Efficacy and Safety of Ninerafaxstat, a Novel Cardiac Mitotrope, in Patients with Symptomatic Nonobstructive Hypertrophic Cardiomyopathy

(Results of IMPROVE-HCM)

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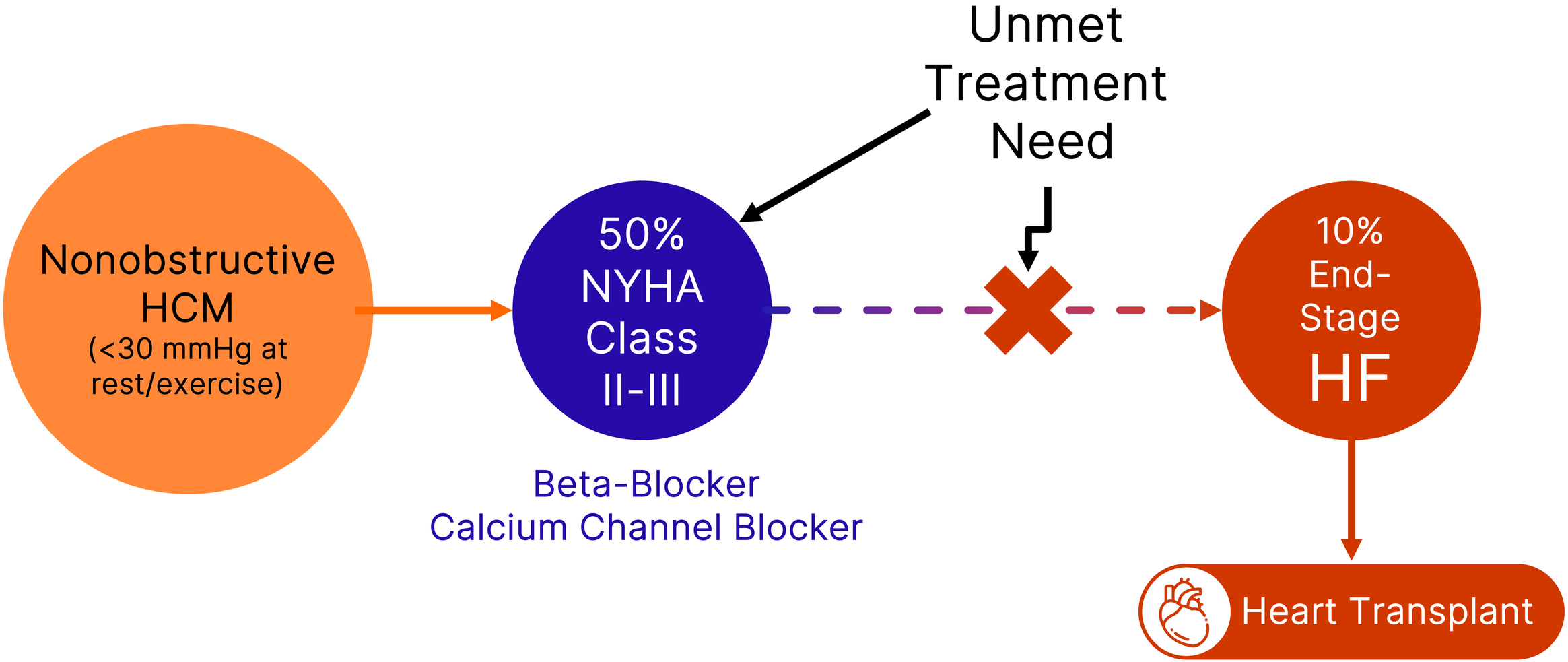
The *Unmet* Treatment Need in *Nonobstructive* HCM



Diastolic Dysfunction in Nonobstructive HCM

LV Relaxation:

- LV Hypertrophy
- Myocardial Ischemia

Heavily Energy Dependent

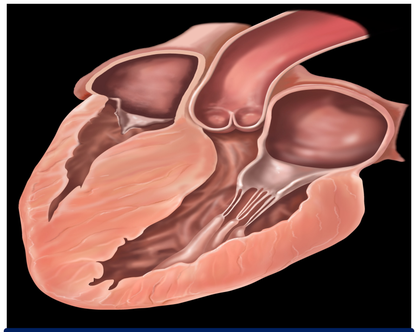
LV Distensibility:

- LV Hypertrophy
- Disarray
- Interstitial Fibrosis
- Replacement Scar

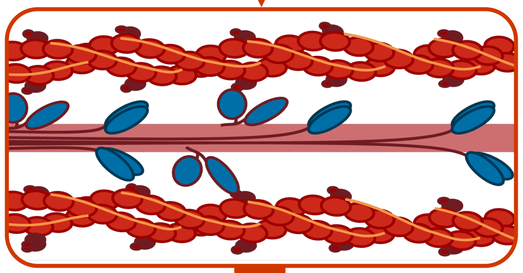
Altered LV Diastolic Filling/Low Stroke Vol

Limiting Symptoms and Decreased Exercise Capacity

Energy Deficiency is a Primary Consequence of HCM Disease Expression

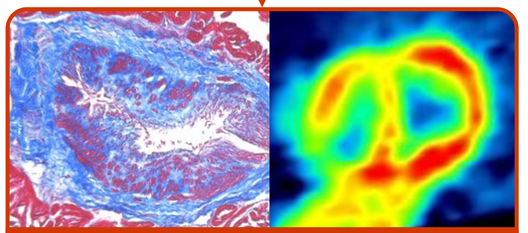


HCM



Energetic Cost of Contraction/Relaxation

PCr/ATP Ratio



Microvacular Ischemia

Exacerbates Primary Energy Deficiency

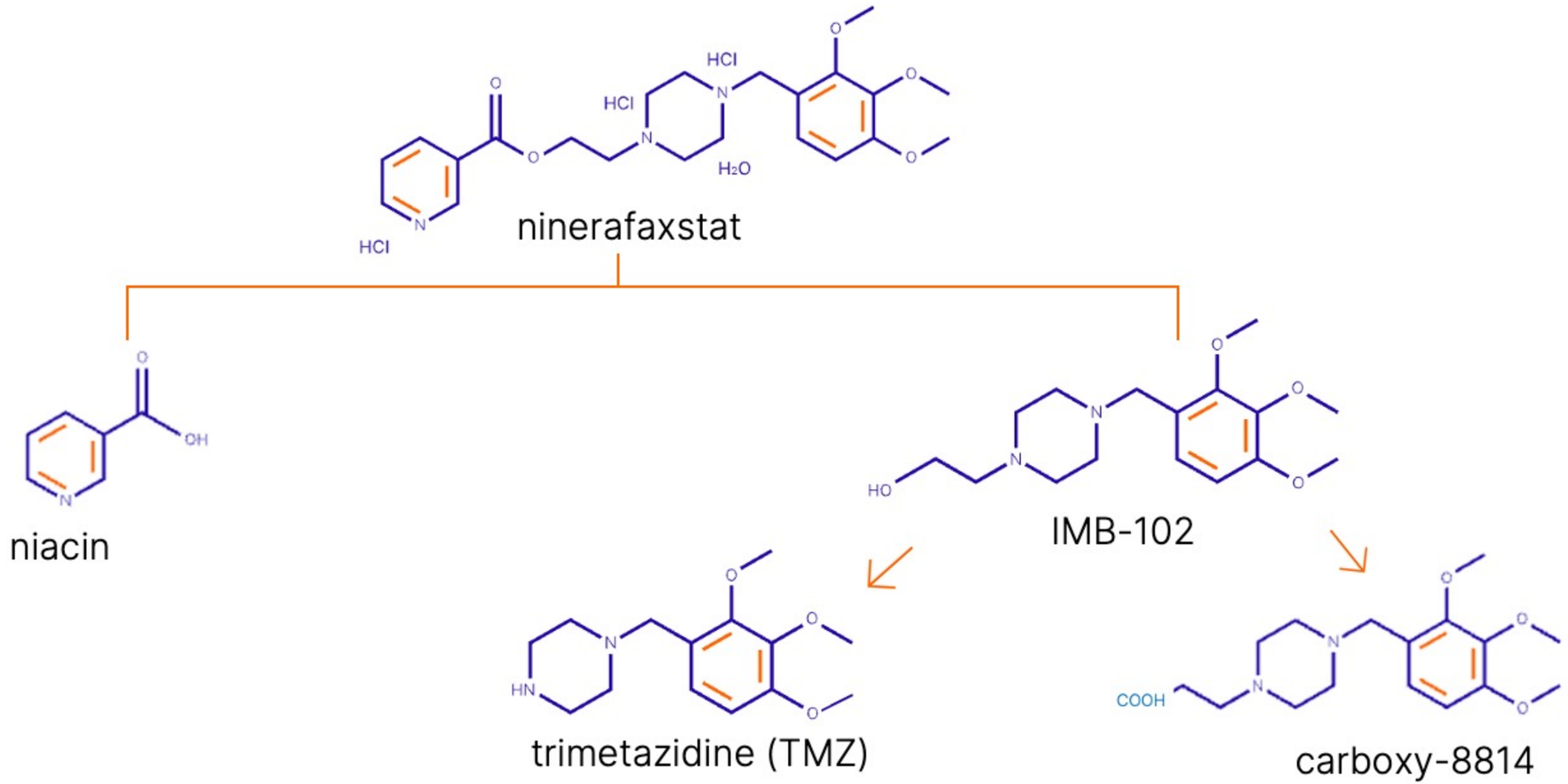
Energy Deficiency is a Primary Consequence of HCM Disease Expression

For these reasons...

Myocardial Energetics Represent an Attractive Therapeutic Target

Mitotropes =
Drugs that influence myocardial energetics

Ninerafaxstat is a Mitotrope that Influences Cardiac Energetics



Approved in some countries for treatment of angina since 1970s & in current ESC treatment guidelines (Class 2a recommendation)

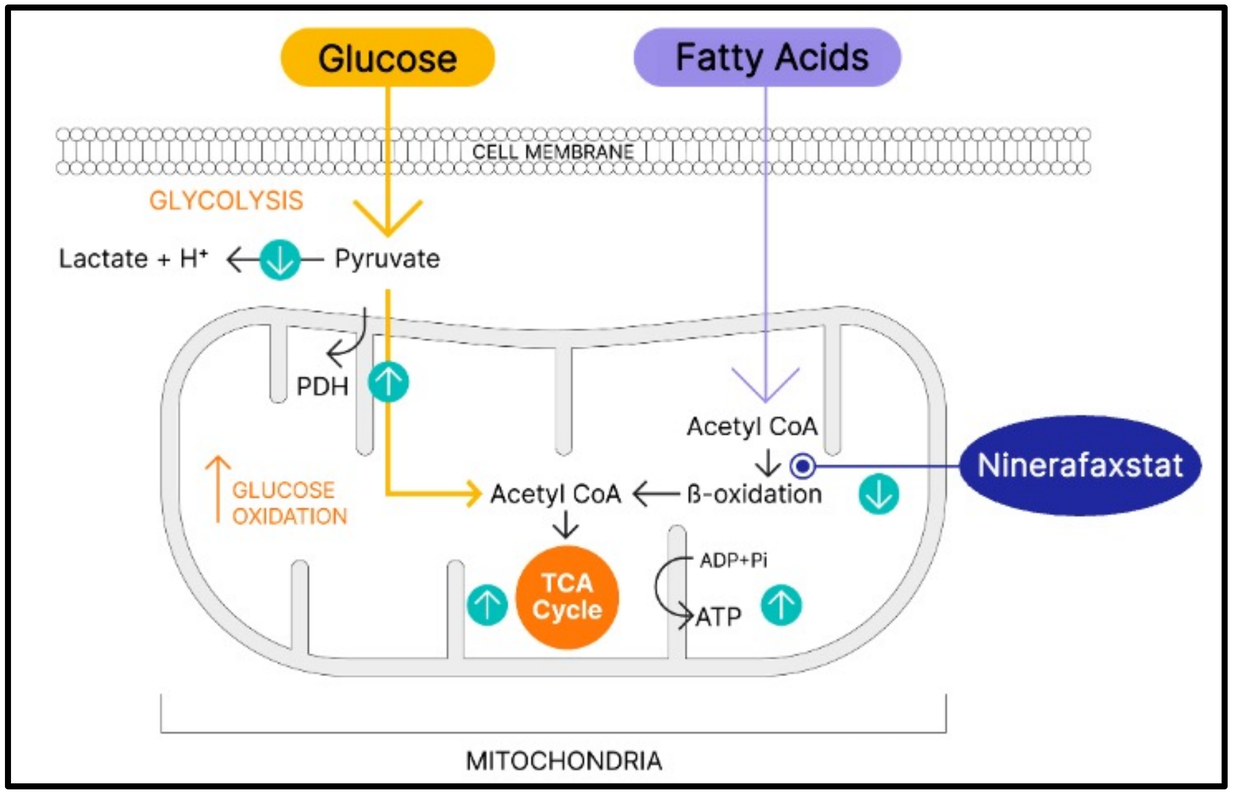
Ninerafaxstat is a Mitotrope that Influences Cardiac Energetics

Ninerafaxstat:

Partial Inhibition of Fatty Acid Oxidation
No Drug Monitoring
No Hemodynamic Effect

Ninerafaxstat: Mechanism of Action
Optimizes Efficiency of ATP Generation to Enhance Cardiac Function

- Partial inhibition of mitochondrial fatty acid oxidation
- Shift of cardiac metabolism from using fatty acids towards glucose
- Recoupling glycolysis and glucose oxidation
- ↑ Efficiency of ATP production per molecule of O_2



Modified from Lopaschuk et al., Physiol. Rev 2010 &
Verma et al J Am Coll Cardiol Basic Trans Science 2018; 3:575-587

IMPROVE-HCM - Key Inclusion Criteria and Endpoints

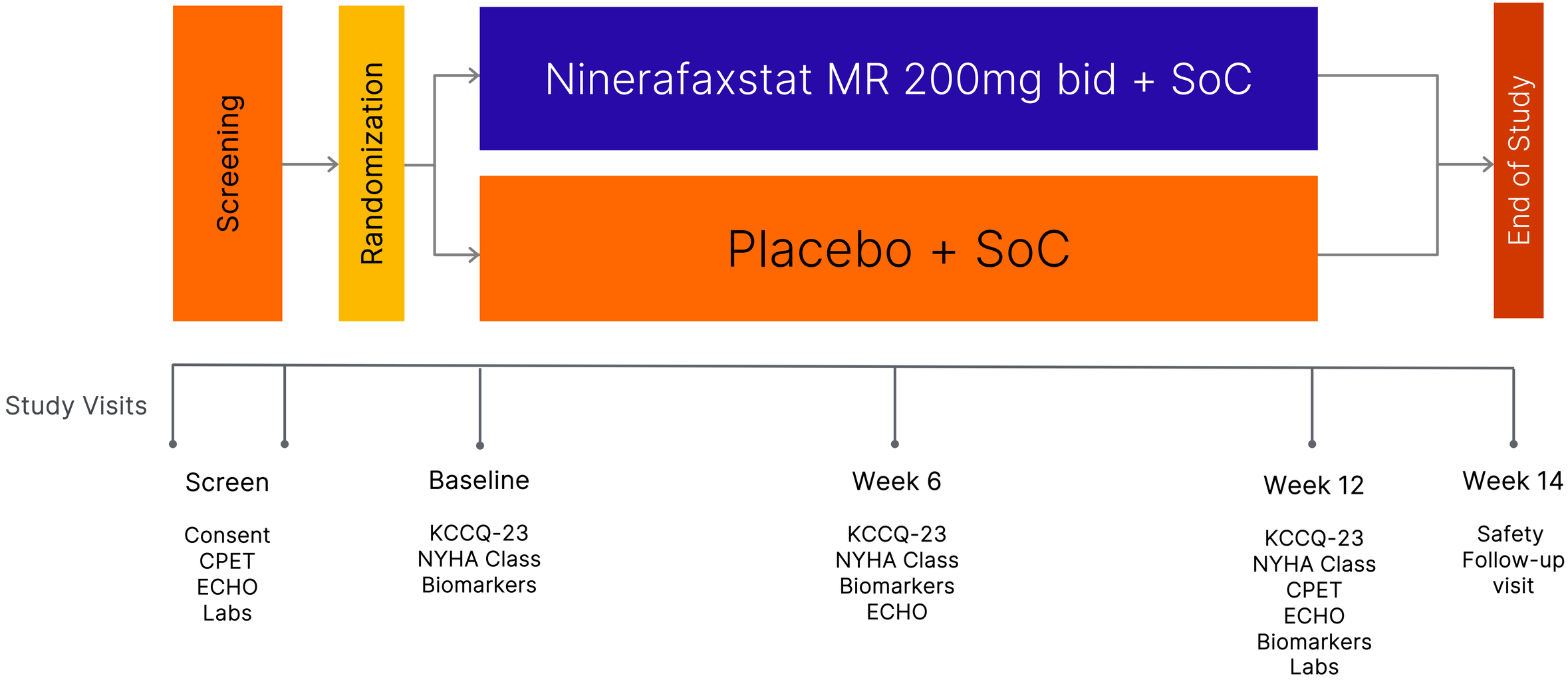
Study Design and Endpoints

- Randomized and blinded prospective trial for 12 weeks
  - Orally administered ninerafaxstat 200 mg MR BID vs. Placebo
  - Evaluating:
    - Safety and Tolerability
    - CPET Measures (pVO_2 and V_E/VCO_2)
    - KCCQ-CSS
    - Echocardiographic Variables
    - NT-proBNP

Key Inclusion Criteria

- 18-80 years old
- LV wall thickness of ≥15 mm
- LV Outflow Tract Gradient <30 mmHg at rest and with exercise
- Baseline LVEF ≥ 50%
- CPET:
  - pVO2 ≤80% predicted for age & gender
  - RER ≥1.05

IMPROVE-HCM - Clinical Trial Design



IMPROVE-HCM – Baseline Characteristics

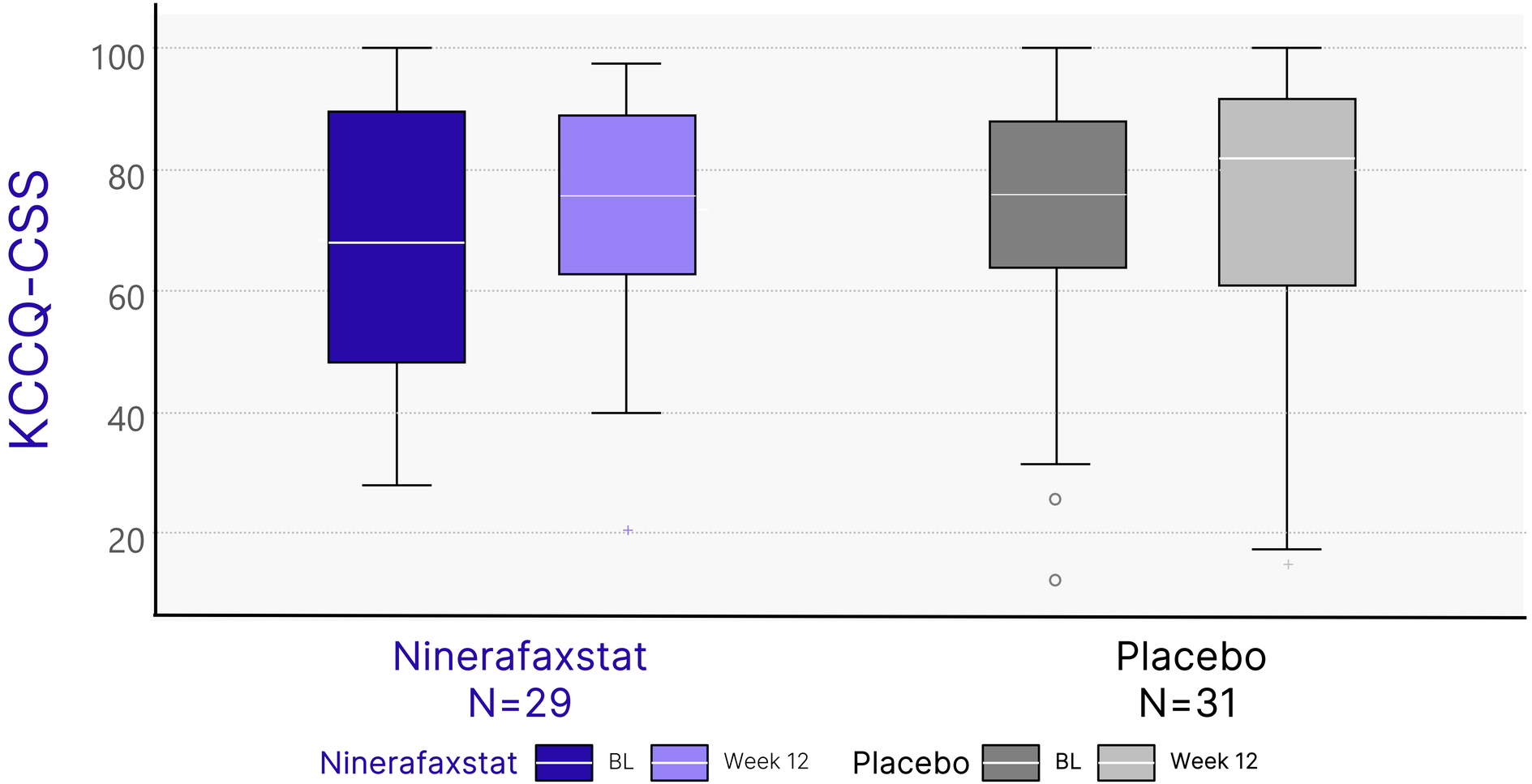
Characteristic	Placebo (n = 33)	*Ninerafaxstat* (n = 34)
Age (Years), Mean (SD)	56 (13)	58 (11)
Male, n (%)	16 (48)	14 (41)
NYHA Functional Class, n (%)		
Class II	20 (61)	20 (59)
Class III	12 (36)	12 (35)
Maximal LV Wall Thickness (mm) Mean (SD)	17 (4)	17 (3)
LVEF (%), Mean (SD)	68 (4)	63 (5)
LA Diameter (mmHg), Mean (SD)	36 (5)	43 (7)
pVO2 (mL/kg/min), Mean (SD)	20 (4)	18 (4)
pVO2 % predicted age and gender, % (SD)	62 (11)	59 (9)
V_E/VCO_2, Mean (SD)	33 (5)	31 (4)
NT-proBNP (pg/mL), Mean (SD)	712 (1150)	606 (634)

IMPROVE-HCM – Ninerafaxstat was well tolerated

- Treatment Emergent Serious Adverse Events
  - Placebo: 2 patients (6%)
    - Sepsis; hypoxia (post CPET)
  - Ninerafaxstat: 4 patients (11%)
    - COVID pneumonia; CABG; pyelonephritis; abdominal abscess
- ≥1 Treatment-emergent adverse event
  - Placebo: 20 patients (61%)
  - Ninerafaxstat: 24 patients (71%)
- Most TEAE were mild to moderate
- Ninerafaxstat was associated with no significant change in LV EF, blood pressure or heart rate at Week 12

Efficacy of Ninerafaxstat on Heart Failure Symptom Burden by KCCQ-CSS (ITT Population)

LS mean difference = 3.2 (-2.9, 9.2)
P value = 0.2

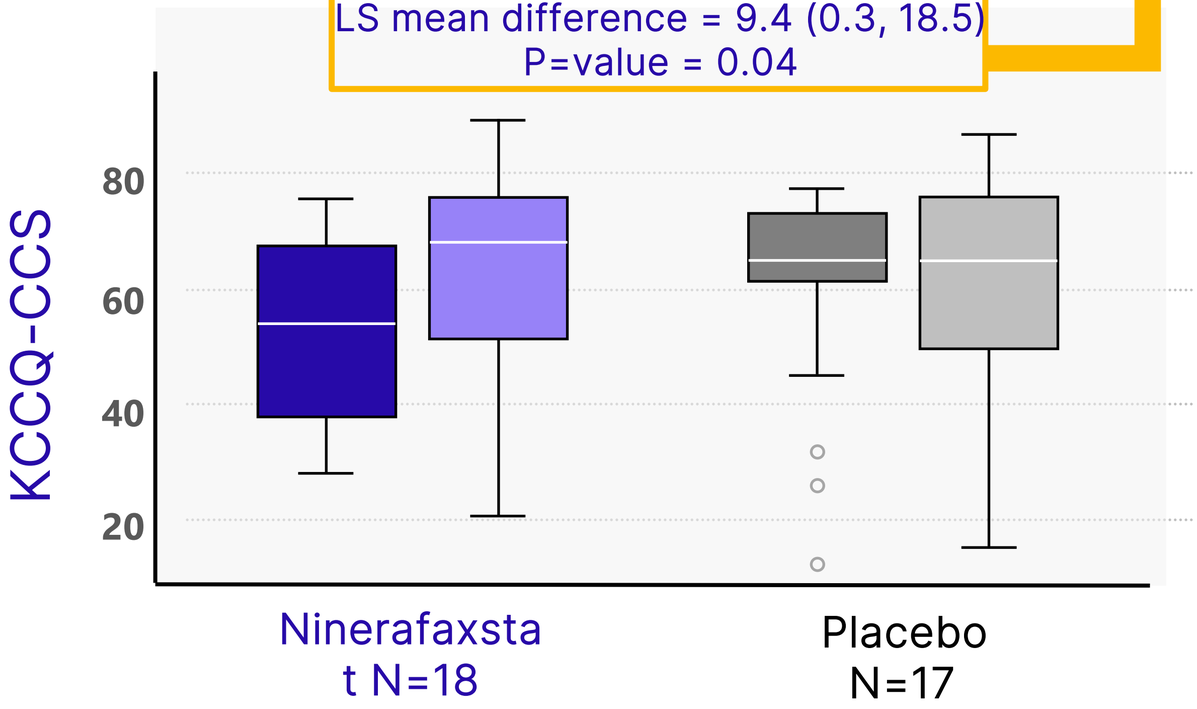


Efficacy of Ninerafaxstat on Heart Failure Symptom Burden by KCCQ-CSS (Patients Limited at Baseline)

≥5 Point Change in KCCQ: Clinically Meaningful

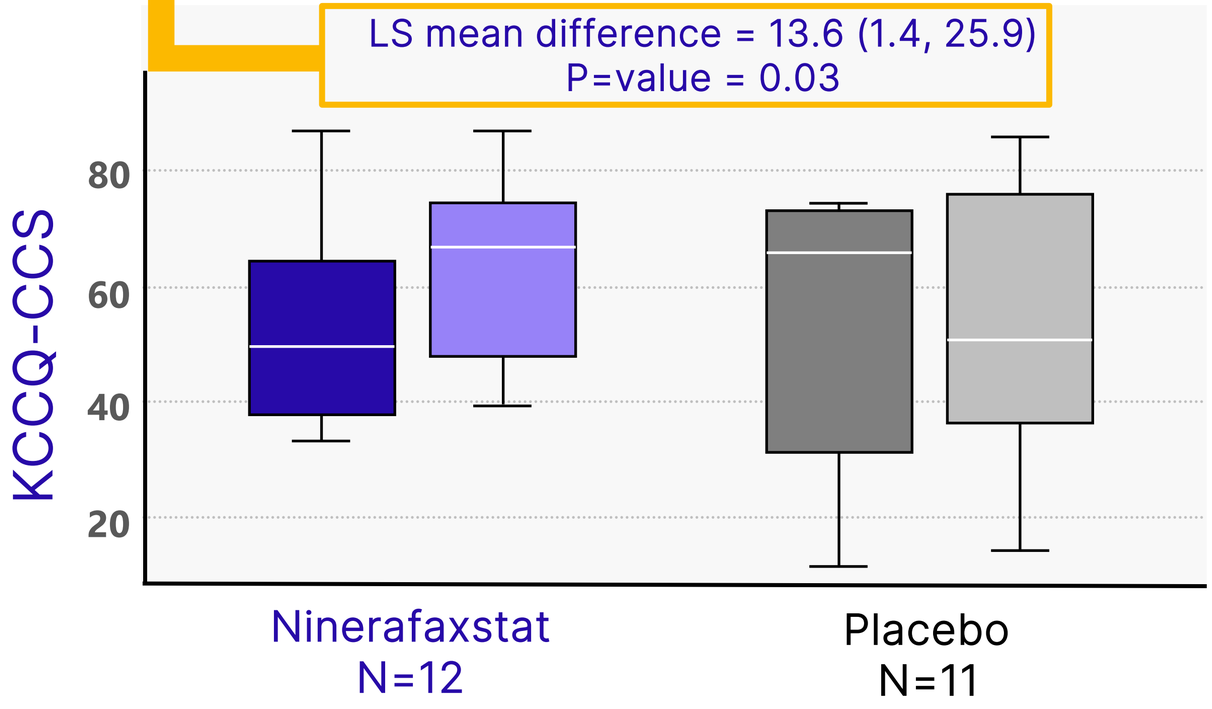
≤80 KCCQ-CSS at Baseline

LS mean difference = 9.4 (0.3, 18.5)
P=value = 0.04



NYHA Class III at Baseline

LS mean difference = 13.6 (1.4, 25.9)
P=value = 0.03

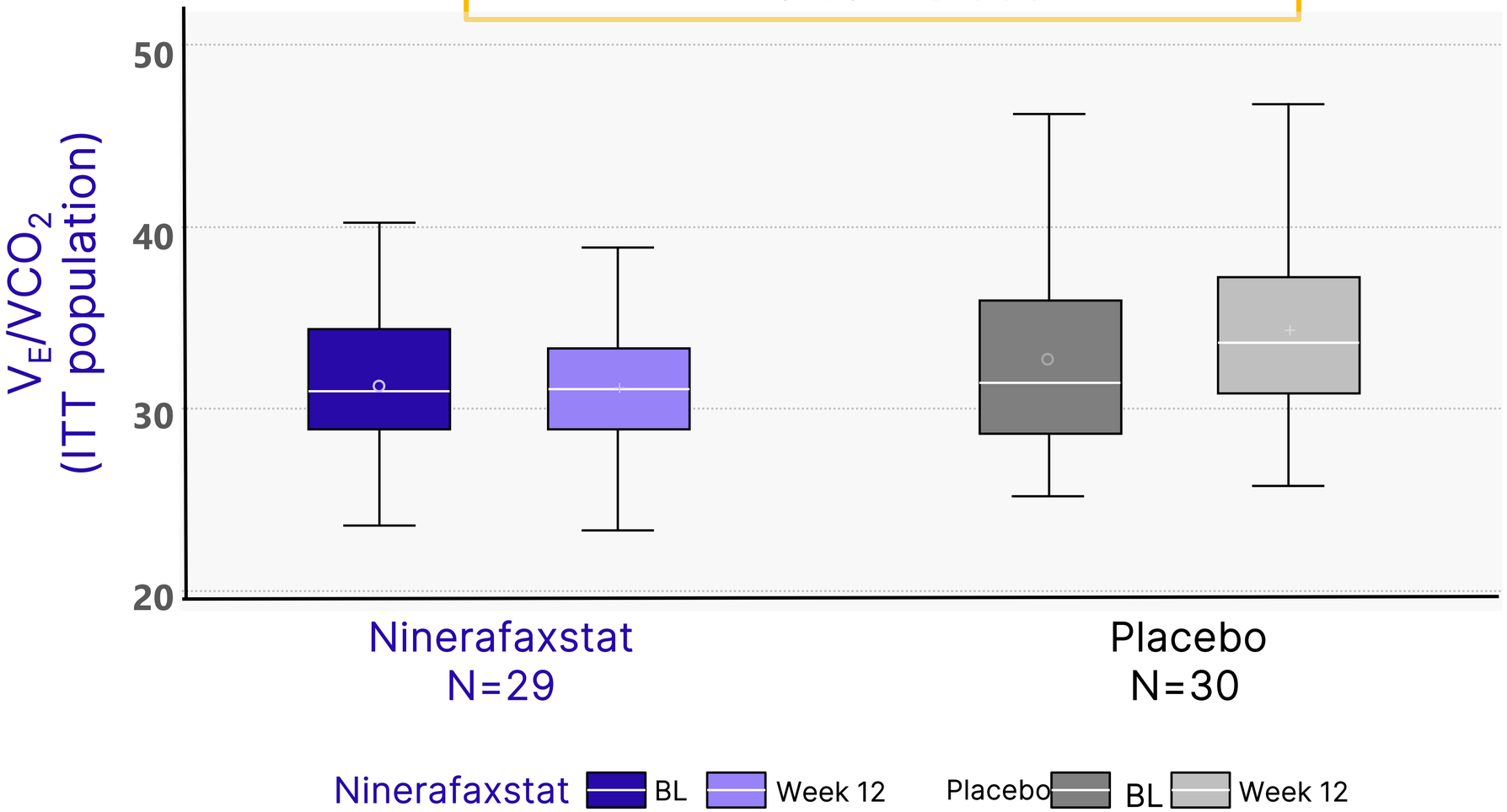


Ninerafaxstat BL Week 12 Placebo BL Week 12

Efficacy of Ninerafaxstat on Exercise Capacity by V_E/CO_2 (ITT Population)

LS mean difference = -2.1 (-3.6, -0.6)
P value = 0.005

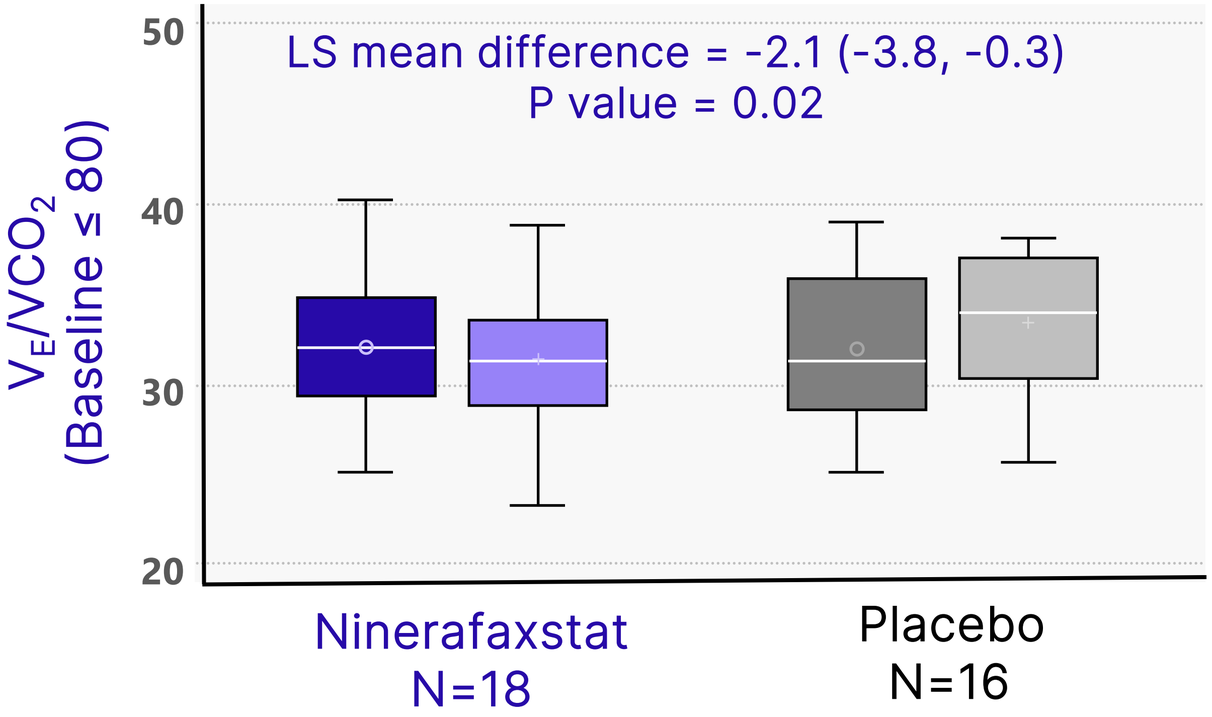
≥1 Unit V_E/VCO_2 Slope Associated with Risk Death/Transplant



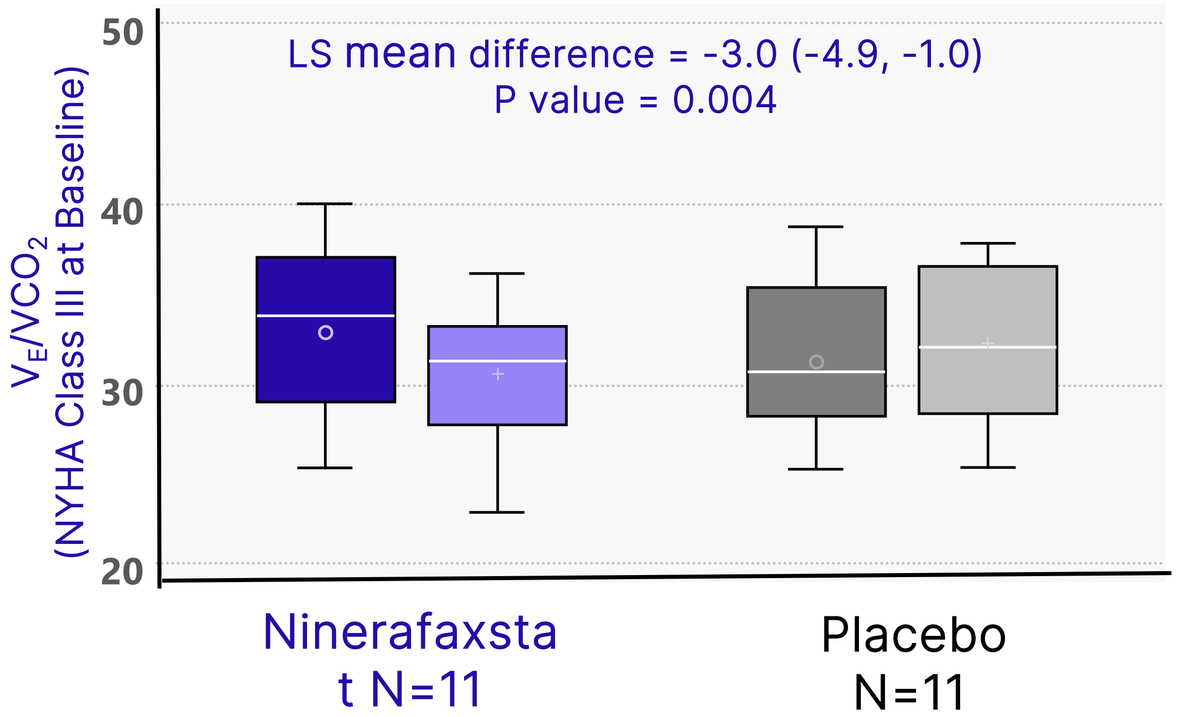
Placebo Corrected Decrease Of 2 Units in V_E/VCO_2: Clinically Meaningful Improvement

Efficacy of Ninerafaxstat on Exercise Capacity by V_E/CO_2 (Patients Limited at Baseline)

≤80 KCCQ-CSS at Baseline



NYHA Class III at Baseline



Ninerafaxstat BL Week 12 Placebo BL Week 12

IMPROVE-HCM – pVO_2, Key Echo Parameters and Biomarkers

Variable	Ninerafaxstat (N=34)		Placebo (N=33)		Treatment Effect	
	n (%)	Change from baseline *Mean ± SD*	*n (%)*	Change from baseline *Mean ± SD*	LSM difference *(95% CI)*	ANCOVA P Value
pVO_2 (ml/kg/min)	29 (85.3)	0.013 ± 2.03	30 (90.9)	0.02 ± 1.91	0.061 (-0.99, 1.1)	0.908
LA Size (mm)	27 (79)	-0.09 ± 0.29	32 (97%)	0.10 ± 0.31	-0.20 (-0.35,-0.05)	0.010
Average E/e’	27 (79.4)	0.27 ±3.4	31 (93.9)	0.93 ± 3.5	-0.76 (-2..6, 1.0)	0.398
Median NT-proBNP (ng/L) (min, max)	29 (85.3)		342 (54, 6123)		98.03 (-110.19, 306.24)	0.85

Conclusions

- In this Phase 2 proof-of-concept study, ninerafaxstat, a novel investigational cardiac mitotrope, was safe and well tolerated in nonobstructive HCM
- Treatment with ninerafaxstat was associated with significant improvement in functional capacity measured by V_E/VCO_2, an important and prognostic submaximal CPET variable in HCM
- In those nonobstructive HCM patients limited at baseline, ninerafaxstat significantly improved limiting symptoms with favorable change in KCCQ-CCS score
- These results support progression to larger Phase 3 study in symptomatic nonobstructive HCM to investigate if targeted therapy at optimizing cardiac energetics may fulfill an important unmet treatment need in this disease