Lanifibranor Improves Metabolic and Histologic Features of MASH Across Multiple Preclinical Models: Convergent Pan-PPAR Activity

A.G. (Onno) Holleboom[1], Sven M. Francque[2], Jason Campagna[3], Simon Hogan[3,*], Guillaume Wettstein[3], Manal F. Abdelmalek[4]

[1]Department of Vascular Medicine, Amsterdam UMC, Amsterdam, The Netherlands; [2]Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium; [3]Inventiva, Daix, France; [4]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

*Presenting author.

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INTRODUCTION

- Metabolic dysfunction–associated steatohepatitis (MASH) is a systemic multi-organ disease characterized by steatosis, inflammation, hepatocyte injury, and progressive hepatic fibrosis that arises in the setting of metabolic disturbances (insulin resistance, dyslipidemia, obesity, systemic inflammation)[1-3]
- Peroxisome proliferator–activated receptors (PPARs) regulate several of the pathways involved in the pathogenesis of MASH, but no single PPAR subtype affects all disease drivers[4]
- Through balanced activation of PPARα, δ, and γ, lanifibranor engages multiple pathologic pathways, enabling both direct antifibrotic and metabolic improvement[5-8]

AIM

- To evaluate the effect of lanifibranor on both the metabolic and histologic antifibrotic components of MASH in preclinical rodent models

METHODS

- The metabolic effects of lanifibranor were evaluated across multiple rodent diabetic-/insulin-resistant and dyslipidemic models, with up to 6 weeks of treatment (**Figure 1**)
  - End points included fasting/nonfasting glucose, glucose and insulin tolerance, glycated hemoglobin (HbA1c), adiponectin, triglycerides, cholesterol/apolipoprotein A1 (apoA1), and body weight
- Histologic and antifibrotic effects of lanifibranor were evaluated in dietary rodent MASH models (**Figure 1**)

Figure 1. Study Design

Diabetic/insulin resistant	**db/db mouse (5-day treatment):** Lanifibranor daily oral doses: 3, 10, 30 mg/kg; rosiglitazone (3 mg/kg) used as a reference; n=9/10 per treatment group
	db/db mouse (4-week treatment): Lanifibranor daily oral doses: 10, 30 mg/kg; rosiglitazone (3 mg/kg) used as a reference; n=10 per treatment group
	ZDF rat (4-week treatment): Lanifibranor daily oral gavage doses: 30, 100 mg/kg; rosiglitazone (3 mg/kg) and muraglitazar (1 or 3 mg/kg) used as references; n~10 per treatment group
	HF/HS mouse (4-week treatment)[9]: Lanifibranor daily oral doses: 3, 10, 30 mg/kg; n=10 per treatment group
Dyslipidemic	**Human apoA1 mouse (2-week treatment):** Lanifibranor daily oral dose: 30 mg/kg; fenofibrate (30 or 100 mg/kg) used as a reference; n=8 per treatment group
	WOKW rat (3-week treatment): Lanifibranor daily oral dose: 100 mg/kg; n~10 in the treatment group
MASH	**CDAA-HFD mouse (6-week diet, 2-week treatment; 12-week diet, 6-week treatment)[10]:** Lanifibranor daily oral gavage dose: 30 mg/kg. Comparators: fenofibrate (100 mg/kg), pioglitazone (30 mg/kg), GW501516 (10 mg/kg)
	WD mouse (6-week treatment)[10]: Lanifibranor daily oral gavage dose: 30 mg/kg. Comparators: fenofibrate (100 mg/kg), pioglitazone (30 mg/kg), GW501516 (10 mg/kg)
	Free-choice diet-induced MASH hamster (5-week treatment): Lanifibranor daily oral doses: 10, 30 mg/kg

apoA1, apolipoprotein A1; CDAA-HFD, choline-deficient L-amino acid–defined high-fat diet; db/db, diabetic; HF/HS, high-fat/high-sucrose; MASH, metabolic dysfunction–associated steatohepatitis; WD, Western diet; WOKW, Wistar Ottawa Karlsburg W; ZDF, Zucker Diabetic Fatty.

RESULTS

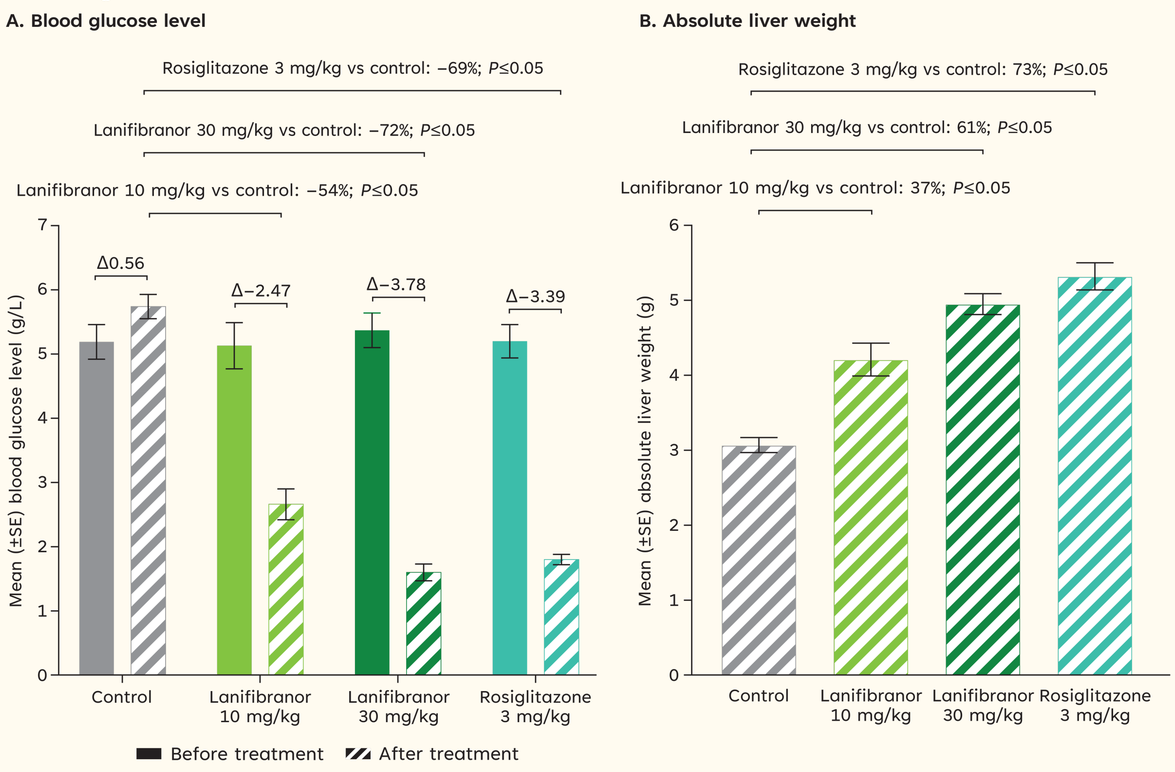
- In diabetic (db/db) mice (model of insulin-resistant type 2 diabetes), lanifibranor dose-dependently reduced glucose levels and triglycerides, with similar trends observed in Zucker Diabetic Fatty (ZDF) rats (**Table 1**)
  - At the highest dose, lanifibranor normalized blood glucose, an effect that was comparable with that of rosiglitazone at 3 mg/kg but without increasing liver weight (**Figure 2**)
- In ZDF rats, the higher lanifibranor dose (100 mg/kg) significantly reduced HbA1c and increased adiponectin (**Table 1**)
  - Lanifibranor did not enhance food consumption and resulted in less body weight gain and less fat accumulation compared with rats treated with rosiglitazone
- Improved glucose tolerance was similarly observed in a high-fat/high-sucrose (HF/HS) diet-induced obesity mouse model as well as dose-dependent improvements to body composition, as measured by decreases in the adiposity index (–60% at 30 mg/kg; $P<0.001$)[9]

Table 1. Effects of Lanifibranor in Diabetic Animal Models

Measurement	Model; treatment duration	Variation (%) of mean reported values relative to vehicle controls: Lanifibranor dose 3 mg/kg	10 mg/kg	30 mg/kg	100 mg/kg
Triglycerides	db/db mice; 5 days	–19	–33	–45	NM
	db/db mice; 4 weeks	NM	–43	–47	NM
	ZDF rats; 4 weeks	NM	NM	+16	–24
Nonfasting glucose	db/db mice; 5 days	0	–40	–58	NM
	ZDF rats; 4 weeks	NM	NM	–6	–36
Fasting glucose	db/db mice; 4 weeks	NM	–54	–72	NM
	ZDF rats; 4 weeks	NM	NM	–7	–22
Adiponectin	db/db mice; 4 weeks	NM	+26	+49	NM
	ZDF rats; 4 weeks	NM	NM	+30	+159
Weight gain	db/db mice; 4 weeks	NM	+5.8 g*	+7.9 g*	NM
Glucose AUC	ZDF rats; 4 weeks	NM	NM	–6	–29
Insulin AUC		NM	NM	–15	+100
HbA1c		NM	NM	–8	–19

*Controls +3.5 g.
AUC, area under the curve; db/db, diabetic; HbA1c, glycated hemoglobin; NM, not measured; ZDF, Zucker Diabetic Fatty.

Figure 2. Blood Glucose Level and Absolute Liver Weight in db/db Mice Treated With Lanifibranor and Rosiglitazone



db/db, diabetic; SE, standard error.

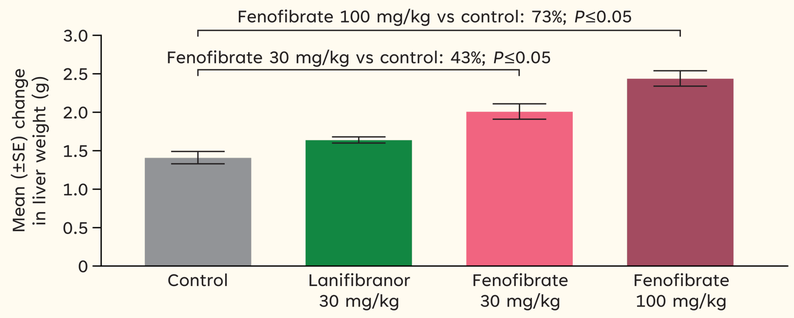
- In the dyslipidemic apoA1-transgenic mouse model, lanifibranor increased serum human apoA1 and reduced triglycerides (**Table 2**) without the liver-weight increase observed with fenofibrate (**Figure 3**)
- In Wistar Ottawa Karlsburg W (WOKW) rats, lanifibranor consistently improved markers of dyslipidemia (ie, reduced triglycerides and very low–density lipoprotein, increased high-density lipoprotein and adiponectin; **Table 2**)
- Across dietary MASH models, lanifibranor reduced steatosis, necroinflammatory activity, and fibrosis (**Table 3**)
- In an obese hamster MASH model, lanifibranor additionally lowered Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score and plasma alanine transaminase (ALT) and improved diastolic dysfunction, which reflects a combined hepatic and cardiometabolic benefit (**Table 3**)

Table 2. Effect of Lanifibranor in Dyslipidemic Animal Models

Measurement	Model; treatment duration	Variation (%) of mean reported values relative to vehicle controls: Lanifibranor dose 30 mg/kg	100 mg/kg
Serum cholesterol	Human apoA1 transgenic mice; 2 weeks	+93	NM
	WOKW rats; 3 weeks	NM	+12
Serum human apoA1	Human apoA1 transgenic mice; 2 weeks	+59	NM
Serum cholesterol		+93	NM
Serum triglycerides		–52	NM
Liver weight		+16	NM
Adiposity index	WOKW rats; 3 weeks	NM	–20
HDL cholesterol		NM	+25
LDL cholesterol		NM	+42
VLDL cholesterol		NM	–50
Triglycerides		NM	–66
Adiponectin		NM	+26
Leptin		NM	–22
Body weight gain		NM	+32.0 g*
AUC insulin (glucose challenge)		NM	–19†

*Controls +43.4 g. †Unchanged AUC glucose.
apoA1, apolipoprotein A1; AUC, area under the curve; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NM, not measured; VLDL, very low–density lipoprotein; WOKW, Wistar-Ottawa-Karlsburg W.

Figure 3. Change in Liver Weight Over 2 Weeks in Human apoA1 Transgenic Mice Treated With Lanifibranor and Fenofibrate



apoA1, apolipoprotein A1; SE, standard error.

Table 3. Effect of Lanifibranor in MASH Animal Models

Measurement	Model; treatment duration	Variation (%) of mean reported values relative to vehicle controls: Lanifibranor 10 mg/kg	30 mg/kg
Steatosis	CDAA-HFD mice; 2 weeks*	NM	–65
	CDAA-HFD mice; 6 weeks†	NM	–74
	WD mice; 6 weeks	NM	–67
	Free-choice diet-induced MASH hamster	–16	–48
Inflammation	CDAA-HFD mice; 2 weeks*	NM	–31
	CDAA-HFD mice; 6 weeks†	NM	–57
	WD mice; 6 weeks	NM	–60
	Free-choice diet-induced MASH hamster	–10	–60
Ballooning	CDAA-HFD mice; 2 weeks*	NM	–100
	CDAA-HFD mice; 6 weeks†	NM	–87
	Free-choice diet-induced MASH hamster	–30	–60
Fibrosis	CDAA-HFD mice; 2 weeks*	NM	–29
	CDAA-HFD mice; 6 weeks†	NM	–43
	Free-choice diet-induced MASH hamster	NE	+16
NAFLD activity	CDAA-HFD mice; 2 weeks*	NM	–50
	CDAA-HFD mice; 6 weeks†	NM	–65
HOMA-IR	Free-choice diet-induced MASH hamster	–39	–41
ALT		–6	–15
Hepatic triglycerides		–22	–36
Hepatic cholesterol		–17	–25

*6-week diet. †12-week diet.
ALT, alanine transaminase; CDAA-HFD choline-deficient L-amino acid–defined high-fat diet; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; MASH, metabolic dysfunction–associated steatohepatitis; NAFLD, nonalcoholic fatty liver disease; NE, no effect; NM, not measured; WD, Western diet.

CONCLUSIONS

- Across multiple animal models of MASH, lanifibranor consistently improved the metabolic and histologic parameters that contribute to MASH progression
- These data support pan-PPAR agonism as a treatment by addressing both the systemic metabolic and hepatic complications of MASH, as seen in the NATIVE clinical study[6]

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