Metabolic Benefits of Pan-PPAR Agonist Lanifibranor In Patients With and Without Type 2 Diabetes

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SCAN AND VIEW POSTER ON OUR WEBSITE

INTRODUCTION

Lanifibranor, an oral pan-peroxisome proliferator-activated receptor (PPAR α/γ/δ) agonist in development for metabolic dysfunction-associated steatohepatitis (MASH), has been shown to improve glucose and lipid metabolism. We assessed whether its observed metabolic benefits depend on a type 2 diabetes mellitus (T2DM) diagnosis by comparing outcomes in lanifibranor-treated patients with and without T2DM across four phase II studies.

METHODS

Data were drawn from S337.2.001 (4-week, T2DM on metformin, non-MASH, N=61); NATIVE (24-week phase IIb MASH, N=247, with pre-specified diabetic-status subgroups [42% T2DM]); a single-center euglycemic-clamp study (NCT03459079; 24-week, T2DM with metabolic dysfunction-associated steatotic liver disease, N=38) providing gold-standard clamp measures of hepatic, muscle and adipose insulin sensitivity; and FASST (48-week systemic sclerosis, non-diabetic, N=145). Comparisons were descriptive, without statistical pooling.

RESULTS

Table 1. Metabolic Response By Diabetes Status (NATIVE, Week 24)

Mean absolute change from baseline; adiponectin shown as fold-increase. Lanifibranor 800 / 1200 mg once daily vs placebo.

	PATIENTS WITH T2DM			PATIENTS WITHOUT T2DM		
PARAMETER	LAN 800	LAN 1200	Placebo	LAN 800	LAN 1200	Placebo
Fasting plasma glucose (mmol/L)	−1.71	−0.88	+0.29	−0.49	−0.39	+0.16
HbA1c (%)	−0.60	−0.72	+0.10	−0.21	−0.25	+0.08
HOMA index	−10.62	−5.52	−0.60	−3.42	−7.27	+0.11
Adiponectin (fold-increase)	4.12	4.44	1.11	3.62	4.54	1.00

KEY POINT: Glucose, HbA1c and insulin resistance improve in patients with AND without T2DM. Absolute glycaemic gains are larger where baseline burden is higher (T2DM), while the adiponectin (PPARγ-engagement) response is essentially identical across strata.

Source: NATIVE (Francque et al., N Engl J Med 2021;385:1547–1558; NCT03008070) — CSR analyses by diabetic status; N=247 (103 T2DM / 144 non-T2DM). Green = lanifibranor; grey = placebo.

Table 2. Tissue-specific insulin sensitization: Euglycemic Clamp Study

Adjusted least-squares mean difference vs placebo at Week 24 (full analysis set, N=38). T2D + MASLD; lanifibranor 800 mg.

PARAMETER	LANIFIBRANOR VS PLACEBO (95% CI)	p
HEPATIC		
Endogenous glucose production (relative %)	**−13% (−20 to −6)**	<0.001
Hepatic insulin-resistance index (relative %)	**−18% (−34 to −2)**	0.04
MUSCLE		
Insulin-stimulated glucose disposal, Rd (relative %)	**+29% (+5 to +54)**	0.02
ADIPOSE TISSUE		
Adipose insulin resistance (Adipo-IR, index)	**−2.0 (−4.2 to +0.3)**	0.08
Adiponectin (fold-increase)	**2.4-fold (Δ +1.4; +0.9 to +1.9)**	<0.001
SYSTEMIC GLYCAEMIA & LIPIDS		
Fasting plasma glucose (mg/dL)	**−19.6 (−34.5 to −4.7)**	0.01
HOMA-IR	**−1.5 (−2.8 to −0.2)**	0.03
HbA1c (%)	**−0.6 (−1.0 to −0.5)**	<0.001
HDL-cholesterol (mg/dL)	**+6.6 (+2.0 to +11.3)**	0.006
Intrahepatic triglyceride (relative %)	**−31% (−51 to −12)**	0.002

KEY POINT: Direct clamp measurements confirm lanifibranor sensitises all three insulin-target tissues — liver, muscle and adipose — addressing the systemic metabolic drivers of MASH rather than the hepatic manifestation alone.

Source: Barb/Cusi et al., J Hepatol 2025;82:979–991 (NCT03459079). Tissue sensitivity measured by two-step euglycaemic hyperinsulinaemic clamp with stable-isotope glucose turnover.

Table 3. Adiponectin Induction Independent of Diabetes and Disease

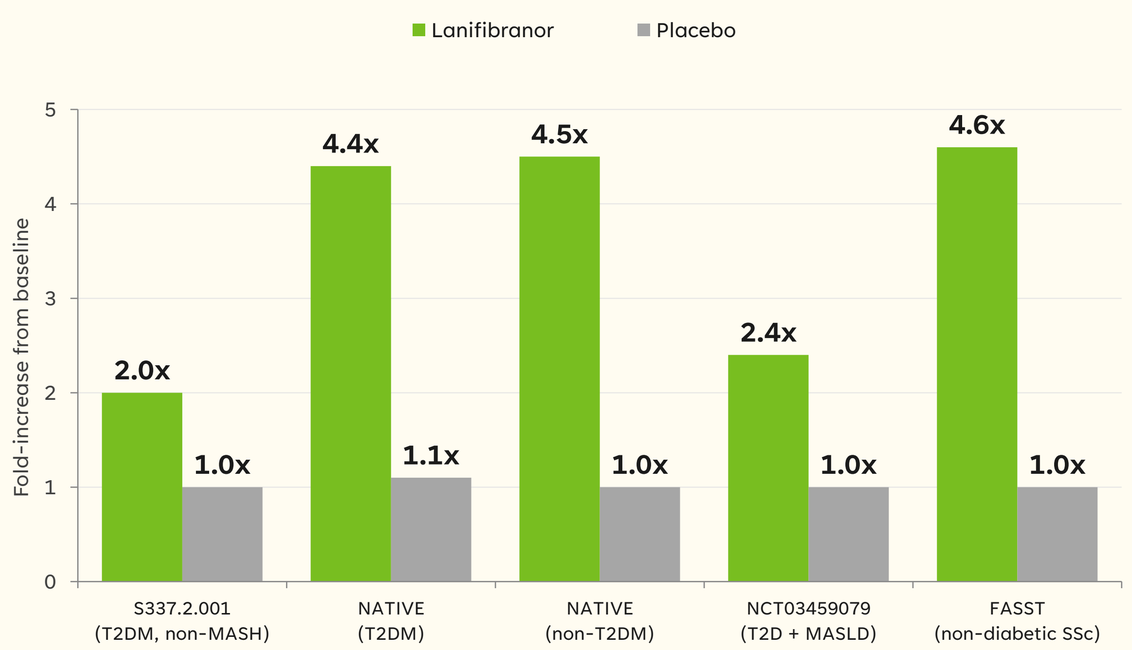
Adiponectin fold-increase from baseline with Lanifibranor (placebo ≈ 1.0-fold throughout).

STUDY	POPULATION	DIABETES STATUS	LANIFIBRANOR DOSE / DURATION	ADIPONECTIN FOLD-INCREASE
S337.2.001	T2DM on metformin (non-MASH)	100% T2DM	400–1400 mg · 4 wk	**≈2-fold***
NATIVE	MASH (biopsy-confirmed)	T2DM subgroup	800 / 1200 mg · 24 wk	**4.1–4.4-fold**
NATIVE	MASH (biopsy-confirmed)	non-T2DM subgroup	800 / 1200 mg · 24 wk	**3.6–4.5-fold**
NCT03459079	T2D + MASLD (clamp study)	100% T2DM	800 mg · 24 wk	**2.4-fold**
FASST	Diffuse systemic sclerosis	Non-diabetic	800 / 1200 mg · 48 wk	**4.6-fold†**

KEY POINT: Adiponectin — a direct marker of PPARγ target engagement — rises 2–5-fold in every population: T2DM, non-T2DM MASH, and non-diabetic systemic sclerosis. Target engagement is therefore independent of diabetes status and of the underlying disease.

*Sources: S337.2.001, NATIVE and FASST Clinical Study Reports; Barb/Cusi et al., J Hepatol 2025 (NCT03459079). *S337.2.001: ≥doubling of mean total adiponectin (dose-related), approximate. †FASST: median fold-increase. Placebo ≈ 1.0-fold in all studies.*

Figure 1. Adiponectin Fold-increase Across Populations



KEY POINT: Every lanifibranor arm rises far above the placebo reference (≈1.0-fold), regardless of diabetes status or underlying disease — confirming diabetes- and disease-independent PPAR-γ engagement.

Sources as Table 3. Cross-study magnitudes are not head-to-head comparable (dose, duration and assay differ); S337.2.001 value approximate (≥doubling), FASST median. Placebo bars shown for reference.

CONCLUSION

Metabolic benefits of lanifibranor were seen in these studies regardless of T2DM diagnosis, reflecting direct PPAR action on adipose, muscle and hepatic components that can be drivers of MASH. Tissue-specific insulin sensitization, adiponectin increases, and HDL-C elevation occurred irrespective of diabetes status or underlying disease. Glycemic improvement scales with baseline burden and is greatest in established T2DM.

Lanifibranor may address the systemic metabolic dysfunction underlying MASH, not the hepatic manifestation alone, and could also potentially support the management of T2DM.

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S337.2.001, NATIVE and FASST Clinical Study Reports

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