Effects of Ninerafaxstat on myocardial energetics, exercise capacity, and cardiac function in heart failure with preserved ejection fraction, Type 2 Diabetes and Obesity- a Phase 2a clinical trial

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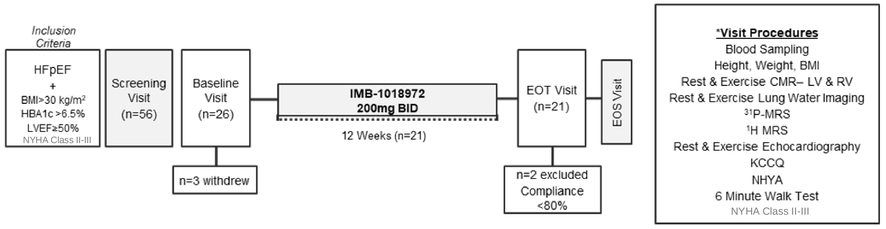
BACKGROUND

Cardiometabolic Heart Failure with preserved ejection fraction (HFpEF), adiposity, insulin resistance, and diabetes, lead to increased cardiac fatty acid oxidation (FAO) and oxygen demand resulting in reduced cardiac energy state. Ninerafaxstat, a cardiac mitotrope, shifts myocardial substrate use towards glucose oxidation via partial FAO inhibition (pFOX), increasing PDH activity and NAD+ synthesis. This enhances substrate flexibility and cardiac energetics.

METHODS

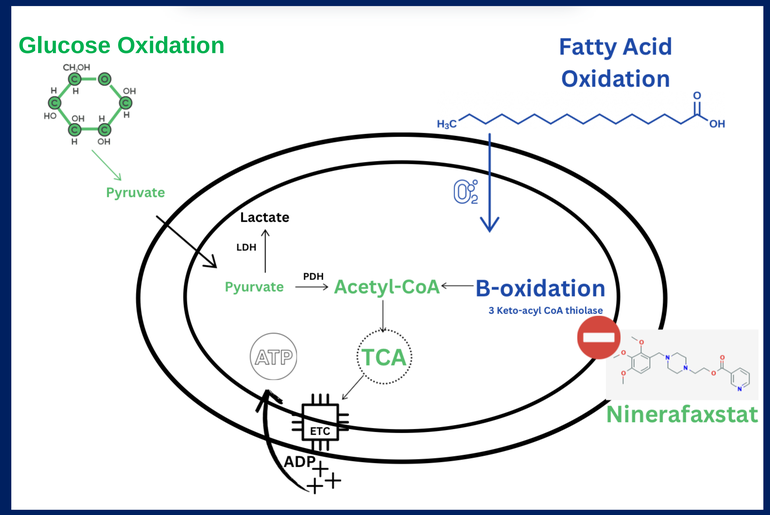
This open-label, phase 2a clinical trial assessed the effects of 3 months of partial fatty acid oxidation inhibitor Ninerafaxstat with the primary endpoint of improvement in cardiac energetics (phosphocreatine /adenosine triphosphate, PCr/ATP).



RESULTS

Characteristic Anthropometrics mean (SD)	Pre-Treatment n=21	Post-Treatment n=21	p-value
Age (years)	71±6		
Female n (% of total)	6 (29)		
White Race n (% of total)	22 (100)		
Weight (kg)	104	103	0.082
BMI (kg/m²)	35.2	34.8	0.040
Systolic BP (mmHg)	137	138	0.719
Diastolic blood pressure (mmHg)	77	75	0.208
Resting HR (bpm)	70	69	0.787
NYHA classification	2 (0.3)	2 (0.4)	
Heart failure scores			
H2PEF score	7 (1.8)		
HFA-PEFF score	5 (1.3)		

Ninerafaxstat in HFpEF, Diabetes and Obesity

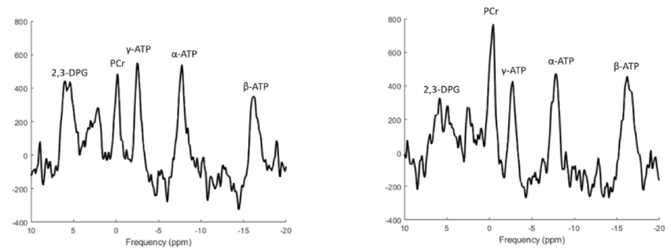


Cardiometabolic Heart Failure

Energy depletion
Symptom burden
Exercise intolerance

Fatty acid Oxidation

HFpEF + T2DM + Obesity



Ninerafaxstat

Glucose Oxidation

Increased cardiac energetics
Reduced symptoms
Improved function

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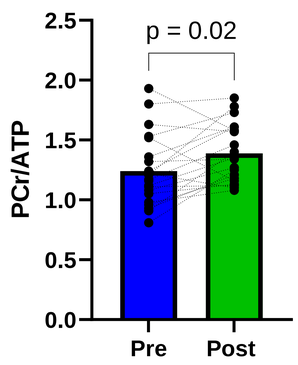
CONCLUSION

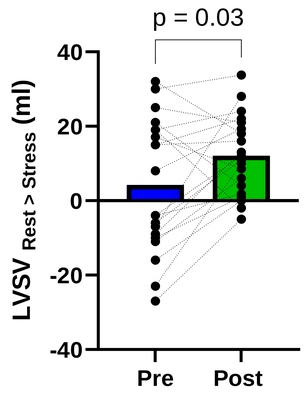
Ninerafaxstat is safely tolerated in cardiometabolic heart disease. Ninerafaxstat is associated with improved cardiac energetics, function and symptom burden in patients with cardiometabolic heart disease and HFpEF.

FIGURE 1



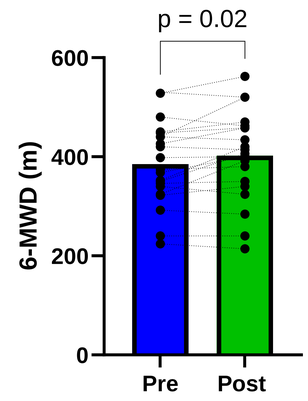
Ninerafaxstat improved phosphocreatine to Adenosine triphosphate ratio (PCr/ATP).

FIGURE 2



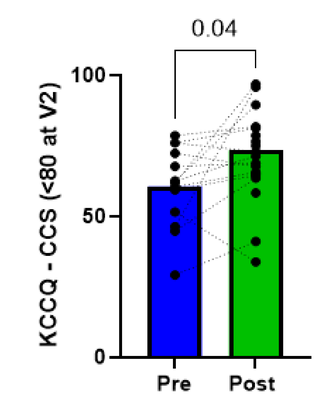
Ninerafaxstat improved systolic augmentation to exercise.

FIGURE 3



Ninerafaxstat resulted in a 14m increase in 6-minute walk distance.

FIGURE 4



Ninerafaxstat improved KCCQ by a mean of 8.3±17 points.

DISCLOSURE INFORMATION

PC and JP are employees of Imbria Pharmaceuticals who supported development of the trial protocol but did not participate in the experiments or writing of this manuscript. AY is an employee of the University of Oxford and Weatherden Ltd and a consultant to Imbria Pharmaceuticals. The other authors report no conflicts.