Lanifibranor Phase 1/2a Experience - PPARγ Engagement and Metabolic Activity Without Early Clinical Fluid Retention

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INTRODUCTION

- Peroxisome proliferator–activated receptors (PPARs) regulate several of the pathways involved in the pathogenesis of metabolic diseases, including metabolic dysfunction–associated steatohepatitis (MASH)[1]
- Lanifibranor is a pan-PPAR agonist with balanced activation of PPARα, δ, and γ that demonstrated strong activity in models relevant to MASH[2]
- Translation of preclinical PPAR pharmacology to human dose selection requires evidence of target engagement, cardiometabolic effects, and an acceptable safety profile at predicted therapeutic exposures

AIM

- To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) effects of lanifibranor treatment in phase 1 and phase 2a study programs, including in patients with type 2 diabetes mellitus (T2DM), focusing on lanifibranor's partial PPARγ activity

METHODS

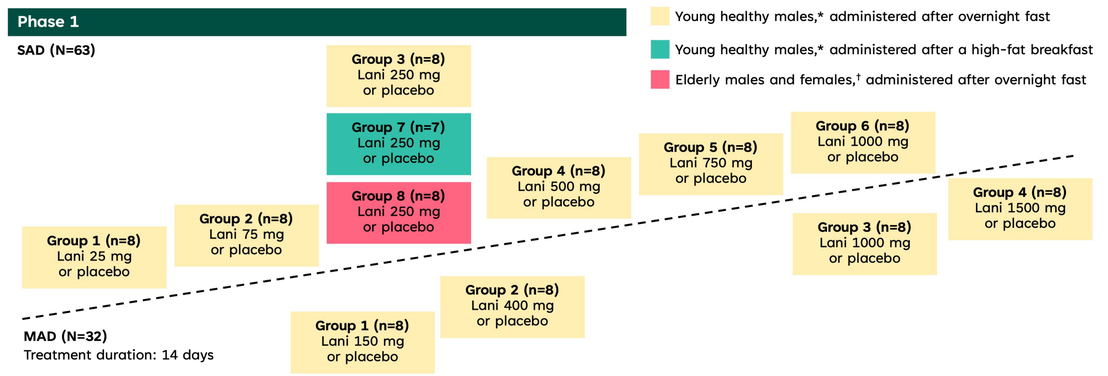
Phase 1 study in healthy participants

- The PK, PD, safety, and tolerability of lanifibranor were evaluated in a phase 1, randomized, double-blind, placebo-controlled study (**Figure 1**)
- Single ascending doses (SAD) of oral lanifibranor were administered to 7 groups of young healthy male participants and 1 group of elderly healthy male and female participants following an interval of at least 6 days between dose levels to ensure safety and tolerability
- After Group 6 of the SAD cohort completed evaluation, multiple ascending doses (MAD) of oral lanifibranor were administered to young healthy males for 14 days, progressing to a higher dose after the safety and tolerability of the previous dose was established

Phase 2 study in participants with T2DM

- The phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 28-day study evaluated lanifibranor in participants with T2DM who were on metformin monotherapy (**Figure 1**)
- Safety, tolerability, PK, and PD were evaluated; focusing on PPARγ, adiponectin was examined as a target-engagement marker and glycemic and lipid parameters as metabolic efficacy signals

Figure 1. Study Design



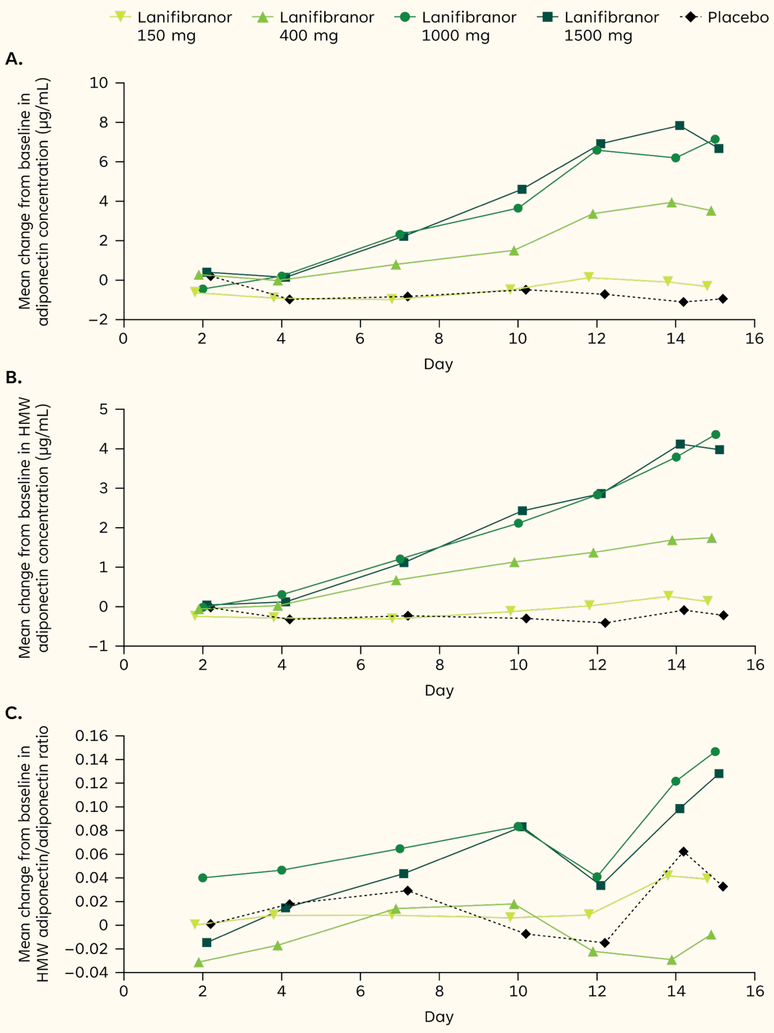
*Aged 18-45 years inclusive. †Aged 60-80 years inclusive.
All treatment was preceded by screening and randomization and followed by discharge and follow-up.
Within each group of 8 participants, 6 participants were randomized to receive lanifibranor and 2 were randomized to receive placebo.
Lani, lanifibranor; MAD, multiple ascending doses; SAD, single ascending doses.

RESULTS

Phase 1 SAD/MAD study

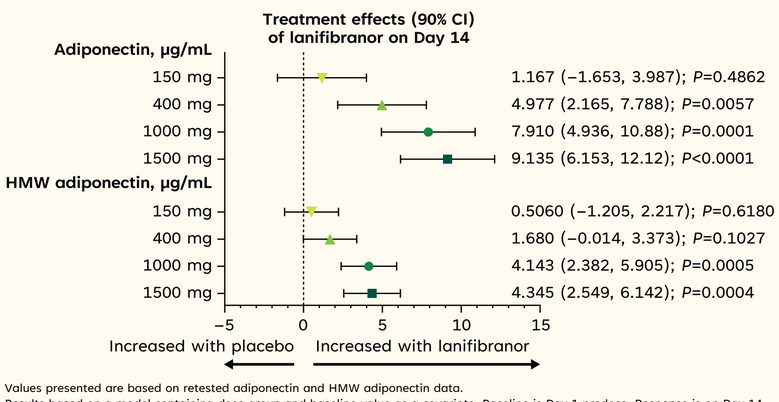
- Single and multiple doses of lanifibranor were safe and well tolerated in study participants
- Lanifibranor significantly increased adiponectin versus placebo at 400, 1000, and 1500 mg daily doses, with high–molecular weight (HMW) adiponectin increases at 1000 and 1500 mg daily (**Figure 2** and **Figure 3**)

Figure 2. Mean Change From Baseline Values of (A) Adiponectin, (B) HMW Adiponectin, and (C) HMW Adiponectin/Adiponectin Ratio Over Time in the Phase 1 MAD Study



Data presented in this figure are based on retested adiponectin and HMW adiponectin data.
HMW, high molecular weight; MAD, multiple ascending doses.

Figure 3. Analysis of Treatment Effects on Observed Adiponectin and HMW Adiponectin on Day 14 Using an ANCOVA Model in the Phase 1 MAD Study



Values presented are based on retested adiponectin and HMW adiponectin data.
Results based on a model containing dose group and baseline value as a covariate. Baseline is Day 1 predose. Response is on Day 14.
ANCOVA, analysis of covariance; CI, confidence interval; HMW, high molecular weight; MAD, multiple ascending doses.

Phase 2a study in participants with T2DM

- Demographic characteristics were well balanced across treatment groups (**Table 1**)

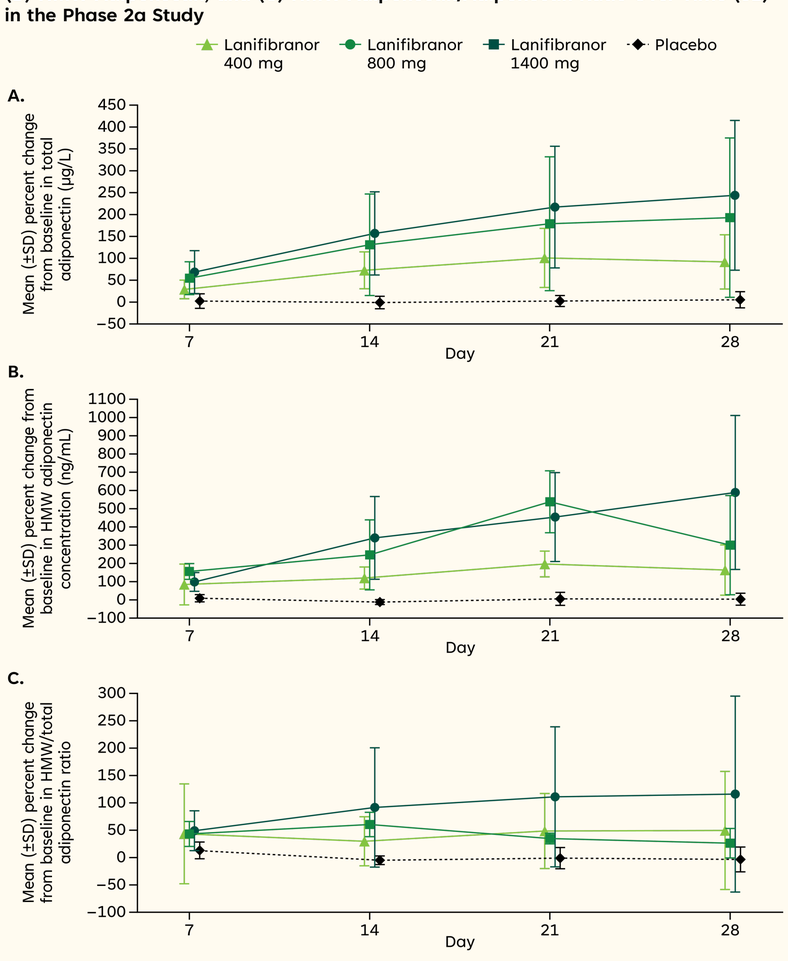
Table 1. Phase 2a Participant Demographic Characteristics

Characteristic	Lanifibranor 400 mg (n=17)	Lanifibranor 800 mg (n=15)	Lanifibranor 1400 mg (n=15)	Placebo (n=14)	All participants (N=61)
Mean (SD) age, years	58.4 (6.6)	57.1 (10.2)	61.5 (5.6)	57.2 (11.8)	58.6 (8.7)
Age category, n (%)					
<65 years	14 (82.4)	11 (73.3)	11 (73.3)	11 (78.6)	47 (77.0)
≥65 years	3 (17.6)	4 (26.7)	4 (26.7)	3 (21.4)	14 (23.0)
Gender, n (%)					
Male	8 (47.1)	9 (60.0)	9 (60.0)	9 (64.3)	35 (57.4)
Female	9 (52.9)	6 (40.0)	6 (40.0)	5 (35.7)	26 (42.6)
Ethnicity, n (%)					
Not Hispanic or Latino	17 (100)	15 (100)	15 (100)	14 (100)	61 (100)
Race, n (%)*					
Asian	1 (5.9)	1 (6.7)	1 (6.7)	1 (7.1)	4 (6.6)
Black or African heritage or African American	4 (23.5)	6 (40.0)	6 (40.0)	6 (42.9)	22 (36.1)
White	16 (94.1)	13 (86.7)	13 (86.7)	12 (85.7)	54 (88.5)

*More than 1 category could be selected.
SD, standard deviation.

- Exposure to lanifibranor increased in a less than dose-proportional manner following oral dosing with 400, 800, and 1400 mg once daily
- Lanifibranor (400, 800, and 1400 mg) consistently induced dose- and time-related increases in total and HMW adiponectin (**Figure 4**), which is indicative of PPARγ engagement
  - Exposures of about 50 µg·h/mL for area under the curve from time zero to the last measurable concentration ($AUC_{0-\tau}$) and about 7 µg/mL for the maximal concentration (C_{max}) resulted in more than 200% increase for the percent change from baseline total adiponectin

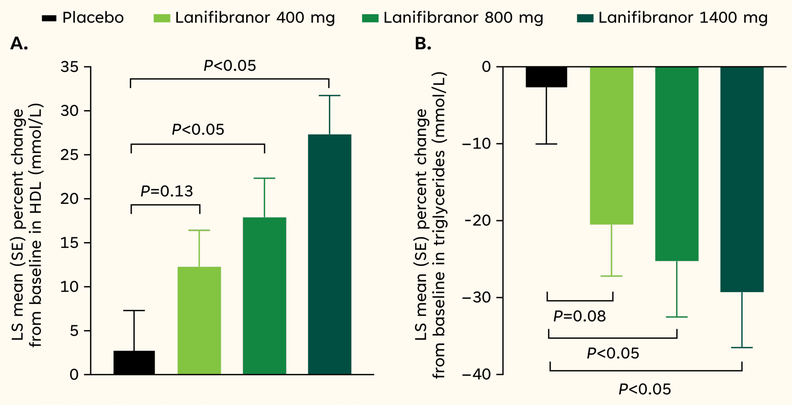
Figure 4. Mean (SD) Percent Change From Baseline of (A) Total Adiponectin, (B) HMW Adiponectin, and (C) HMW Adiponectin/Adiponectin Ratio Over Time (SE) in the Phase 2a Study



HMW, high molecular weight; SD, standard deviation; SE, standard error.

- Lanifibranor 800 and 1400 mg showed significant ($P<0.05$) change from baseline in high-density lipoprotein (HDL) cholesterol and triglycerides compared with placebo (**Figure 5** and **Table 2**)

Figure 5. Mean (SE) Percent Change From Baseline in (A) HDL Cholesterol and (B) Triglycerides on Day 28 in the Phase 2a Study



HDL, high-density lipoprotein; LS, least squares; SE, standard error.

- Dose-related improvements in insulin, pro-insulin, and insulin resistance were observed with lanifibranor, with a significant reduction in pro-insulin with 1400 mg versus placebo. Reductions in average and postprandial blood glucose were observed at 1400 mg (**Table 2**), which were consistent with the PPARγ insulin-sensitizing mechanism

Table 2. Mean (SD) Percent Change From Baseline Values of Key Lipid- and Glucose-Related PD Parameters at Day 28 in the Phase 2a Study

Parameter	Lanifibranor 400 mg (n=17)	Lanifibranor 800 mg (n=15)	Lanifibranor 1400 mg (n=15)	Placebo (n=14)
Triglycerides	−19.7 (33.9)	−20.8 (23.5)*	−31.7 (31.2)*	−5.81 (27.6)
HDL-C	13.4 (15.3)	16.7 (17.2)*	27.7 (25.9)*	2.52 (12.2)
FPG	−4.05 (27.2)	−11.1 (20.0)	−14.6 (10.4)	−11.1 (10.3)
Mean 7 glucose	−4.50 (19.0)	−5.16 (15.0)	−13.4 (13.3)	−7.69 (12.1)
Mean 3 PP glucose	0.515 (28.0)	−3.89 (17.2)	−12.6 (12.9)	−3.39 (15.6)
Insulin	−21.1 (63.3)	−15.3 (57.1)	−42.2 (29.8)	−3.93 (48.1)
Pro-insulin	−26.7 (35.6)	−21.1 (45.0)	−37.4 (26.3)*	−3.28 (49.9)
Pro-insulin/insulin	131 (162)	59.6 (159)	114 (153)	196 (420)
HOMA-IR	−17.6 (84.8)	−20.9 (74.6)	−43.7 (27.0)	−6.81 (51.2)
HbA1c	−2.62 (12.4)	−2.31 (7.23)	0.162 (6.54)	−4.53 (10.7)

*Significant difference versus placebo ($P<0.05$).
FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model of Assessment-Insulin Resistance; mean 3 PP glucose, average postprandial blood glucose; mean 7 glucose, average blood glucose; PD, pharmacodynamics; SD, standard deviation.

- At Day 28, lanifibranor showed no fluid-retention signals (pedal edema, ankle foot volume, ankle circumference, or body-weight increase) versus placebo, with no changes in hematology, albumin, or brain natriuretic peptide (BNP; **Table 3**)
- Overall, lanifibranor was safe and well tolerated in participants with T2DM on metformin monotherapy

Table 3. Mean (SD) Percent Change From Baseline Values at Day 28 for Key Signals of Fluid Retention in the Phase 2a Study

Parameter	Lanifibranor 400 mg (n=17)	Lanifibranor 800 mg (n=15)	Lanifibranor 1400 mg (n=15)	Placebo (n=14)	All participants (N=61)
Ankle foot volume, cm^3	3.75 (14.51)	−5.31 (15.51)	3.91 (11.14)	−5.42 (11.07)	−0.46 (13.71)
Left ankle circumference, cm	−0.20 (5.33)	−0.55 (2.95)	−1.40 (3.52)	−0.97 (4.57)	−0.76 (4.15)
Right ankle circumference, cm	−0.57 (5.82)	−1.02 (3.29)	−1.39 (4.63)	−1.17 (3.75)	−1.02 (4.44)
Body weight change at Day 7, kg*	0.66 (1.32)	0.51 (1.37)	0.17 (1.50)	0.37 (2.07)	0.44 (1.55)
Body weight change at Day 28, kg	0.55 (1.97)	0.11 (1.72)	0.94 (2.05)	−0.36 (2.68)	0.33 (2.12)
Hematocrit, V/V	−5.88 (5.12)	−4.03 (6.24)	−5.38 (6.49)	−4.26 (5.72)	−4.94 (5.80)
Hemoglobin, g/L	−5.63 (4.81)	−5.04 (6.75)	−5.96 (5.55)	−3.70 (5.29)	−5.15 (5.53)
Albumin, g/L	0.2 (5.2)	1.4 (7.4)	0.4 (8.5)	−1.4 (4.5)	0.2 (6.5)
BNP, ng/L	191.53 (328.06)	256.94 (422.80)	149.26 (209.69)	112.86 (196.09)	184.68 (308.18)
NT-proBNP, pmol/L	46.48 (89.09)	74.48 (101.28)	64.96 (100.35)	68.36 (120.30)	63.21 (100.72)

Baseline is defined as the last available observation prior to the first study drug administration.
*Body weight change reported for Day 7 to identify the presence of rapid weight gain associated with fluid retention.
BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SD, standard deviation.

CONCLUSIONS

- These data support lanifibranor's balanced pan-PPAR activity (inclusive of partial PPARγ activation), underlying both the adiponectin effect and related metabolic improvements, alongside the absence of clinically detectable fluid retention signals within the first 28 days of use
- Initial efficacy signals in glycemic control and lipids in people with T2DM support further investigation of lanifibranor for metabolic dysfunction and associated complications of MASH, permitting more accurate characterization of fluid distribution
- Investigation of lanifibranor's efficacy in MASH patients is ongoing in the current phase 3 trial: NATiV3. ClinicalTrials.gov identifier: NCT04849728[3]

REFERENCES

1. Staels B, et al. *J Hepatol*. 2023;79(5):1302-1316.
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3. ClinicalTrials.gov identifier: NCT04849728. Accessed August 7, 2026. https://clinicaltrials.gov/study/NCT04849728.

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DISCLOSURES

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