Treatment of PH-HFpEF: Potential Role for Levosimendan

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I, Sanjiv Shah do have any financial relationships to disclose.

PI of the Tenax Therapeutics LEVEL Trial

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Faculty disclosure information can be found on the app

The Underlying Pathophysiology of PH-HFpEF Can Be Attributed to:

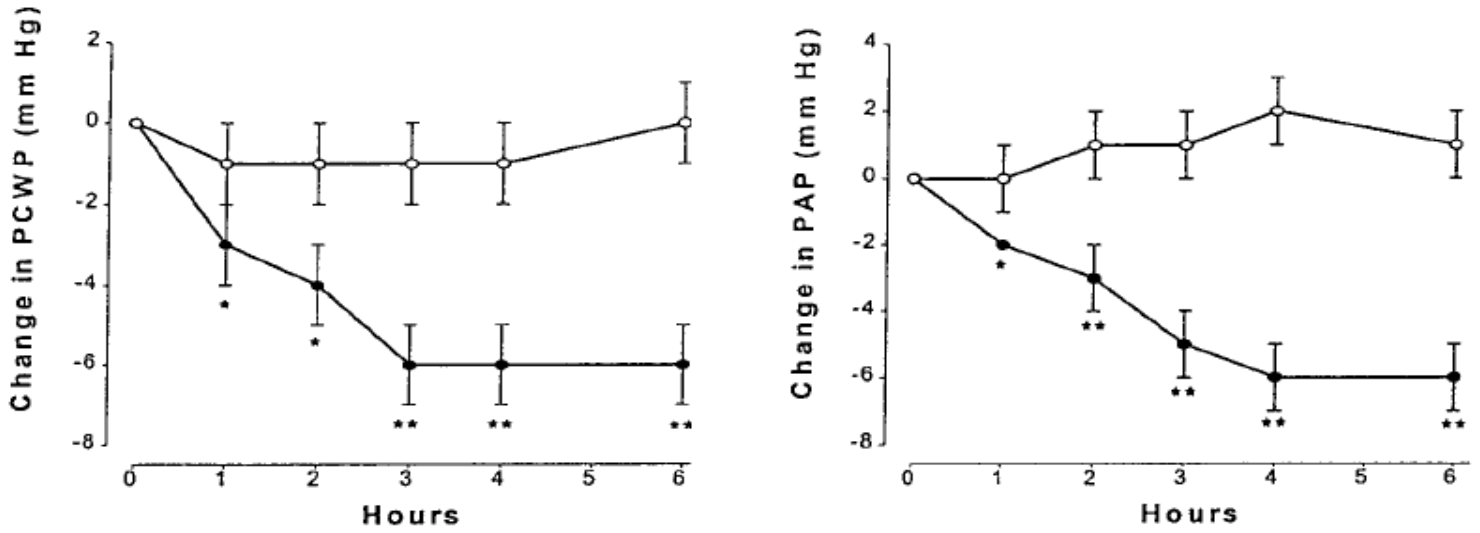
1. **Chronic elevation of the PCWP associated with:**
   - Reduced compliance of the ventricles
   - Increased stressed blood volume
2. **Which results in a pulmonary vasculopathy**
   - Affecting pulmonary arteries and veins
3. **That is driven by abnormalities in K+ channel signaling**
   - Promotes systemic and pulmonary vasoconstriction, and pulmonary vascular proliferation

Levosimendan Background

- **Consistent evidence of biventricular hemodynamic effects in HFrEF**
  - Reduces PCWP
  - Reduces CVP
  - Reduces PAP
  - Does not impair diastolic function
- **Not previously studied in HFpEF**
  - Hemodynamic effects may have application in HFpEF and PH-HFpEF
  - HELP Study designed as proof-of-concept study

Levosimendan MOA

- Combined Ca sensitizer and K_{ATP} channel activator

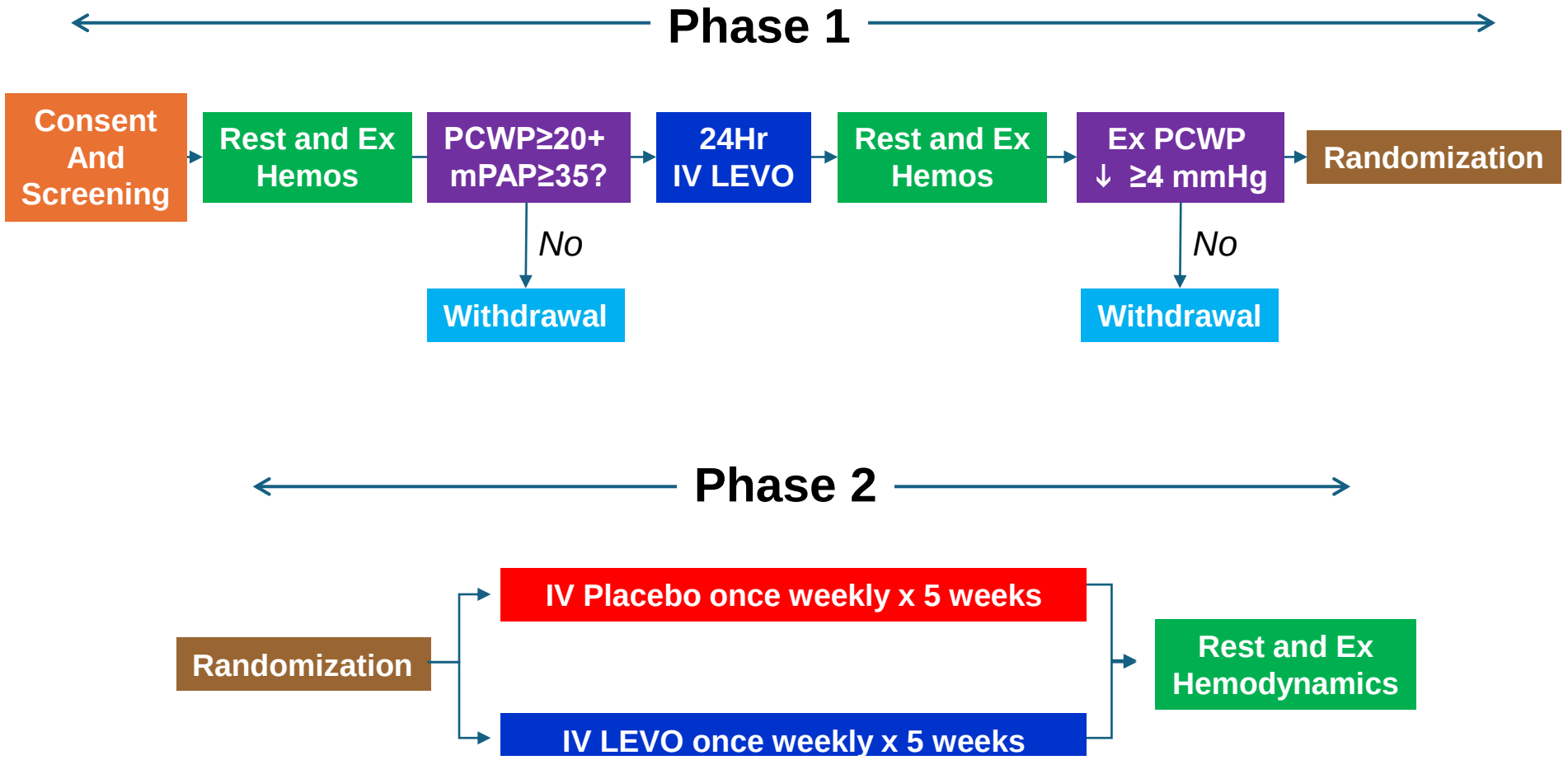


- $t_{1/2}$ for LEVO is ~1 hour, but its active metabolite (OR-1896) has $t_{1/2}$ ~75 hours enabling once weekly dosing

HELP Study population: HFpEF with PH

- Group 2 PH due to HF with EF≥40%
- NYHA class II-III symptoms
- PCWP≥20 *and* mPAP≥35 mmHg
- Key exclusion criteria
  - Coronary disease unless negative perfusion scan
  - Significant mitral and aortic valve disease
  - SBP<100 mmHg
  - Other causes of PH (lung, congenital)
  - Planned transplant or cardiac surgery

HELP Study Design:
Randomized, double-blind, placebo controlled trial



HELP Study Trial Endpoints

Primary

- Change in PCWP at 25 W exercise at 6 weeks

Secondary

- Change in 6 minute walk distance
- Change in PCWP incorporating rest, PLR and exercise using a mixed effect model with repeated measures (post hoc)

Baseline Characteristics

Characteristic	Placebo (n=19)	Levo (N = 18)
Age (years)	67 (11)	69 (8)
Women (%)	68	56
White (%)	84	89
BMI (kg/m^2)	33.0 (7.2)	35.6 (9.2)
Atrial fibrillation (%)	63	89

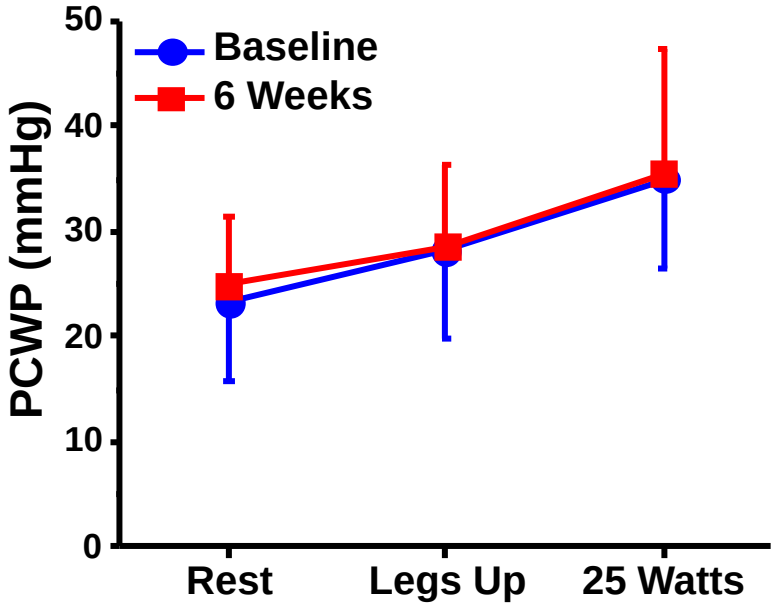
Baseline Characteristics

Characteristic	Placebo (n=19)	Levo (N = 18)
NYHA class II/III (%)	16/84	11/89
6 minute walk distance (m)	280 (85)	290 (127)
Ejection fraction (%)	59 (8)	58 (7)

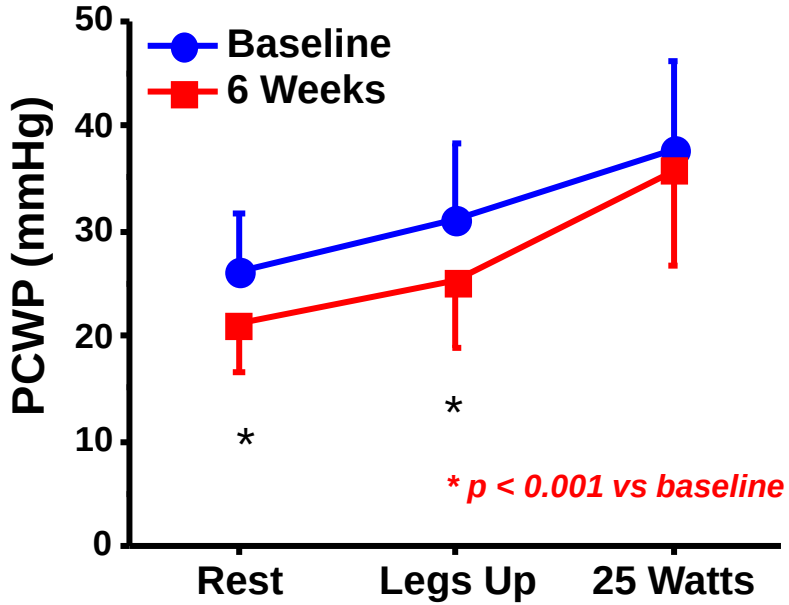
Hemodynamics at Baseline

Characteristic	Placebo (n=19)	Levo (N = 18)
Right atrial pressure (mmHg)	17 (5)	15 (5)
Mean PA pressure (mmHg)	42 (11)	41 (9)
PCWP (mmHg)	25 (7)	26 (5)
Cardiac index (l/min/m^2)	2.3 (0.6)	2.7 (1.0)
PVR (WU)	4.1 (3.6)	2.7 (1.5)

Placebo



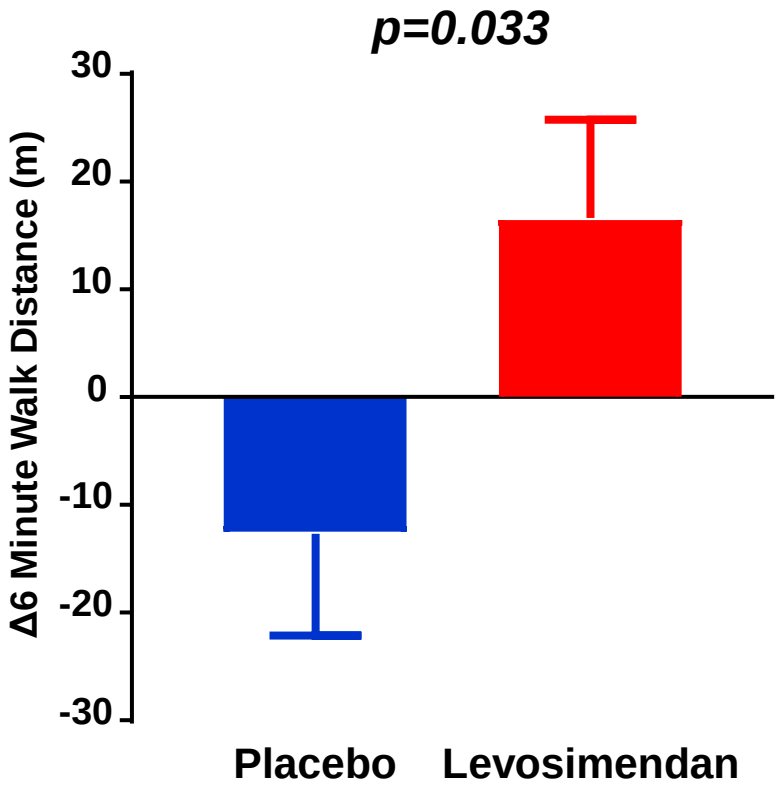
Levosimendan



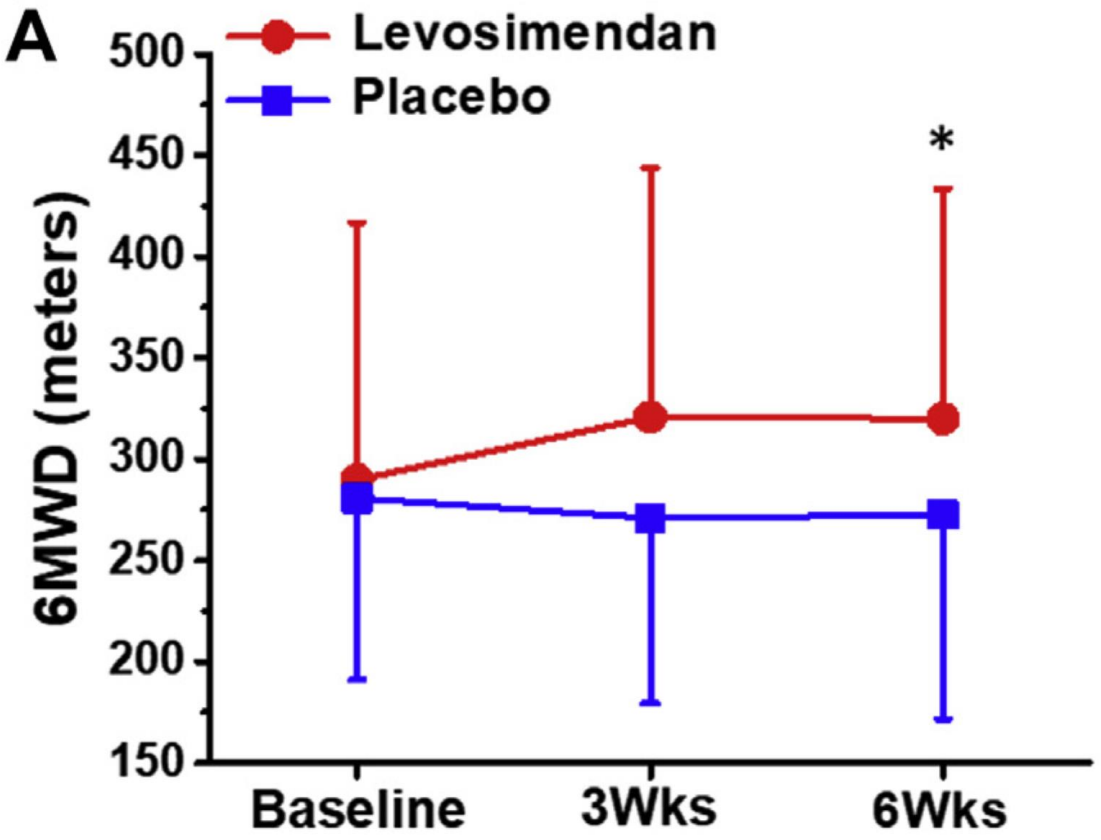
Primary Endpoint ex PCWP (-1.4 mmHg, 95% CI, -7.7 to 4.8, p=0.65)

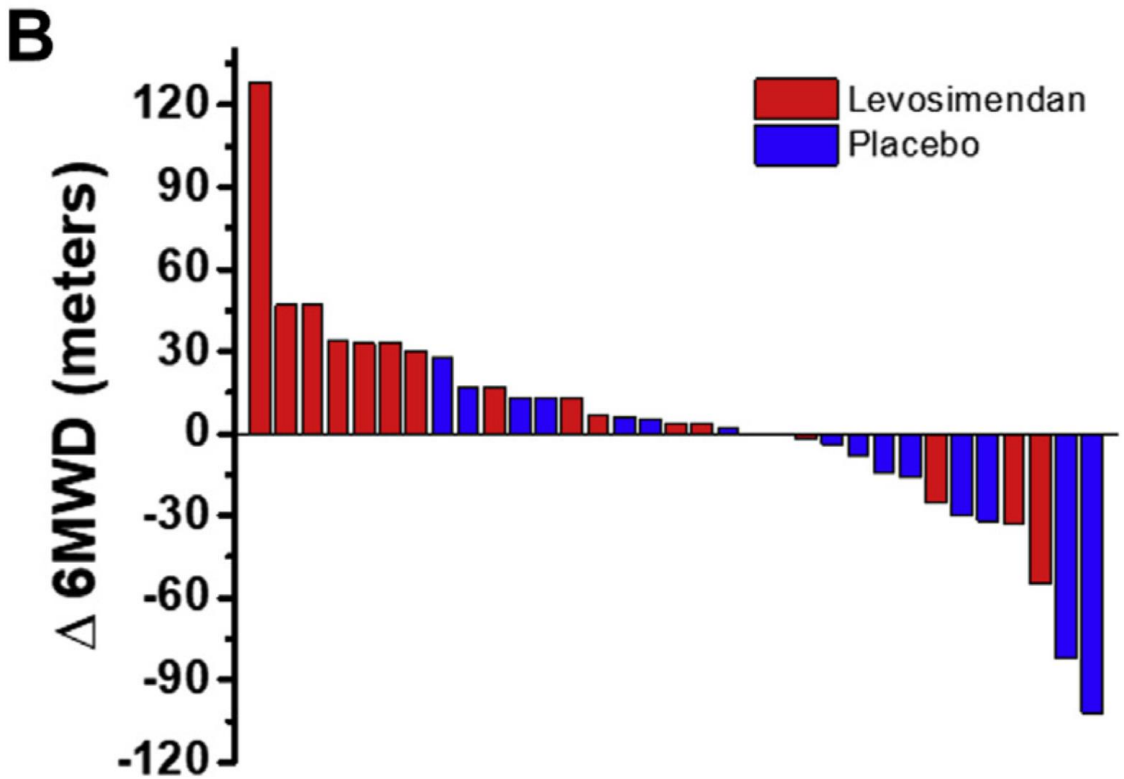
Mixed-effect repeated measure regression analysis: -3.9±2.0 mmHg as compared to placebo (p=0.047)

Effects on 6 minute walk distance

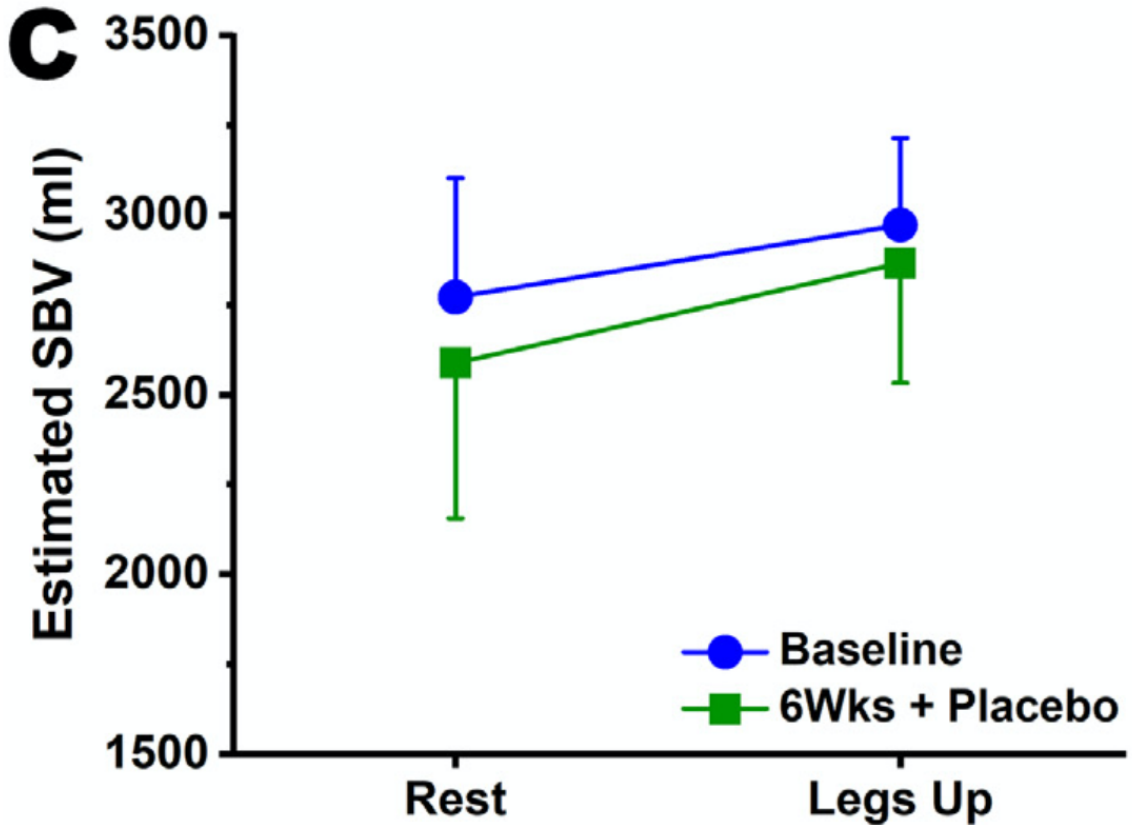


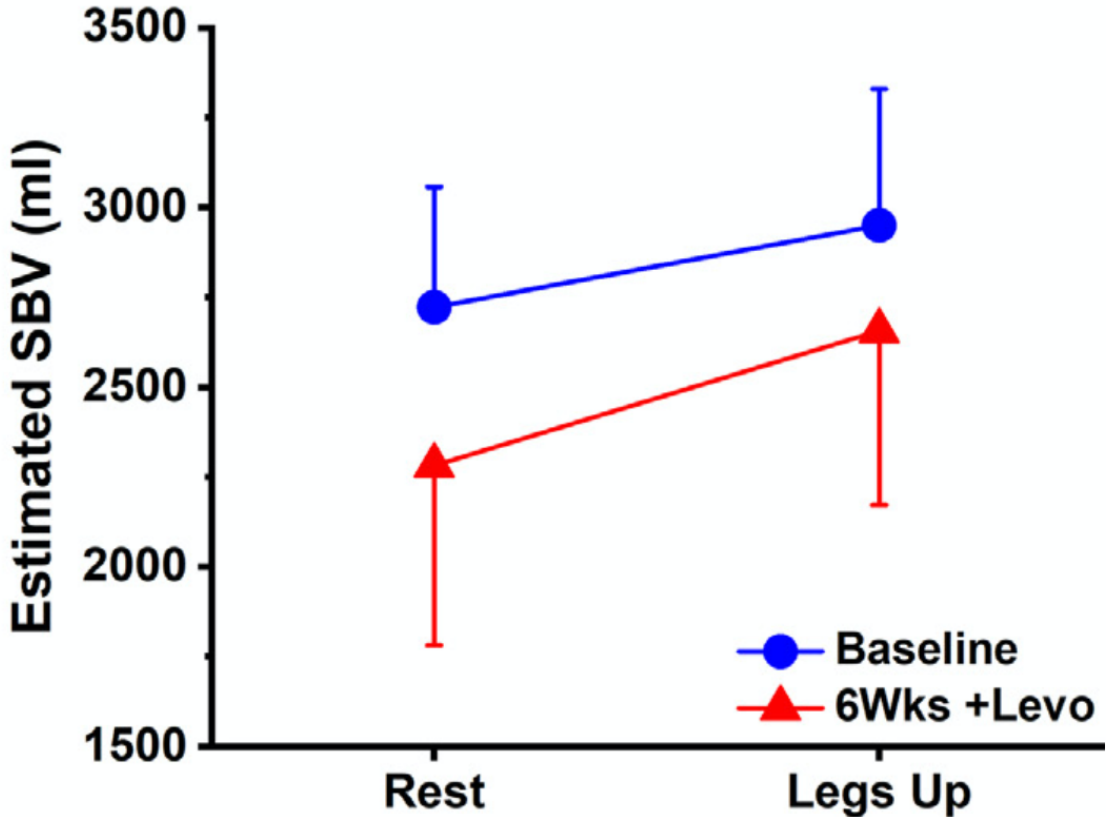
Effects on 6 minute walk distance





Effect on estimated stressed blood volume



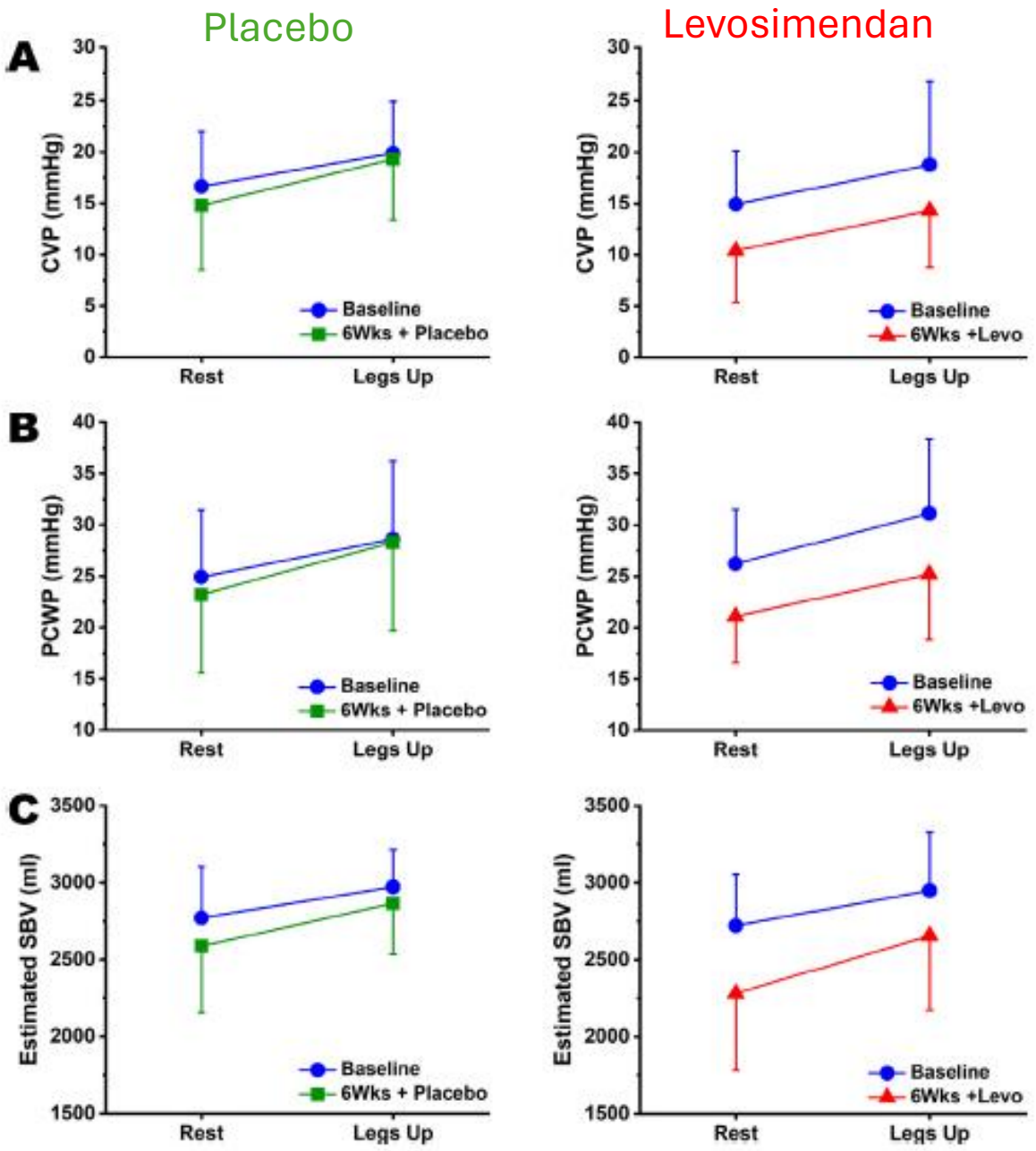


Changes in key hemodynamic parameters between treatment and placebo groups

CVP

PCWP

Stressed Blood Volume



Brener, Michael I., et al 2021

Safety

Characteristic	Placebo (n=18)	LEVO (n=19)
Discontinued study drug	2	0
PICC Line Infection	0	2
Arrhythmia	0	0
Worsening HF	1	2
Stroke	0	0
Syncope	0	0
SAE - Death	0	0

All p > 0.05

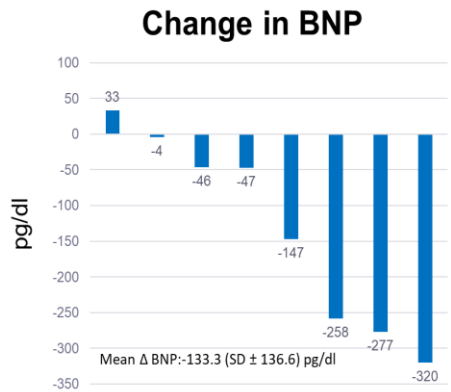
Secondary Endpoints: Oral Levosimendan Transition Study

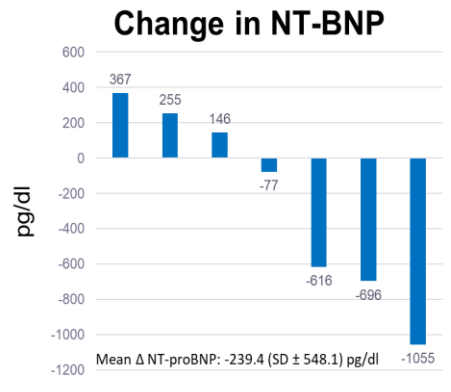
In patients with PH-HFpEF who had been receiving IV levosimendan for more than 18 months, oral levosimendan was also associated with **further improvements** in **6MWD, BNP/NT-ProBNP, and KCCQ scores**.

KCCQ Summary Scores

	mean △
Symptom Stability	+9.4
Symptom Frequency	+3.1
Symptom Burden	+6.3
TOTAL SYMPTOM	+4.7

	mean △
•PHYSICAL LIMITATION	+0.3
•SELF EFFICACY	-2.3
•QUALITY OF LIFE	+4.2
•SOCIAL LIMITATION	+5.5
•OVERALL SUMMARY	+3.7





LEVEL

a PH-HFpEF study

A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of Levosimendan in Pulmonary Hypertension Patients With Heart Failure With Preserved Left Ventricular Ejection Fraction (PH-HFpEF);

LEVosimendan to Improve **E**xercise **L**imitation in Patients With PH-HFpEF

CRF THT

LEVEL Study Objectives/Endpoints

- ***N=152 randomized patients***
- ***Primary Study Objective:***
  - To evaluate the efficacy of levosimendan (TNX-103) compared with placebo in subjects with PH-HFpEF as measured by the change in 6-MWD (Day 1 to Week 12)
- ***Secondary Study Objective:***
  - Change in KCCQ - Total Symptom Score (KCCQ-TSS) (Day 1 to Week 12)
  - Number of Clinical Worsening Events (Day 1 to Week 12)
  - Change in NT-proBNP (Day 1 to Week 12)
  - Improvement in NYHA Functional Class (Day 1 to Week 12)

Conclusions

- Levosimendan is a novel potential therapy for PH-HFpEF
- Oral formulation now available
- Potential mechanism of action: Lowers stress blood volume while maintaining RV contractility