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Virtual KOL Call

November 13, 2025

Forward-Looking Statements

Disclaimers

Except for historical information, all of the statements, expectations and assumptions contained in this presentation are forward-looking statements. These forward-looking statements may include information concerning possible or projected future business operations. Actual results might differ materially from those explicit or implicit in the forward-looking statements. Important factors that could cause actual results to differ materially include: risks of our clinical trials, including, but not limited to, the timing, delays, costs, design, location, initiation, enrollment, and results of such trials; our ability to maintain our culture and recruit, integrate and retain qualified personnel and advisors, including on our Board of Directors; any delays in regulatory review and approval of product candidates in development; risks related to our business strategy, including the prioritization and development of product candidates; intellectual property risks; reliance on third parties, including Orion Corporation, our manufacturers and CROs; risks regarding the formulation, production, marketing, customer acceptance and clinical utility of our product candidates; our estimates regarding the potential market opportunity for our product candidates; the potential advantages of our product candidates; our competitive position; risks associated with our cash needs; volatility and uncertainty in the global economy and financial markets in light of unexpected changes in tariffs and the possibility of pandemics, global financial and geopolitical uncertainties, including in the Middle East and the Russian invasion of and war against the country of Ukraine; changes in legal, regulatory and legislative environments in the markets in which we operate and the impact of these changes on our ability to obtain regulatory approval for our products; and other risks and uncertainties set forth from time to time in our SEC filings. Tenax Therapeutics assumes no obligation and does not intend to update these forward-looking statements except as required by law. This presentation shall not constitute an offer to sell or the solicitation of an offer to buy any securities of the Company.

Today’s Speakers

Chris Giordano
President & CEO
Tenax Therapeutics

Stuart Rich, MD
CMO
Tenax Therapeutics

Barry Borlaug, MD
Professor of Cardiology
Mayo Clinic

Sanjiv Shah, MD
Director of HFpEF Program
Northwestern University

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Volume Overload as a Cause of PH-HFpEF

Is it accepted that excessive blood volume in the heart and lungs of patients is a cause of PH-HFpEF?

Impaired Systemic Venous Capacitance: The Neglected Mechanism In Patients With Heart Failure And A Preserved Ejection Fraction?

HYPERTROPHIC/HYPERTENSIVE PHENOTYPE

- Naturetic peptides markedly elevated
- LV wall thickness increased
- LV volume reduced
- Venous blood volume mildly increased
- Less common

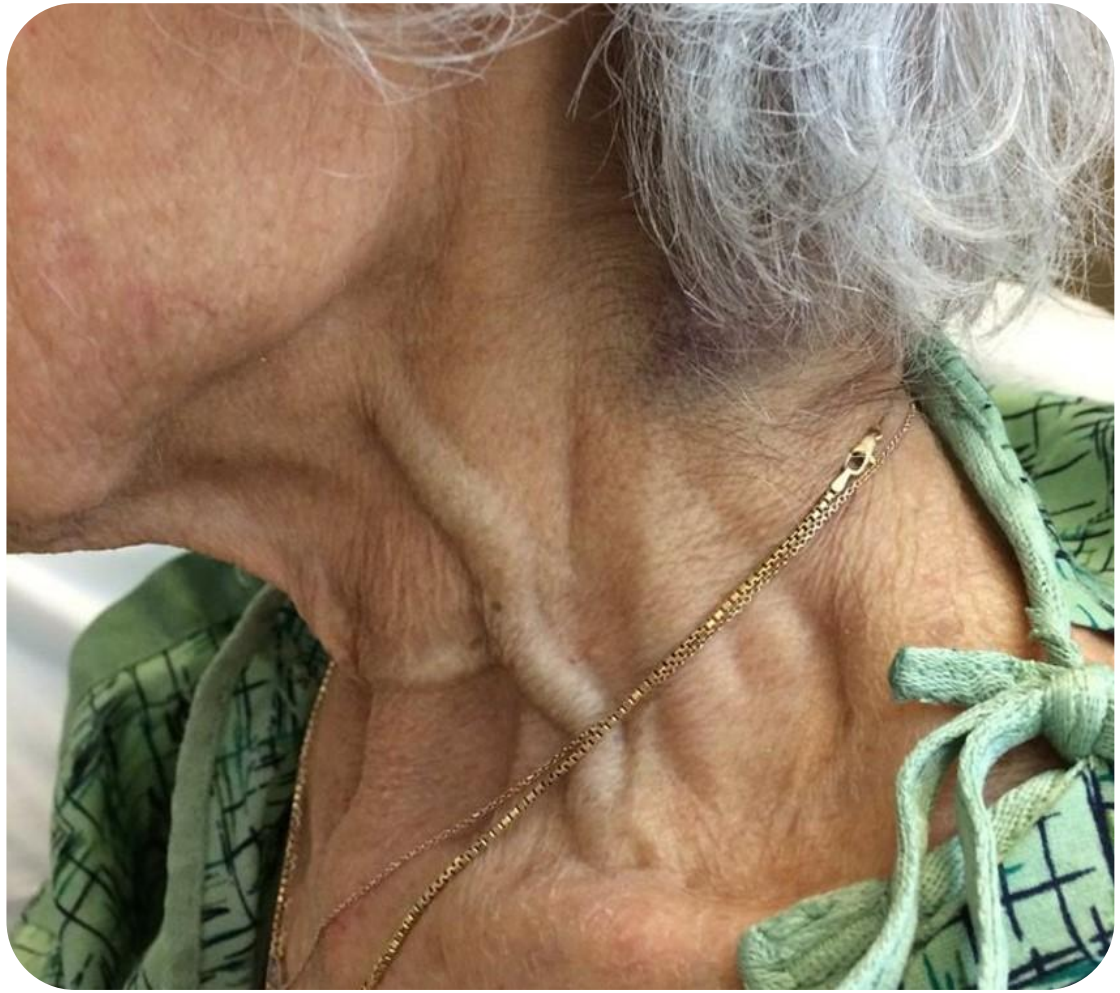
OBESE/METABOLIC PHENOTYPE

- Naturetic peptides mildly elevated
- LV wall thickness normal
- LV volume normal
- Venous blood volume markedly increased
- More common

Maurer MS and Packer M. *European journal of heart failure* vol. 22,2 (2020): 173-176.

Excessive Blood in Venous Circulation

The elevated jugular venous pressure in this patient who is sitting is a representation of the **excessive blood volume** in her venous circulation



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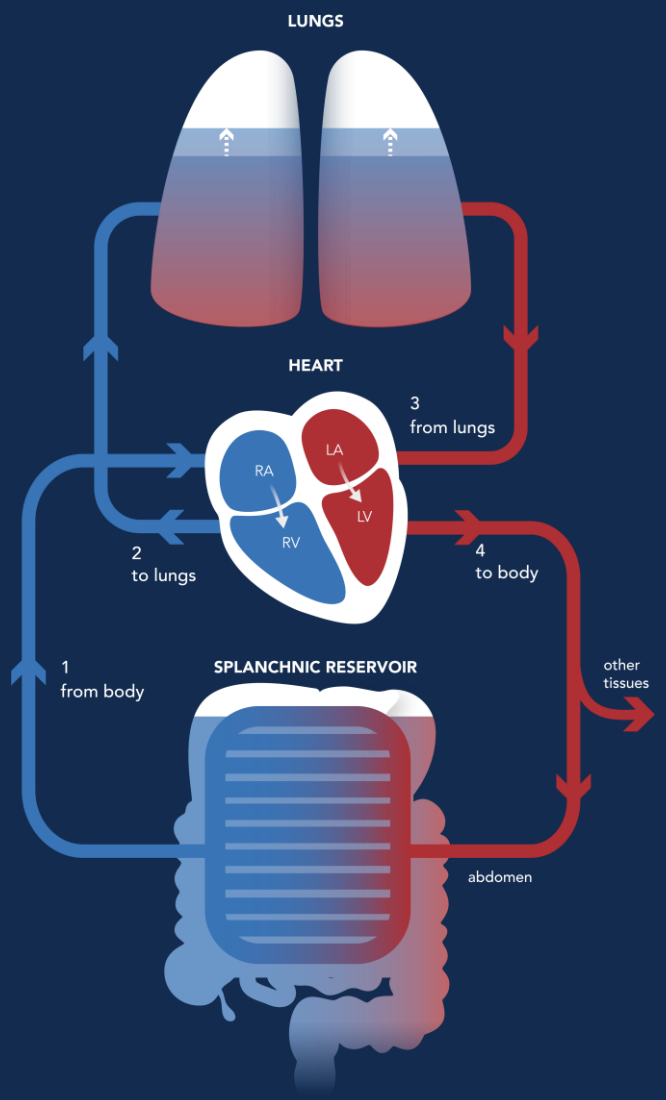
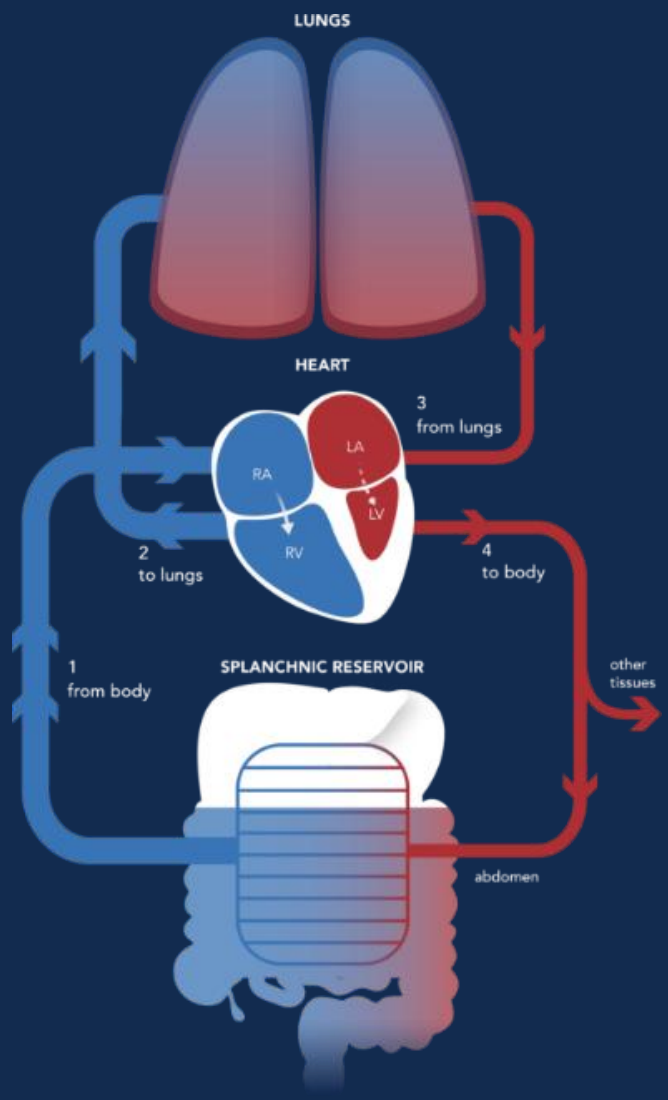
Healthy



PH-HFpEF



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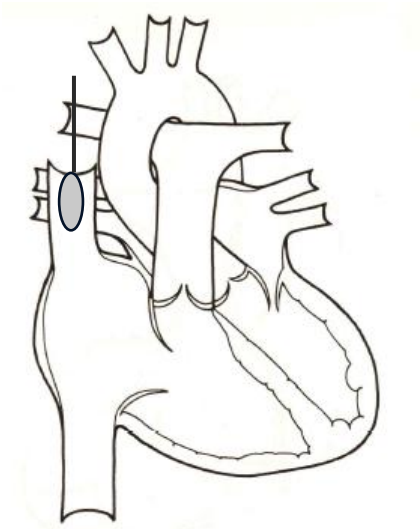
Proof-of-Concept

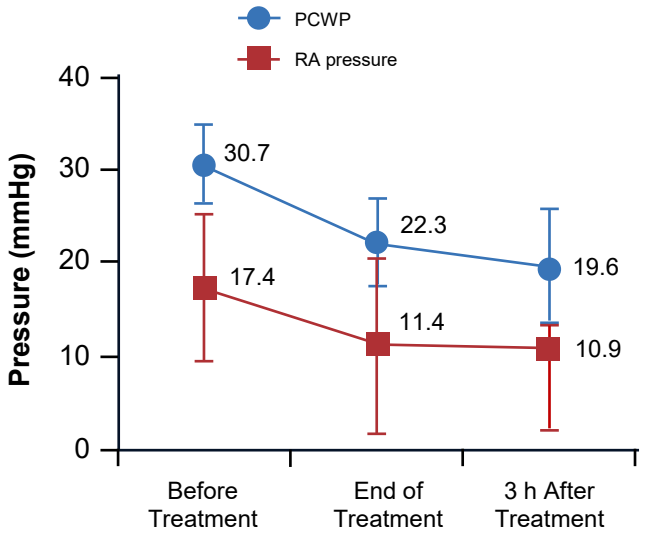
Is there data that shows reducing blood volume in the heart and lungs of patients with PH-HFpEF will result in hemodynamic improvement?

Mechanical Preload Reducing Devices

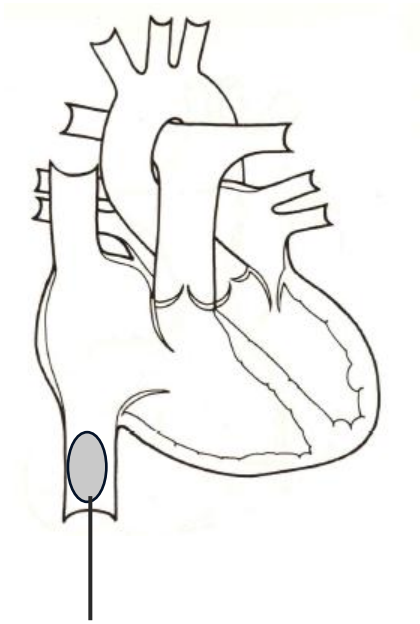
PROOF-OF-CONCEPT FOR VENOUS MODULATING THERAPIES

SVC Balloon Occlusion





IVC Balloon Occlusion



Balloon inflation within the inferior vena cava during exercise maintains PA diastolic at 25 mmHg

- RA pressure: ↓
- PA pressure: ↓
- Cardiac output: **no change**

IVC: inferior vena cava; SVC: superior vena cava; PA: pulmonary arterial; RA: right arterial; PCWP: pulmonary capillary wedge pressure; PH-HFpEF: pulmonary hypertension and heart failure with preserved ejection fraction.

Kapur NK, et al. *Circulation. Heart failure* vol. 15,2 (2022): e008934.; Atkins J, et al. *JACC. Basic to translational science* vol. 6,3 (2021): 199-201.

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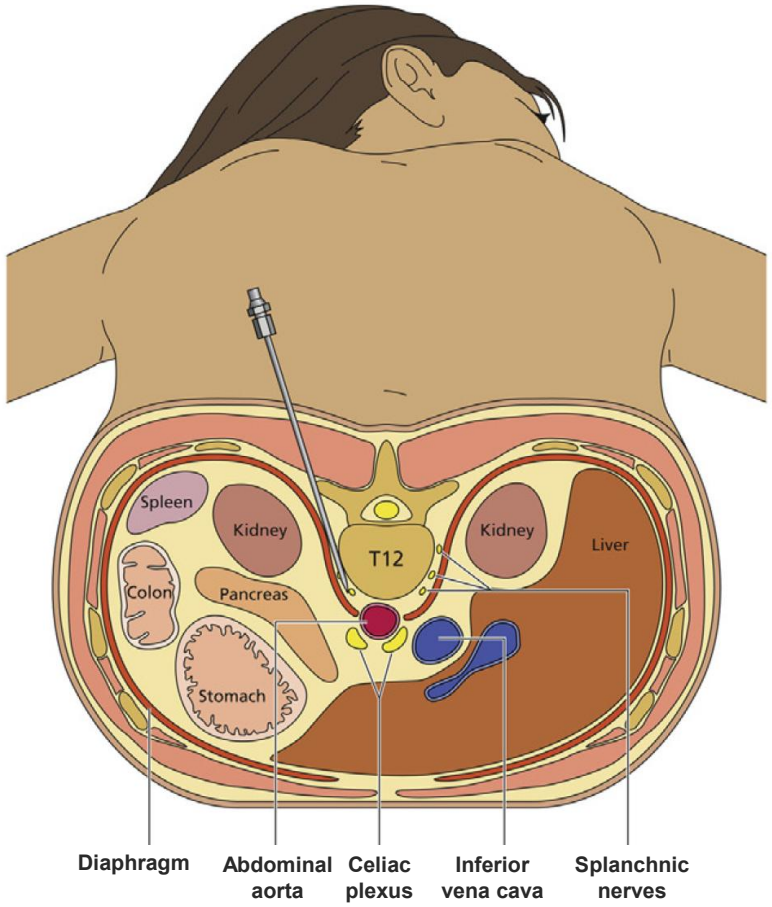
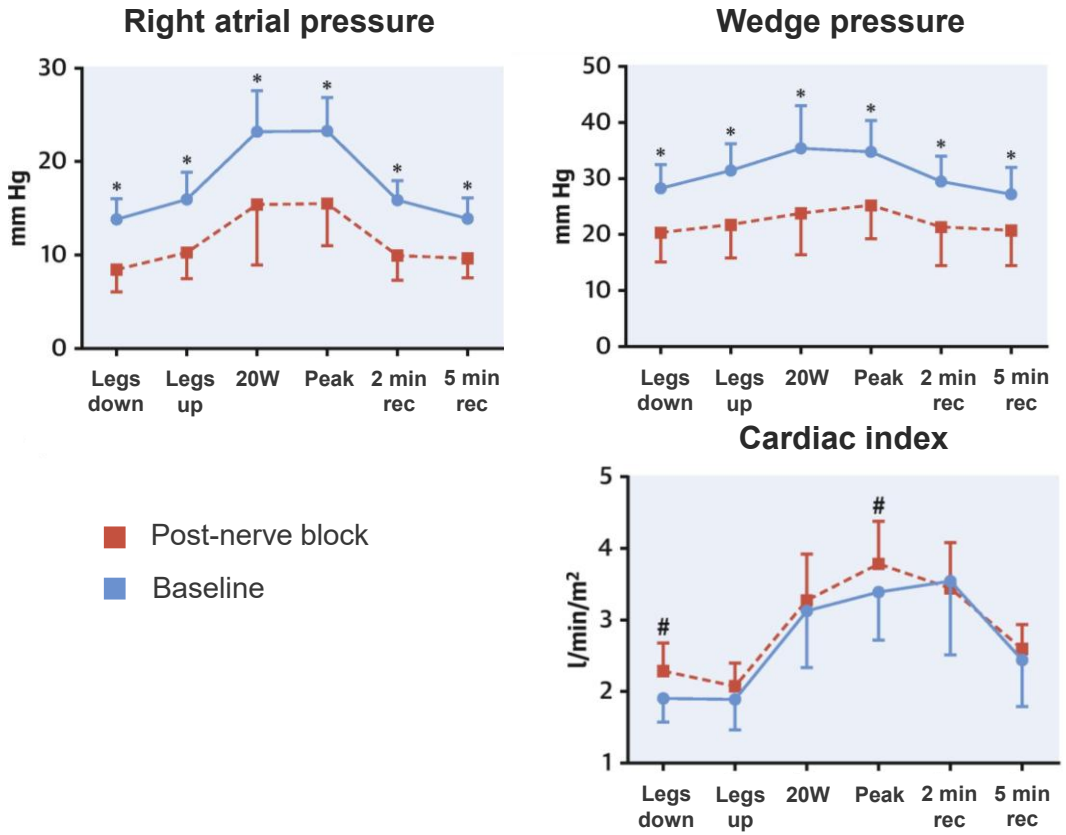
Splanchnic Nerve Block

PROOF-OF-CONCEPT FOR VENOUS MODULATING THERAPIES



Splanchnic nerve block provides proof of concept for benefit of volume modulating therapies



*Adjusted P<0.01 for a pairwise comparison with the pre-SNB value; #Unadjusted P<0.05, adjusted P>0.05.
rec: recovery after peak exercise; SNB: splanchnic nerve block; W: watt.
Fudim M, et al. *JACC. Heart failure* vol. 8,9 (2020): 742-752.

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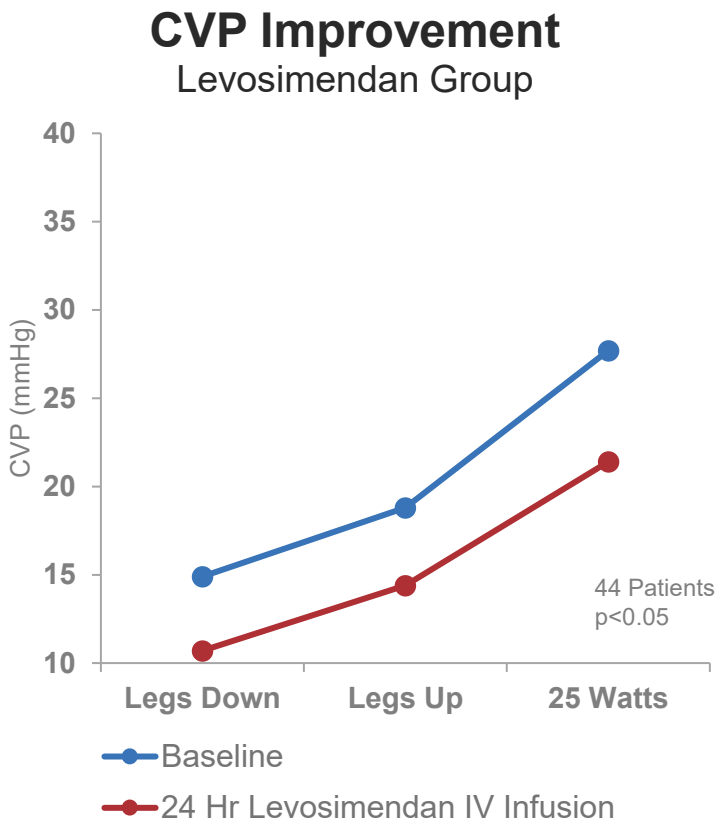
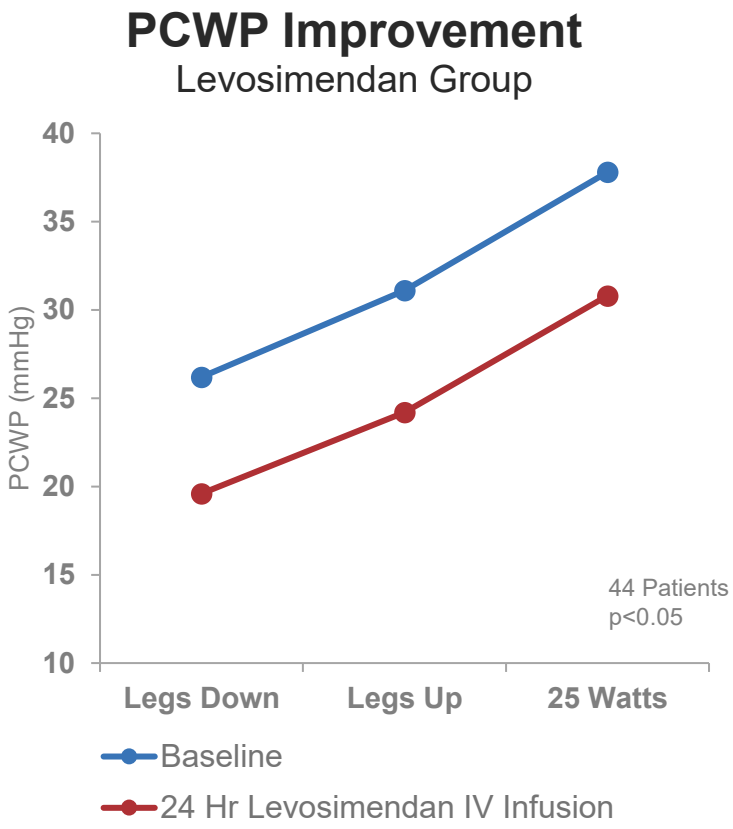
IV Levosimendan Improves CVP and PCWP After 24 Hour Infusion

- Improvements seen at rest and with exercise
- 85% of patients enrolled responded with robust decrease (>4mm Hg) in exercise PCWP





CVP: central venous pressure; PCWP: pulmonary capillary wedge pressure.
Burkhoff D, et al. *JACC. Heart failure* vol. 9,5 (2021): 360-370.

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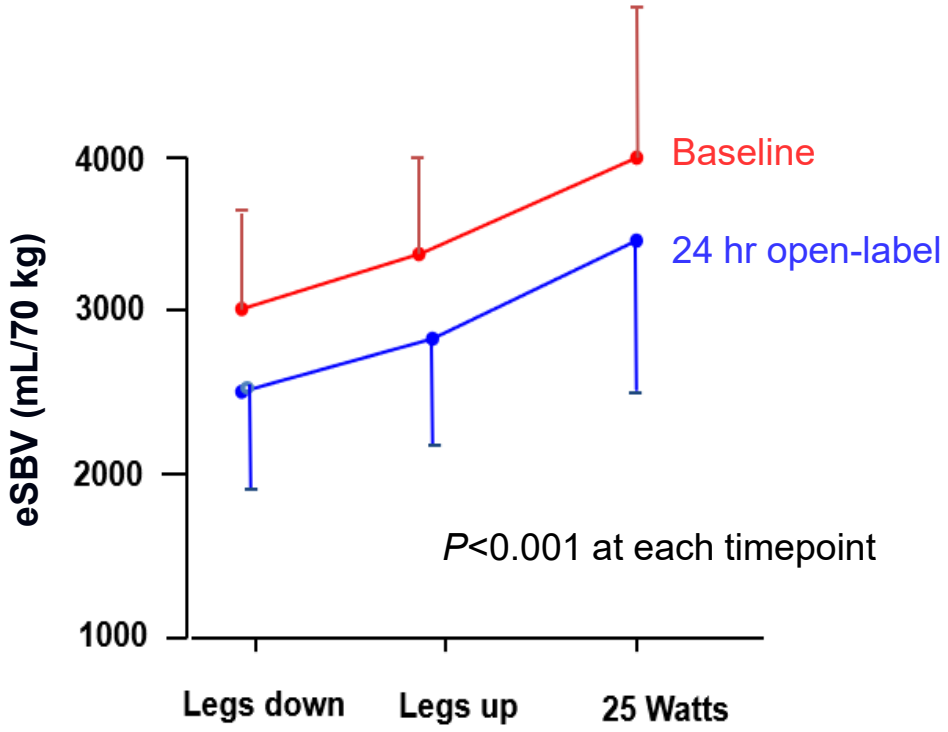
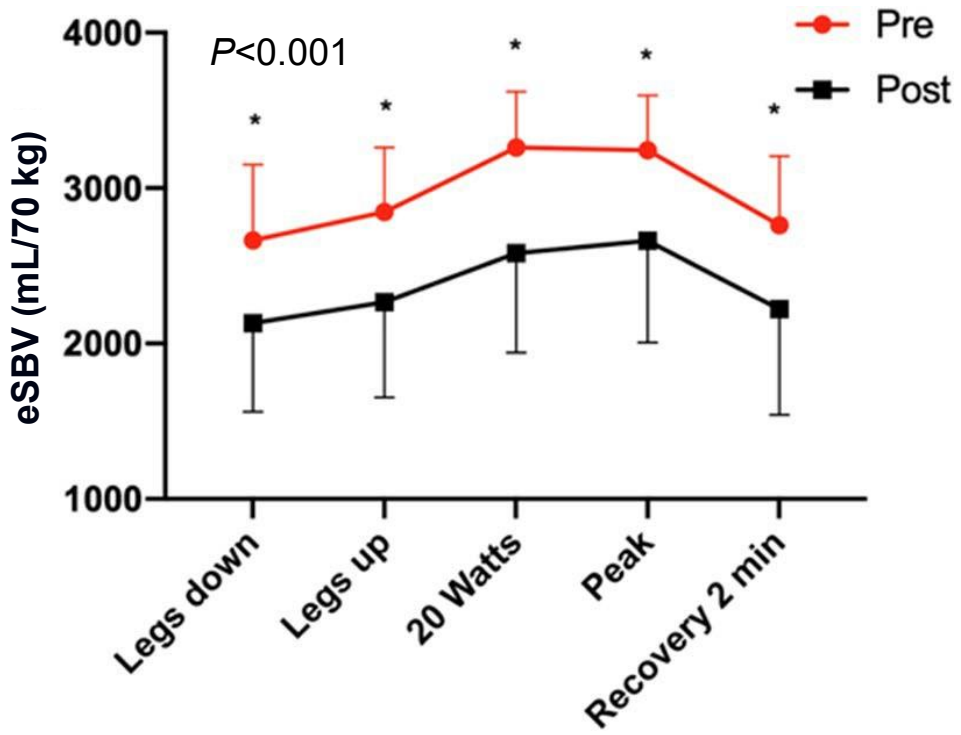
Levosimendan vs Splanchnic Nerve Block

EFFECT ON REDUCING BLOOD VOLUME PROVIDES PROOF-OF-CONCEPT

Levosimendan



Splanchnic Nerve Block



eSbv: estimated stressed blood volume.

Data on file, Tenax 2025.; Fudim M, et al. *J Am Coll Cardiol HF*. Vol. 9 (2021): 293-300.

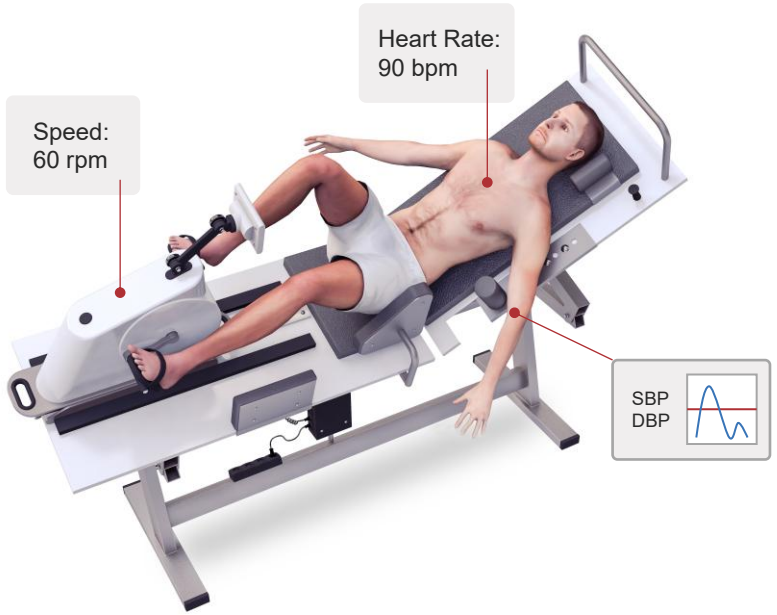
Confidence in the LEVEL Study

How has the Phase 3 LEVEL study been derisked to assure a positive outcome?

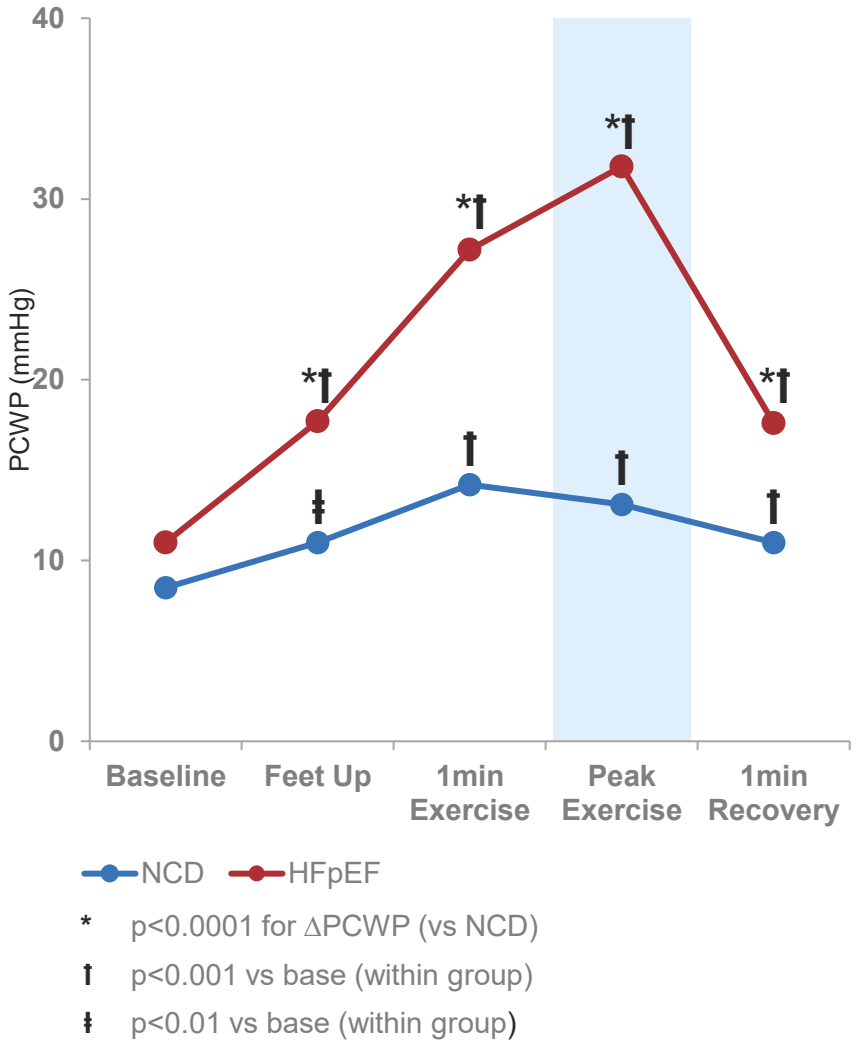
Phase 2 HELP study confirmed that levosimendan produces a reduction in PCWP with exercise in these patients

No other study in PH-HFpEF has ever provided supporting exercise hemodynamic data

Experimental Set Up During Isometric Leg Exercise



ΔPCWP at Rest and Exercise



DBP: diastolic blood pressure; NCD: noncardiac dyspnea; PCWP: pulmonary capillary wedge pressure; SBP: systolic blood pressure.
Borlaug BA, et al. *Circulation. Heart failure* vol. 3,5 (2010): 588-95.

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The Phase 3 LEVEL Study is Enriched

ENROLLS PATIENTS WITH THE SAME HEMODYNAMIC PROFILE AS THOSE IN THE PHASE 2 HELP STUDY

The resting hemodynamics in the HELP study predicted a positive response

Hemodynamics at <u>rest</u>:

a. Pulmonary capillary wedge pressure (PCWP) ≥**18 mmHg,** and

b. Mean pulmonary arterial pressure (mPAP) ≥ **30 mmHg,** and

OR, Hemodynamics with <u>passive leg raise</u>.

a. PCWP ≥**20** mmHg, and

b. mPAP ≥ **32** mmHg, and

OR, Hemodynamics with <u>bicycle exercise</u>.

a. PCWP ≥ **25** mmHg, and

b. mPAP ≥ **35** mmHg, and

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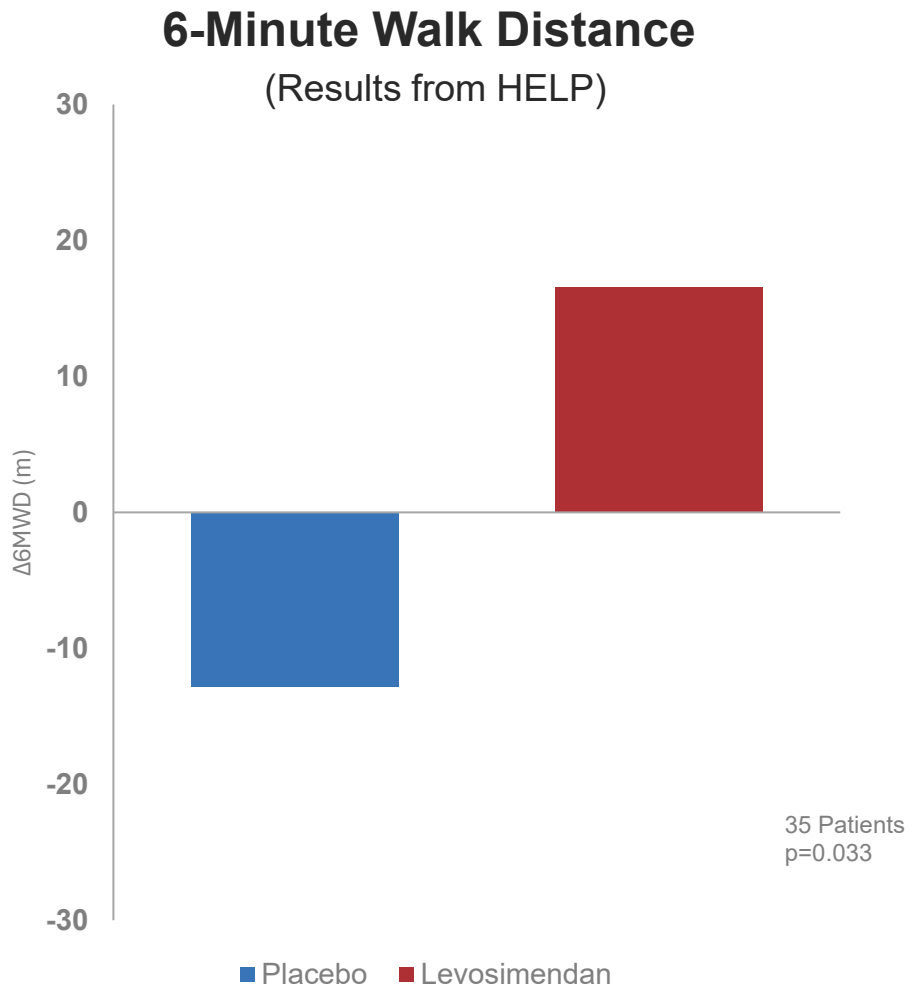
LEVEL Uses TNX-103, the Oral Formulation of Levosimendan

PRODUCES STEADY STATE OF THERAPEUTIC LEVELS OF OR-1896 METABOLITE RESPONSIBLE FOR CHRONIC DRUG EFFICACY

- Weekly IV administration produced a 29-meter improvement in 6MW when measured at the end of the week (trough)
- Legacy studies with oral levosimendan, administered for 6 months (PERSIST) and 12 months (REFALS), have provided valuable data on optimal daily dosing, efficacy, and safety



37 patients met hemodynamic criteria and were randomized, of these, 2 patients dropped out due to palpitations and COVID-
Burkhoff D, et al. *JACC. Heart failure* vol. 9,5 (2021): 360-370.

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HELP Study OLE: Transition from IV to Oral Levosimendan was Effective

Exercise capacity

+ 7 meters

6MWD was improved
by an additional 7 meters

Cardiac function

↓ 23% over IV

BNP/NT-proBNP
improved by 23%
with oral levosimendan vs IV

Patient-reported outcomes

↑ in 6 of 7 domains

KCCQ improved further
in 6 of 7 different domains

6MWD: 6-minute walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; KCCQ: Kansas City cardiomyopathy questionnaire; OLE: open-label extension.
Thenappan T, et al. *J Card Fail*. Vol. 29,4 (2023): 714-715. ; Data on file, Tenax 2025.

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Pulmonary Vascular Resistance (PVR)

Is the change in PVR an appropriate hemodynamic endpoint to measure drug efficacy in PH-HFpEF?

The Hemodynamic Definition of PVR

$$PVR = \frac{\text{mean PAP} - \text{PCWP}}{\text{Cardiac Output}}$$

PVR cannot be directly measured in the pulmonary circulation. It is estimated from an equation based on Poiseuille's Law

PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance.

Naeije R. *Intensive Care Med*. 2003;29(4):526-529. ; https://www.mdapp.co/pulmonary-vascular-resistance-pvr-calculator-314/.

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Why PVR is a Misleading Efficacy Measure in PH-HFpEF

$$PVR = \frac{mean\ PAP - mean\ PCWP}{CO}$$

Baseline

- $\frac{40 - 25}{5.0}$ = 3 WU

After treatment

- $\frac{35 - 15}{5.0}$ = 4 WU

- This is a desirable treatment effect because it lowered the PCWP to normal, even though the PVR increased
- This is characteristic of levosimendan

Baseline

- $\frac{40 - 25}{5.0}$ = 3 WU

After treatment

- $\frac{34 - 27}{7.0}$ = 1 WU

- This is an undesirable treatment effect because it increased PCWP, even though it lowered PAP and raised CO
- This is characteristic of pulmonary vasodilators

CO: cardiac output; PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PH-HFpEF: pulmonary hypertension and heart failure with preserved ejection fraction; PVR: pulmonary vascular resistance; WU: wood units.

Naeije R. *Intensive Care Med*. 2003;29(4):526-529. ; Simonneau G, et al. *Eur Respir J*. 2019;53(1):1801913. ; Burkhoff D, et al. *JACC Heart Fail*. 2021;9(5):360-370. ; Vachiéry J-L, et al. *Eur Respir J*. 2018;51(12):1701886. ; Dachs T-M, et al. *Eur Heart J*. 2022;43:3402-3413.

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Other Clinical Studies in PH-HFpEF

Are there data showing pulmonary vasodilators or relaxin analogues in PH-HFpEF will result in hemodynamic or clinical improvement?

Other Current PH-HFpEF Trials Are All in Phase 2

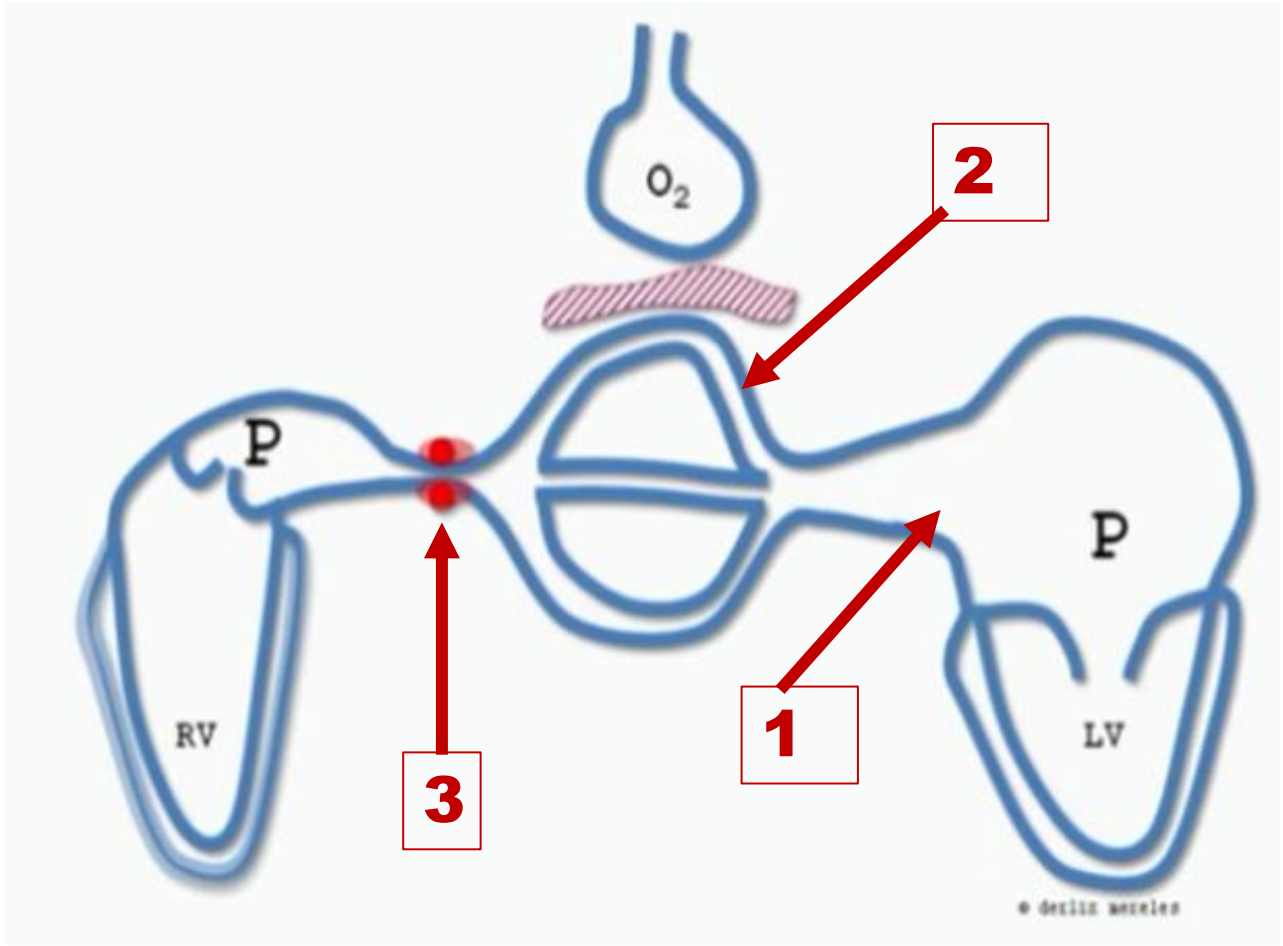
- **Sotatercept for Cpc-PH Due to HFpEF (CADENCE/Merck)**
- **TX000045 for Cpc-PH Due to HFpEF (APEX/Tectonic)**
- **AZD3427 for Group 2 PH with Heart Failure (REPHIRE/Astra Zeneca)**

- All three studies use a standard definition of PH-HFpEF without enrichment
  - Baseline mPAP of >**20** mmHg at rest
  - Baseline PCWP >**15** mmHg at rest
  - **(beware of misclassification of patients)**
- All three studies designate a reduction in PVR at rest as the primary endpoint
  - **(target PA pressure instead of PCWP)**
- All three drugs have a mechanism of action as a pulmonary arterial vasodilator
  - **(6 previous pulmonary vasodilator studies have failed)**

Protective Pulmonary Arterial Hypertension in PH-HFpEF

1. LA enlargement from elevated PCWP
2. Elevated pulmonary venous pressure creates injury in the alveolar capillaries
3. To protect the alveolar-capillary interface, the pulmonary arterioles vasoconstrict to reduce blood flow into the LA

Dilating the pulmonary arterioles will increase the cardiac output and PCWP.



LA: left artery; LV, left ventricle; LVEDP: left ventricular end-diastolic pressure; PH-HFpEF: pulmonary hypertension and heart failure with preserved ejection fraction; RV: right ventricle.

Hermo-Weiler CI, Koizumi T, et al. *J Appl Physiol.*1985;85(5):1655-1660.

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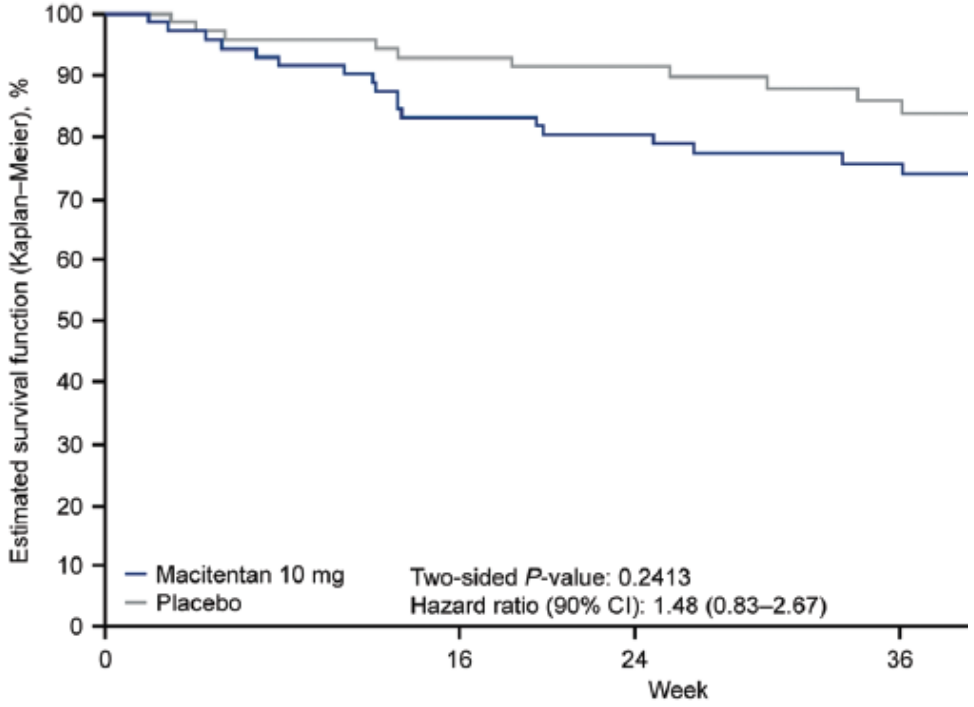
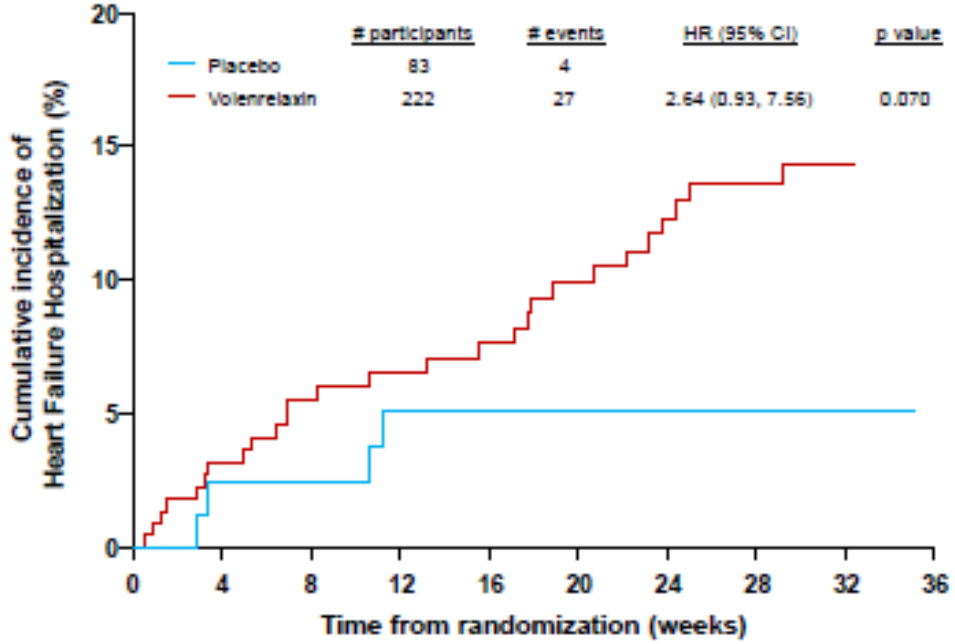
Unsuccessful Clinical Trials in HFpEF

Macitentan for HFpEF (SERENADE)



Volenrelaxin for HFpEF



Borlaug B, et al. *Nature medicine*, 10.1038/s41591-025-03939-6. 31 Aug. 2025. ; Shah SJ, et al. *Circulation. Heart failure* vol. 18,3 (2025): e011381.

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Q&A

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