Partial PPARγ Agonism Underlies Lanifibranor's Preclinical Fluid/Cardiovascular Safety Versus Full and Dual PPAR Agonists

SCAN AND VIEW
POSTER ON OUR WEBSITE

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INTRODUCTION

- Some peroxisome proliferator–activated receptor agonists (PPAR)γ, such as rosiglitazone, and dual PPARα/γ agonists, such as pioglitazone, have been variably associated with plasma volume expansion, secondary cardiac hypertrophy, and heart failure in animal models and clinical trials[1,2]
- Lanifibranor was intentionally designed as a well-balanced pan-PPAR agonist with partial PPARγ activity and a distinct coregulator recruitment profile,[3] and it aims to preserve the beneficial metabolic effects of the class while attenuating adverse ones

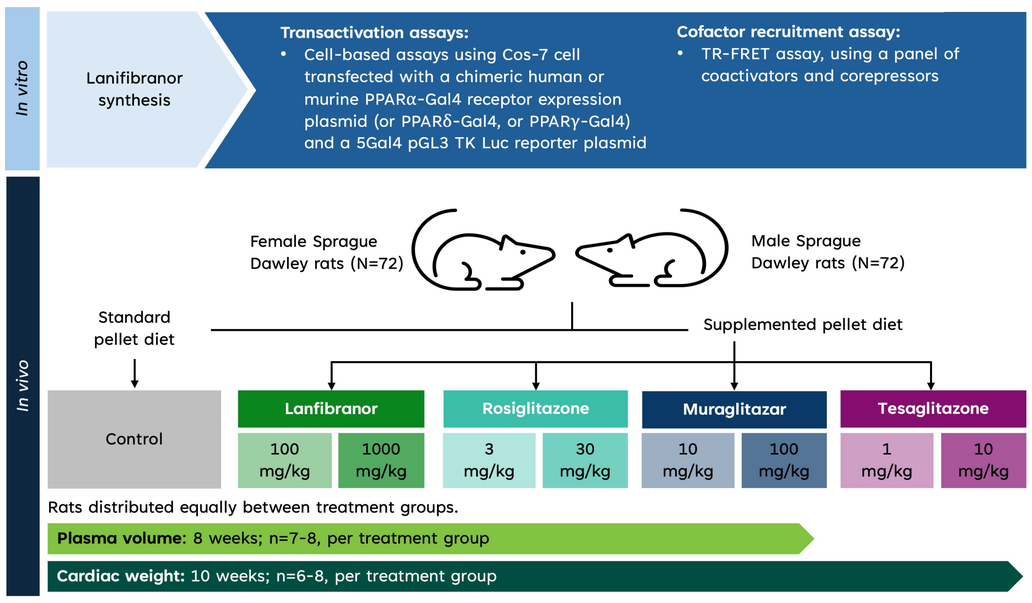
AIM

- To evaluate whether lanifibranor's calibrated pharmacology translates to a differentiated fluid and cardiac safety profile by characterizing lanifibranor's PPAR isoform activity and its effects on plasma volume and cardiac weight in preclinical models in direct comparison with reference PPARγ and dual PPARα/γ agonists

METHODS

- *In vitro* PPAR isoform activity and coregulator recruitment were characterized in transactivation and cofactor-recruitment assays as part of the molecular development of lanifibranor[3] (**Figure 1**)
- The *in vivo* effects on plasma volume and cardiac weight of lanifibranor versus single PPARγ (rosiglitazone) and dual PPARα/γ (muraglitazar, tesaglitazar) agonists were evaluated in male and female Sprague Dawley rats (**Figure 1**)
  - Each compound was evaluated at 2 dosages
  - Plasma volume was assessed at Week 8 and cardiac weight at Week 10

Figure 1. Study Design



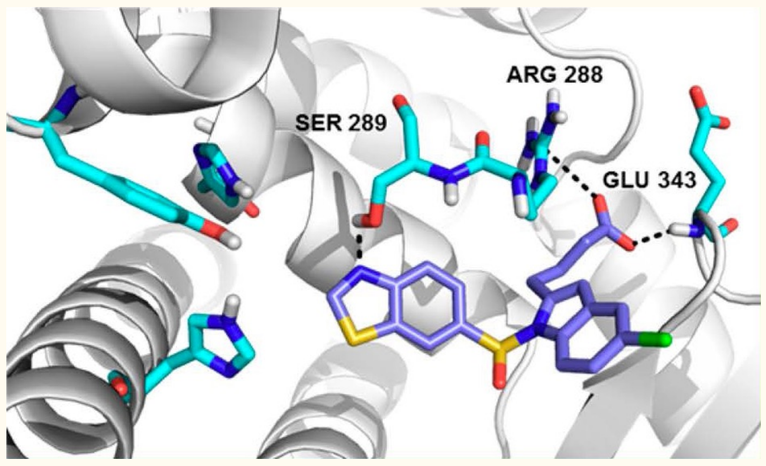
PPAR, peroxisome proliferator–activated receptor; TR-FRET, time-resolved fluorescence energy transfer.

RESULTS

In vitro

- Lanifibranor (**Figure 2**), a derivative of an initial indole hit that was identified from a high throughput screening campaign and optimized for its balanced pan-PPAR agonism, compared favorably against the other molecules in the development series[3]
- Lanifibranor demonstrated partial PPARγ agonism with full activity at PPARα and PPARδ (**Table 1**)[3]
- Lanifibranor demonstrated a distinct cofactor recruitment profile compared with rosiglitazone; while efficacy remained highly comparable, lanifibranor had moderate potency, which may confer a favorable safety profile (**Figure 3**)[3]

Figure 2. Co-Crystal Structure of Lanifibranor With PPARγ Ligand–Binding Domain (6ENQ)[3]



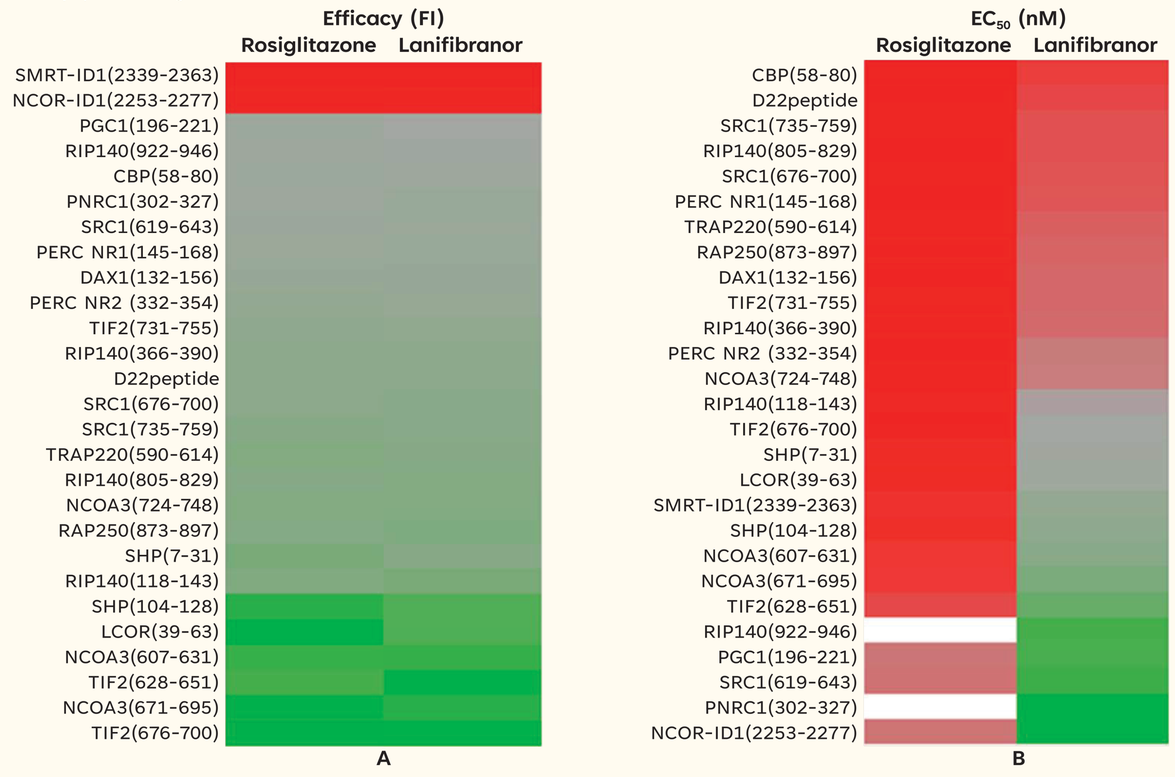
ARG, arginine; E, glutamic acid; GLU, glutamic acid; N, asparagine; PPAR, peroxisome proliferator–activated receptor; Q, glutamine; SER, serine.

Table 1. Transactivation Activity: Exploring the R[1] (Cl) Substituent of Lanifibranor[3]

	hPPARα	hPPARδ	hPPARγ
EC_{50} (nM)	1537 ± 278	866 ± 180	206 ± 71
E_{max} (%)	106 ± 30	105 ± 16	79 ± 15

E_{max} is the maximum activation in percent of control. All EC_{50} values are the mean of ≥2 independent experiments performed in triplicate.
Cl, chloro substituent; EC_{50}, half-maximal effective concentration; E_{max}, maximum effective concentration; PPAR, peroxisome proliferator–activated receptor; R, arginine.

Figure 3. Dendograms of Cofactor Recruitment Profiles for Lanifibranor and Rosiglitazone, (A) Efficacy and (B) Potency[3]



(A) Scale: red, FI <1, de-recruitment; gray, FI = 1, no activity; green, FI >1, recruitment. (B) Scale: red, 10 nM; gray, 500 nM; green, 5000 nM.
EC_{50}, half-maximal effective concentration; FI, fold induction.

In vivo

- Lanifibranor had no significant effect on plasma volume in male or female rats, whereas rosiglitazone, muraglitazar, and tesaglitazar produced dose-related increases in plasma volume, with some differences between sexes (**Table 2**)

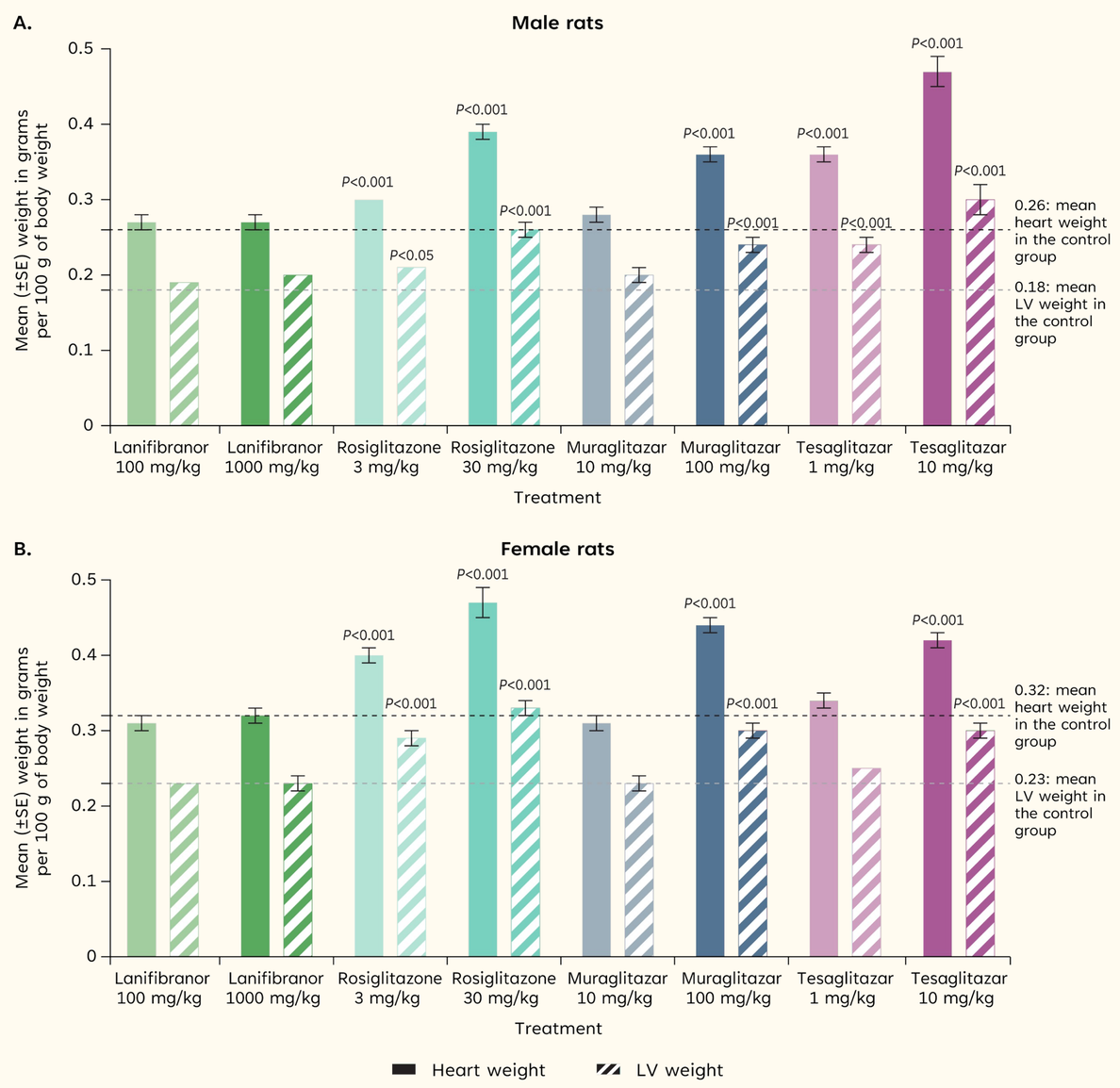
Table 2. Plasma Volume Changes With PPAR Agonists

Change from baseline, %	Lanifibranor		Rosiglitazone		Muraglitazar		Tesaglitazar	
	100 mg/kg	1000 mg/kg	3 mg/kg	30 mg/kg	10 mg/kg	100 mg/kg	1 mg/kg	10 mg/kg
Male	+27	+18	+29	+86	0	+85	+50	+84
Female	+20	+35	+99	+143	+21	+112	+48	+124

Percentages are % of variation of the means relative to controls.
PPAR, peroxisome proliferator–activated receptor.

- Lanifibranor had no significant effect on heart or left ventricular weight. In contrast, rosiglitazone, muraglitazar, and tesaglitazar significantly increased heart weight, paralleled by increased left ventricle weight, dose-dependently across sexes (**Figure 4**)

Figure 4. Heart and LV Weight After 10 Weeks of Treatment in (A) Male and (B) Female Rats



LV, left ventricle; SE, standard error.

CONCLUSIONS

- Unlike single PPARγ and dual PPARα/γ agonists, lanifibranor did not induce the plasma volume expansion or cardiac hypertrophy that is characteristic of the class; partial PPARγ agonism with a distinct cofactor recruitment profile provides a mechanistic basis for this separation
- This preclinical profile is consistent with lanifibranor's intentional partial PPARγ agonism within a balanced pan-PPAR activation profile, and it was designed to attenuate the adverse effects often associated with PPARγ activation; these findings support a differentiated preclinical fluid and cardiac profile within the PPAR class

REFERENCES

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DISCLOSURES

Sven M. Francque has served as a lecturer for AbbVie, Allergan, Bayer, Eisai, GENFIT, Gilead Sciences, Janssen-Cilag, Intercept, Inventiva, Merck Sharp & Dohme, Novo Nordisk, Promethera, and Siemens. A.G. (Onno) Holleboom has nothing to disclose. Jason Campagna, Simon Hogan, and Guillaume Wettstein are employees of Inventiva Pharma. Manal F. Abdelmalek reports research funding paid to her institution from 89bio, Akero, Gilead Sciences, Hanmi, Inventiva, Madrigal, and Oasis Pharmaceuticals; consulting for 89bio, Akero, Boehringer Ingelheim, Hanmi, Inventiva, Kriya, Madrigal, Medscape, Merck, MetaSight, Novo Nordisk, and Regeneron; speaking honoraria from Avalere Health, Chronic Liver Disease Foundation, Medscape, Pri-Med Institute, and PRIME Education; and royalties from UpToDate.

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