucose (reduced A1c) and lipid metabolism (increased HDL-C levels).
- Treatment with lanifibranor was well tolerated, with the most common AE being mild and gastrointestinal in nature.
- *Clinical implication:* Lanifibranor improves liver and cardiometabolic health and it is a promising investigational agent for the treatment of MASLD.

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