IMPROVE-DiCE: A Phase IIa Trial Investigating Ninerafaxstat - A Novel Cardiac Mitotrope for the treatment of Diabetic Cardiomyopathy

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PURPOSE

The type 2 diabetic (T2D) heart is characterised by reduced energy reserves and overly excessive use of fatty acids (FA) for mitochondrial replenishment of adenosine triphosphate (ATP). Furthermore, regeneration of phosphocreatine (PCr), a main provider of high-energy phosphates during increased demand, is blunted.

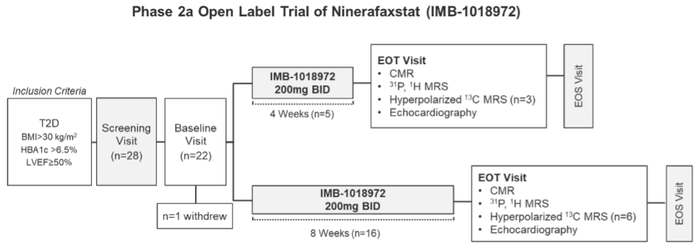
Myocardial steatosis, via deposition of triglycerides and intermediates of FA-metabolism, contributes to lipotoxicity and diastolic dysfunction.
Ninerafaxstat is a novel cardiac mitotrope designed to normalise myocardial substrate selection in favour of glucose by partially inhibiting FA-oxidation.

IMPROVE-DiCE is the first trial assessing Ninerafaxstat's effects on myocardial energetics (PCr/ATP), cardiac metabolism and function in patients with T2D and obesity.
Furthermore, it is the first study successfully using tri-nuclear and hyperpolarized magnetic resonance spectroscopy (MRS) to investigate a drug intervention in a clinical trial of cardiovascular patients.

METHODS

IMPROVE-DiCE is a mechanistic, open-label, phase IIa trial.
21 patients with T2D and obesity (median HbA1c 7.0 % [6.6, 7.8], 97 kg [90, 102]) received 200mg ninerafaxstat twice daily for 4 (n=5) or 8 weeks (n=16).

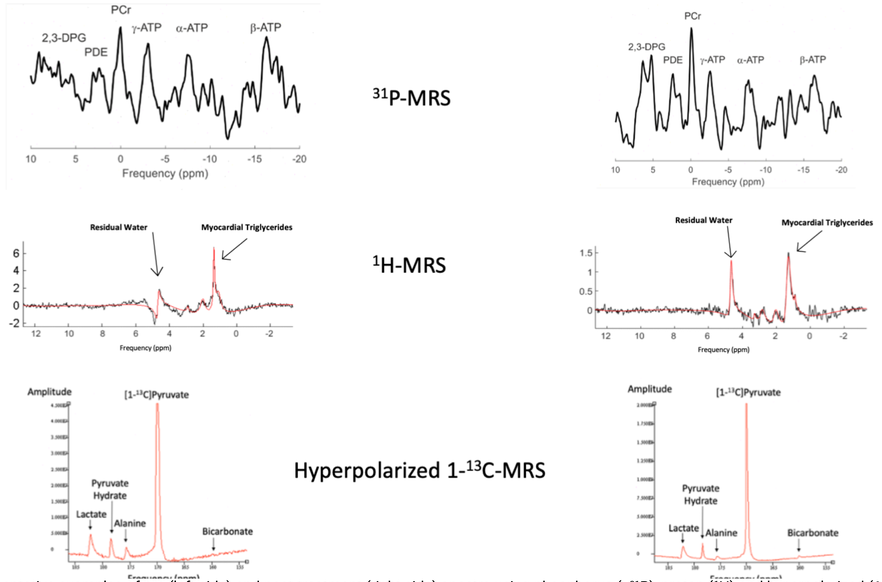
Myocardial energetics, metabolism and function were assessed pre- & post-treatment using magnetic resonance imaging (MRI). ^{31}P- and ^{1}H-magnetic resonance spectroscopy (MRS) in all patients, while PDH-flux using hyperpolarized [1-^{13}C]pyruvate MRS, was assessed in a subset (n=9).



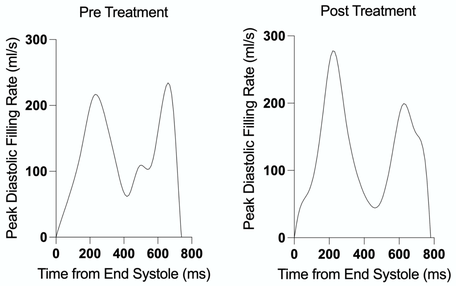
A schematic overview of the study design and visit schedule. ^{1}H-MRS = proton magnetic resonance spectroscopy, ^{31}P-MRS = phosphorus magnetic resonance spectroscopy, BID = twice daily, BMI = Body Mass Index, CMR = cardiovascular magnetic resonance, EOS = end of study, EOT = end of treatment, LVEF = left ventricular ejection fraction, T2D = type 2 diabetes.

RESULTS

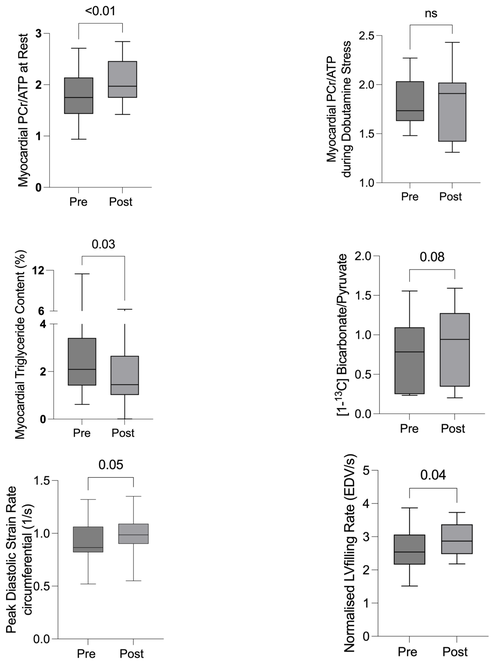
4- or 8 weeks of ninerafaxstat modulates cardiac metabolism and improves early left ventricular (LV) filling in patients with type 2 diabetes and obesity



Representative examples of pre (left side) and post-treatment (right side) spectra using phosphorus (^{31}P), proton (^{1}H) and hyperpolarized (1-^{13}C pyruvate) magnetic resonance spectroscopy (MRS). As presented here, the phosphocreatine to adenosine triphosphate ratio (PCr/ATP) was higher (upper right panel), myocardial triglyceride content lower (middle panel) and pyruvate dehydrogenase flux (PDH) enhanced, mirrored by an increased bicarbonate peak (lower right panel) following treatment with ninerafaxstat for 4- or 8 weeks.



Average values of the peak diastolic filling rate (ml/s) generates by magnetic resonance imaging (MRI) of all participants (4- and 8 weeks datasets combined) before (left panel) and after treatment (right panel) with ninerafaxstat.



4- or 8 week treatment with ninerafaxstat significantly improved resting PCr/ATP (upper left panel) but not stress PCr/ATP (upper right), reduced myocardial steatosis (middle left) and improved PDH-flux in 7/9 subjects (middle right panel). Furthermore, peak diastolic strain rate (lower left) and early LV-filling, normalised to end-diastolic volume, improved likewise.

CONCLUSIONS

- In participants with T2D and obesity, short-term treatment with ninerafaxstat significantly improved myocardial energetics, reduced myocardial steatosis and improved LV diastolic filling.
- These findings support further investigation of the potential of ninerafaxstat to treat or prevent the progression of heart failure states associated with diabetes.
- Stage 2 of the study will investigate the impact of ninerafaxstat in patients with HFpEF
- Ninerafaxstat was well tolerated with no treatment-emergent serious adverse events
- Therapeutic manipulation of myocardial energy metabolism represents a promising approach to treat cardiac disorders characterized by energetic deficit to improve cardiac functional reserve and alleviate symptoms.

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