



NASDAQ: TENX

February 2020

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Mission Statement



Specialty pharmaceutical company focused on identifying and developing therapeutics that address diseases with high unmet medical need with an initial therapeutic focus on Cardio-Pulmonary diseases

Levosimendan History

- Levosimendan is a calcium sensitizer/K-ATP channel activator
- First approved in Sweden (Orion) in 2000 for acute decompensated heart failure
- Approved/marketed in >60 countries
 - To date >1.5 million patients have been treated with levosimendan
 - Not Approved in US or Canada

Scientific Advisory Board

PH-HFpEF Development Plan Guided by World Recognized Experts in Pulmonary Hypertension and HFpEF

Stuart Rich, MD

- Professor of Medicine, Northwestern University Feinberg School of Medicine
- Director, Pulmonary Vascular Disease Program, Bluhm Cardiovascular Institute
- Previous FDA Cardio-Renal Advisory Committee Member
- Recognized Global Pulmonary Hypertension Expert



Daniel Burkhoff, MD, PhD

- Director Heart Failure, Hemodynamics and MCS Research at the Cardiovascular Research Foundation
- Adjunct Associate Professor of Medicine, Columbia University



Sanjiv Shah, MD, FAHA, FACC, FASE

- Professor of Medicine, Northwestern University Feinberg School of Medicine
- Director, T1 Center for Cardiovascular Therapeutics
- Director, Northwestern HFpEF Program, Division of Cardiology, Dept of Medicine, Northwestern University Feinberg School of Medicine



Barry Borlaug, MD

- Professor of Medicine, Mayo Clinic
- Chair for Research, Division of Circulatory Failure, Department of Cardiovascular Medicine, Mayo Clinic

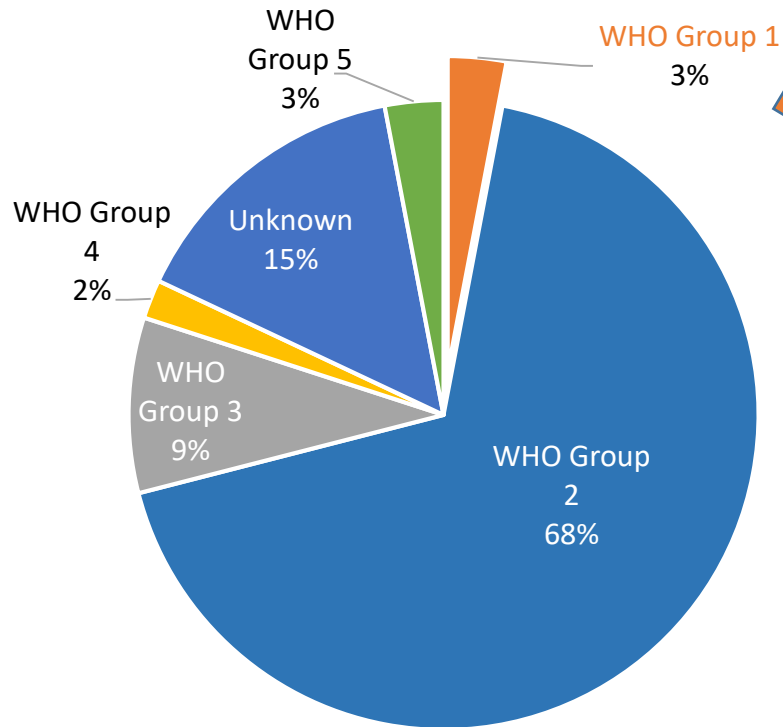


Levosimendan in PH-HFpEF

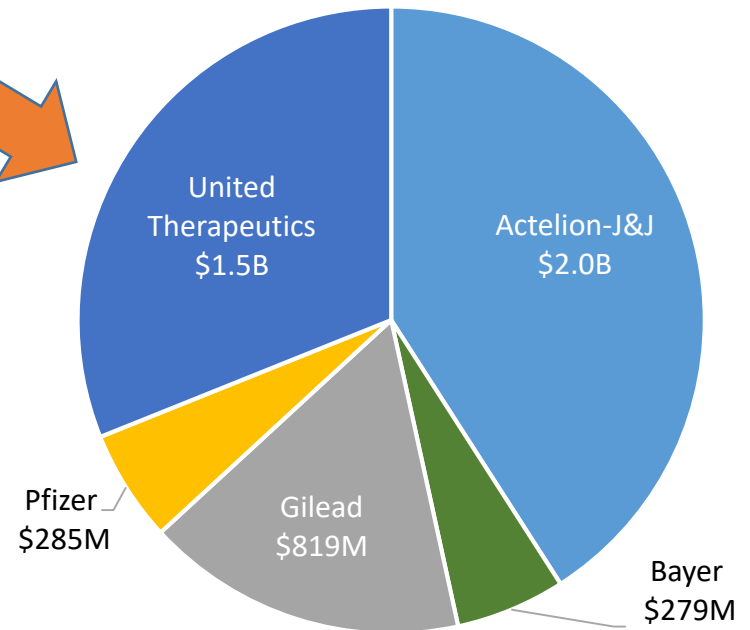
- **PH-HFpEF (pulmonary hypertension) represents a potential \$Billion US opportunity**
 - > 2 million US PH-HFpEF patients
 - High mortality and poor quality of life
 - No effective therapies
- **Phase 2 Trial of Levosimendan in PH-HFpEF is ongoing (HELP Study)**
 - Levosimendan is an NCE with a unique calcium sensitizer/K-ATP channel mechanism
 - >1.5 million patient exposures provide a large safety database in HF
 - Enriched trial design
 - Encouraging preliminary open-label hemodynamic data
- **A positive HELP Study would represent a potential major breakthrough in PH-HFpEF**
 - Leading PH focused companies unsuccessful in developing PAH drugs for PH-HFpEF
- **Potential for Additional IP to 2038**
 - HELP study discoveries provide the basis for multiple patent claims in PH-HFpEF

Pulmonary Hypertension Prevalence and Market Size

Estimated Prevalence by WHO Group



Pharmaceutical Sales >\$5 billion in 2016
(primarily in Group 1)

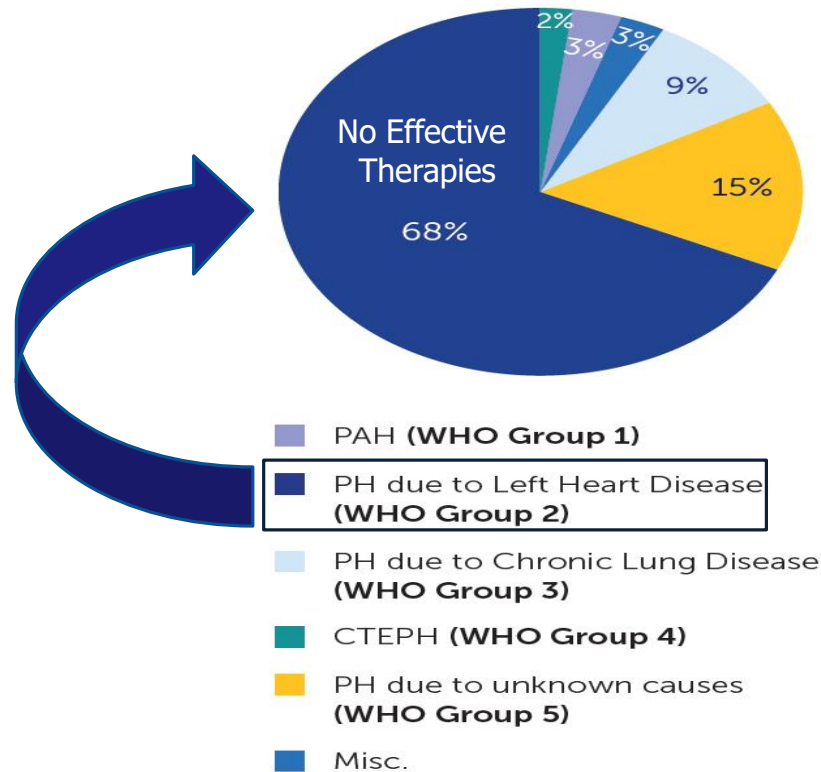


Source: Pulmonary Hypertension Association Strange G, et al. Heart. 2012;98(24):1805-11

Source: Company Annual Reports

PH-HFpEF Represents a Large Unmet Medical Need

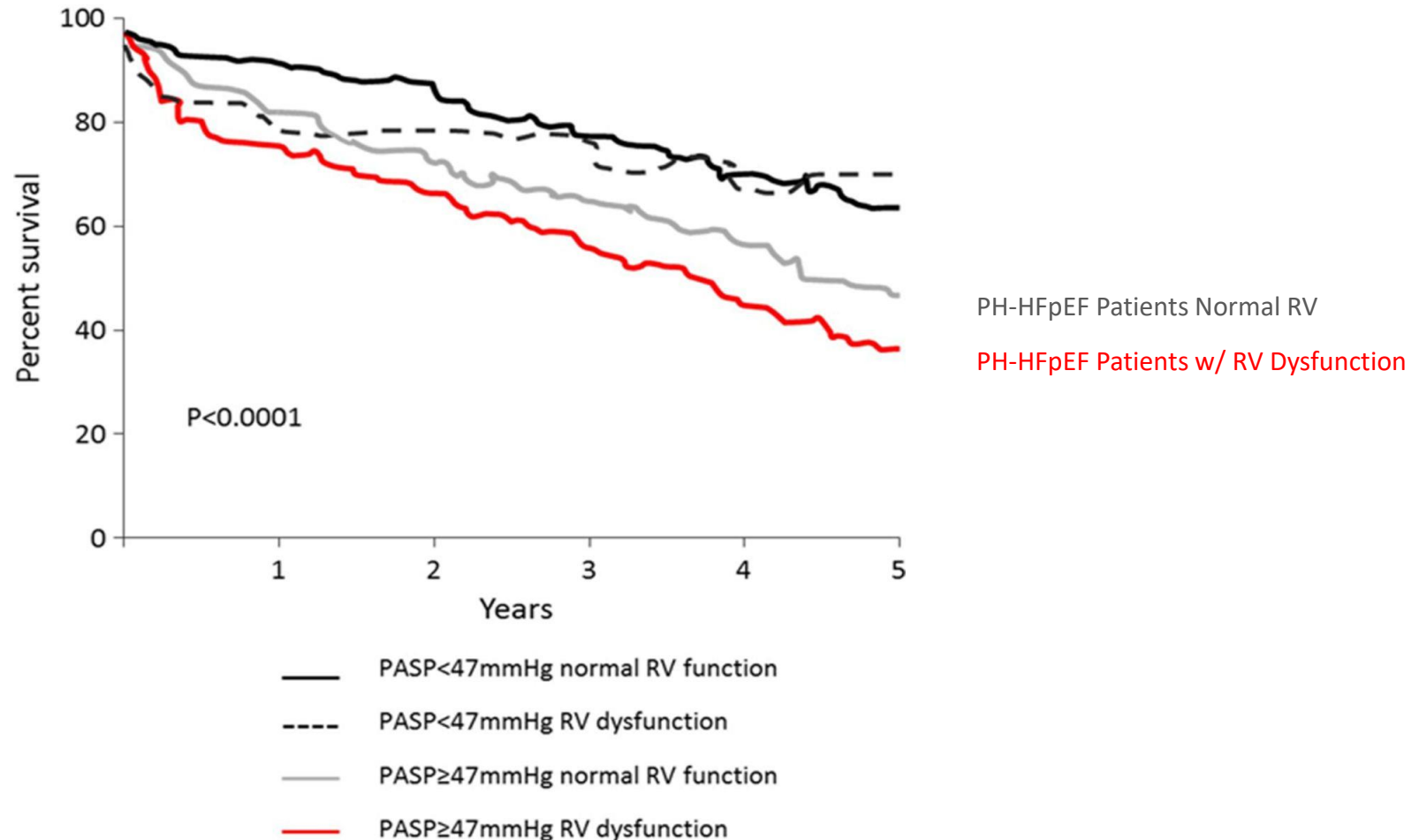
**Estimated
PH-HFpEF
US Prevalence
>2 Million Patients
(1,2,3)**



1) Dixon, et al. "Combined post-and pre-capillary pulmonary hypertension in HFpEF." *Heart failure reviews* 21.3 (2016): 285-297.(Estimates 2.2M PH-HFpEF patients
2) Guazzi, et al "Pulmonary hypertension in HFpEF: prevalence, pathophysiology, and clinical perspectives." *Circulation: Heart Failure* 7.2 (2014): 367-377.(PH-HFpEF =~50% of all US pts
3) Global Data epidemiological estimates
4) <https://phassociation.org/types-pulmonary-hypertension-groups/>

Poor PH-HFpEF Patients Outcomes

PH-HFpEF + Right Ventricle Dysfunction
Associated with Highest Mortality



Comparison of HELP Study to Other Multicenter Phase 2 Trials in PH-HFpEF

Trial	BADDHY	MELODY	DILATE	HELP
Sponsor	Actelion/J&J	Actelion/J&J	Bayer	Tenax
Product	Bosentan	Macitentan	Riocigaut	Levosimendan
Approved Indication	PAH	PAH	PAH/CETPH	ADHF- Outside US
Patients (#)	20	63	39	36
Design	Randomized, Placebo- Controlled	Randomized, Placebo- Controlled	Randomized, Placebo- Controlled	Randomized, Placebo- Controlled
Study Duration	12 weeks	12 weeks	Single Dose	6 weeks
MOA	Pulmonary Vasodilator	Pulmonary Vasodilator	Pulmonary Vasodilator	Lusitrope Inotrope Vasodilator
Result	Ineffective, Stopped early	Ineffective, Fluid retention	Ineffective	Ongoing- TBD

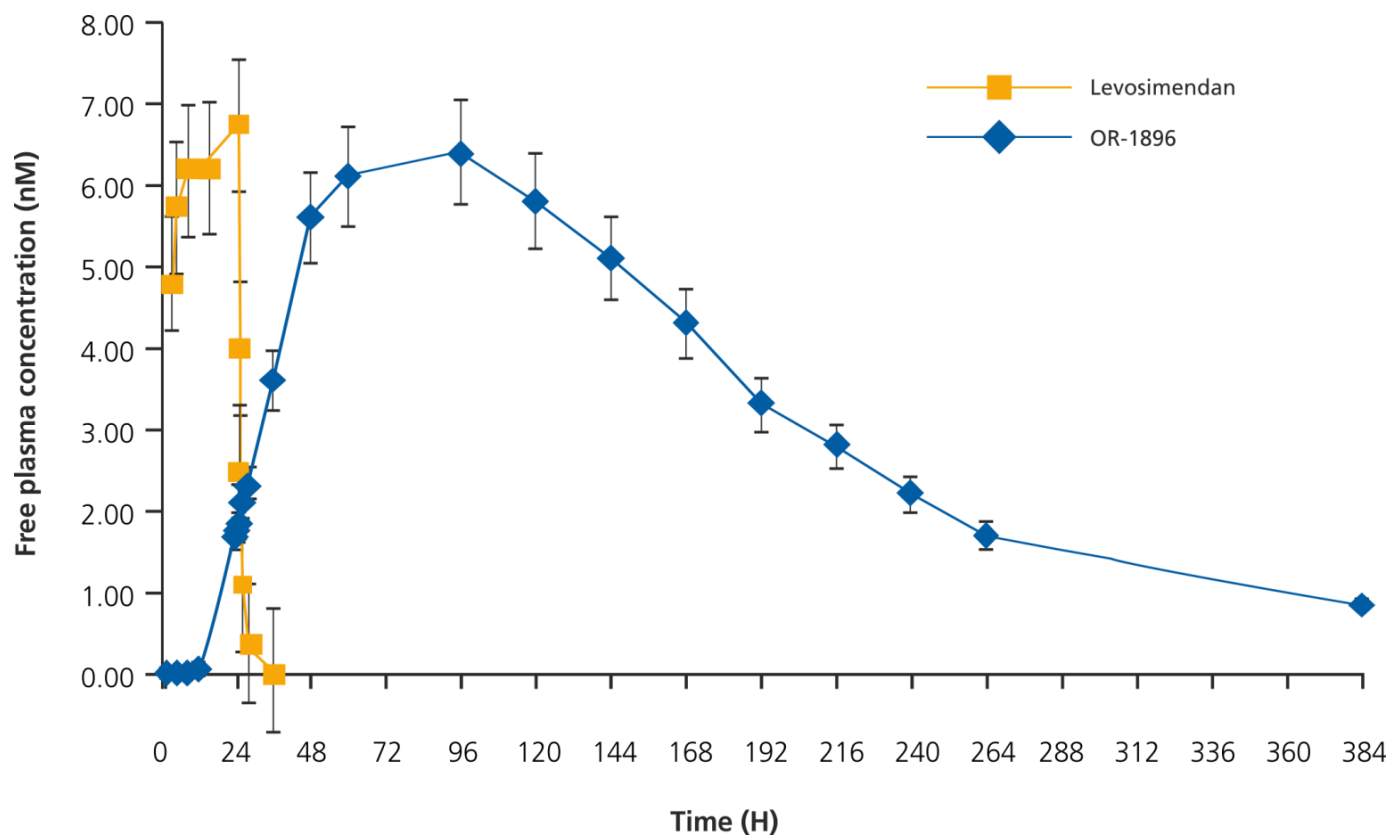
Levosimendan

Mechanism of Action

	Molecular targets	Mechanisms of action	Pharmacological effects	Therapeutic effects
1.	<u>Selective binding to the calcium-saturated form of cardiac troponin C</u>	Calcium sensitization	Positive inotropic Positive lusitropic	<ul style="list-style-type: none"> Increased ejection fraction Decreased left ventricular filling pressures
2.	Opening of sarcolemma <u>K_{ATP}</u> channels on <u>smooth-muscle</u> cells in vasculature	Hyperpolarization	Vasodilation in all vascular beds (also coronary and peripheral circulation)	<ul style="list-style-type: none"> Lowered pre- and after-load Anti-ischemic Better tissue perfusion Normalization of neurohormones
3.	Opening of mitochondrial <u>K_{ATP}</u> channels in <u>cardiomyocytes</u>	Protection of mitochondria in ischemia-reperfusion	Preconditioning, anti-stunning anti-apoptotic	<ul style="list-style-type: none"> Cardioprotection Anti-ischemic

Parissis, John T., et al. "Levosimendan: from basic science to clinical practice." *Heart failure reviews* 14.4 (2009): 265.

Levosimendan and Active Metabolite; non-protein bound plasma concentrations



Levosimendan Phase 2 for PH-HFpEF

- **Multi-center, double-blind placebo-controlled study**
- **Enroll 36 evaluable patients at 12-15 sites**
 - PAP ≥ 35 , PCWP ≥ 20 , NYHA Class IIb/III, LVEF $\geq 40\%$
- **Primary Endpoints:**
 - Change from baseline PCWP with bicycle exercise (25Watts) at Week 6
 - 80% power to detect a ≥ 4.8 mmHg change in PCWP from baseline
- **Secondary Endpoints:**
 - Change in Cardiac Index at rest and with exercise
 - Change in PVR effect at rest and with exercise
 - Change in PCWP when supine and legs elevated
 - Patient global assessment
 - Exercise duration via 6-minute walk test
 - Physician's assessment of functional class
 - Clinical events: death and hospitalizations

Levosimendan Phase 2 for in PH-HFpEF Study Design

Open-Label Lead-In

24 hours
(0.1 µg/kg/min)

Levosimendan
enrolled patients

Responders

n=36

Non-Responders

Chronic Phase

5 weeks

Levosimendan
n=18

weekly infusion
through Week 5

Placebo
n=18

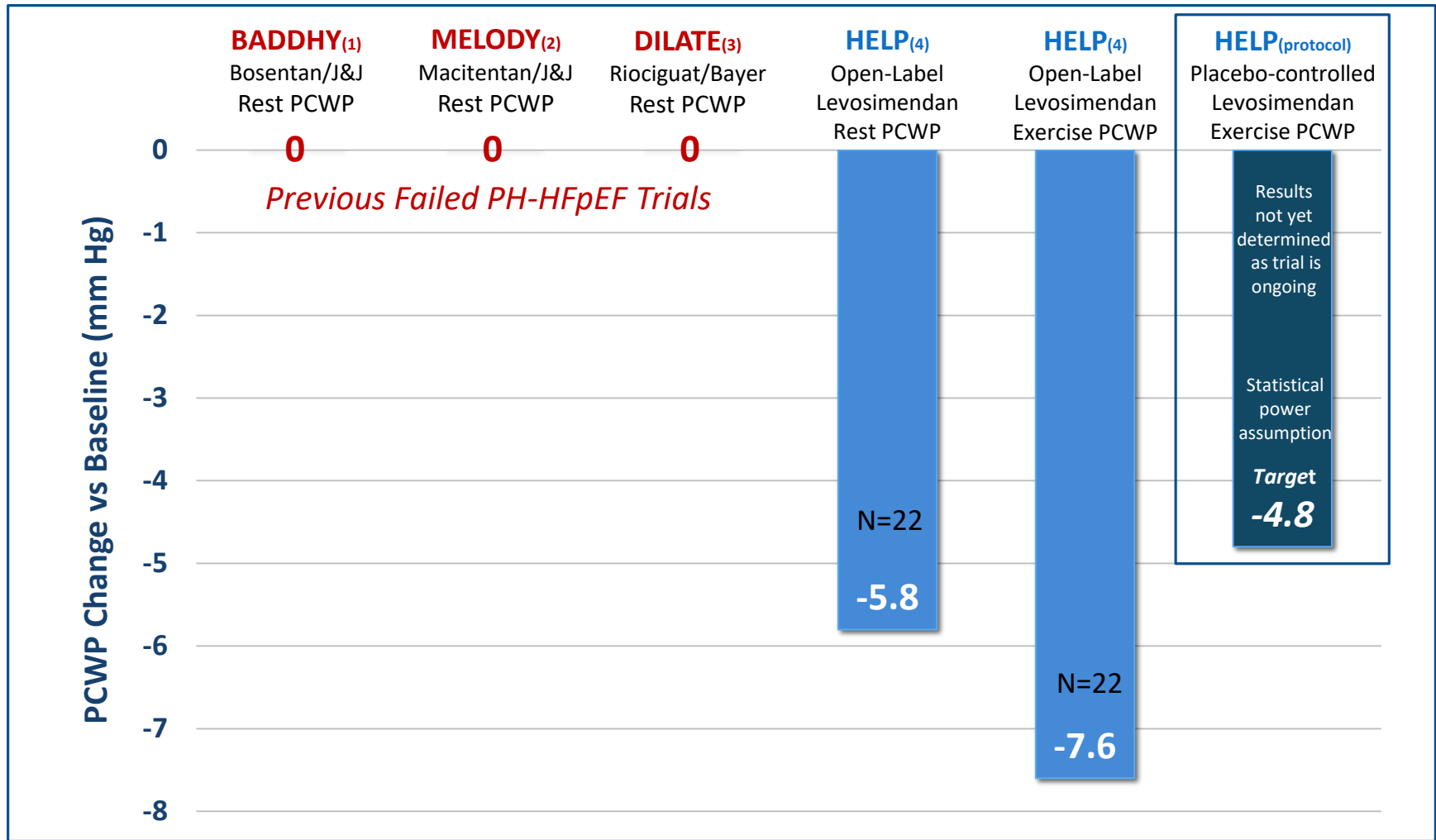
Week 6

Final Evaluation

Preliminary Open Label Data from the Help Study are Very Encouraging

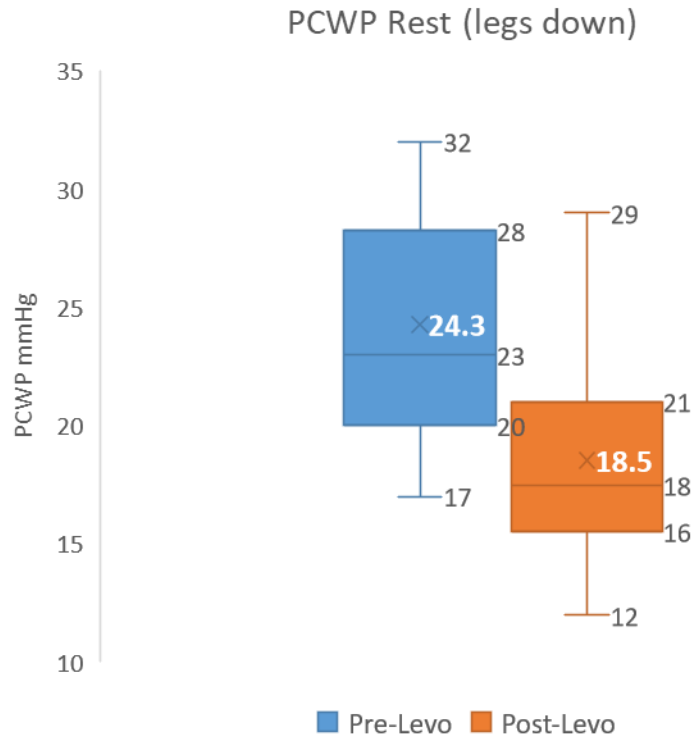
- 85% Responder rate during lead-in infusion (23/27)
- 23 Randomized patients (target 36)
- Encouraging and consistent open-label hemodynamic improvements
 - Reduced PCWP
 - Reduced RAP
 - Reduced mPAP
 - Increased cardiac output
 - 100% of patients have opted to participate in the extension study
 - No drug related serious adverse events

A Positive HELP Study Would Represent a Breakthrough in PH-HFpEF

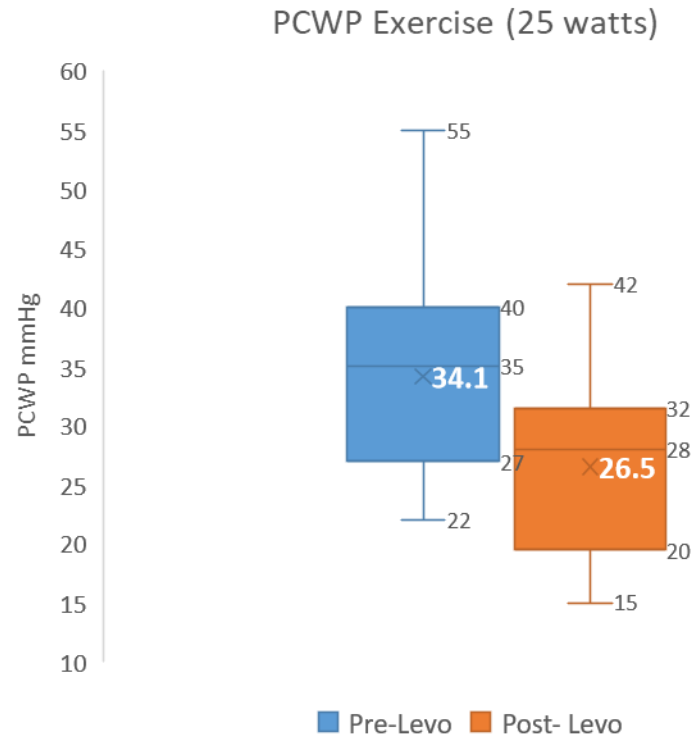


PCWP – Pre vs Post Lead-in Infusion

Open Label Levosimendan Responders (n=22)



$P < 0.0001$

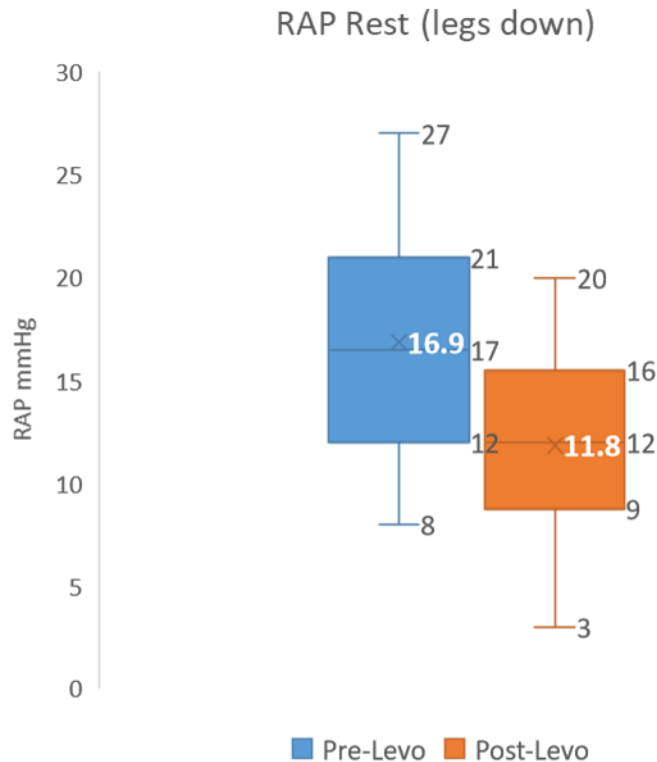


$P < 0.0000001$

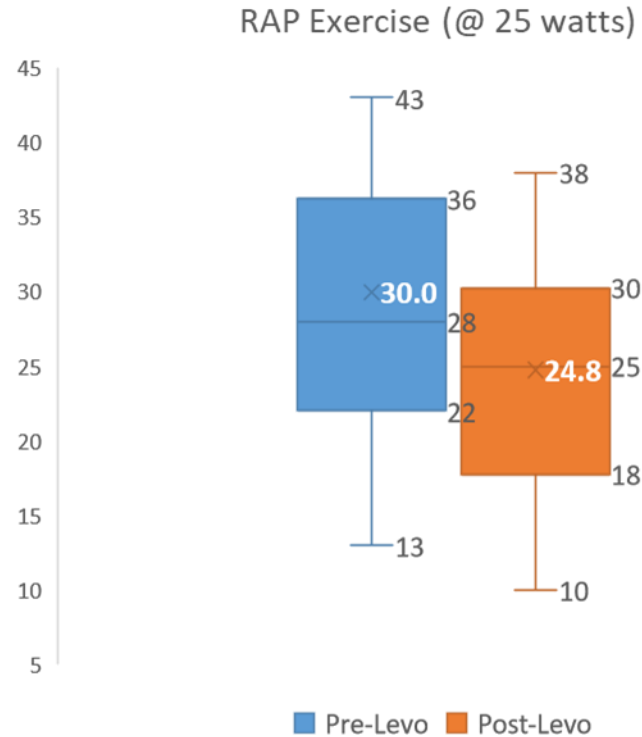
Data is from investigator reported hemodynamics during open-label lead in phase. Statistical analysis via Paired t-Test

RAP – Pre vs Post Lead-in Infusion

Open-Label Levosimendan Responders (n=22)



$P < 0.0001$

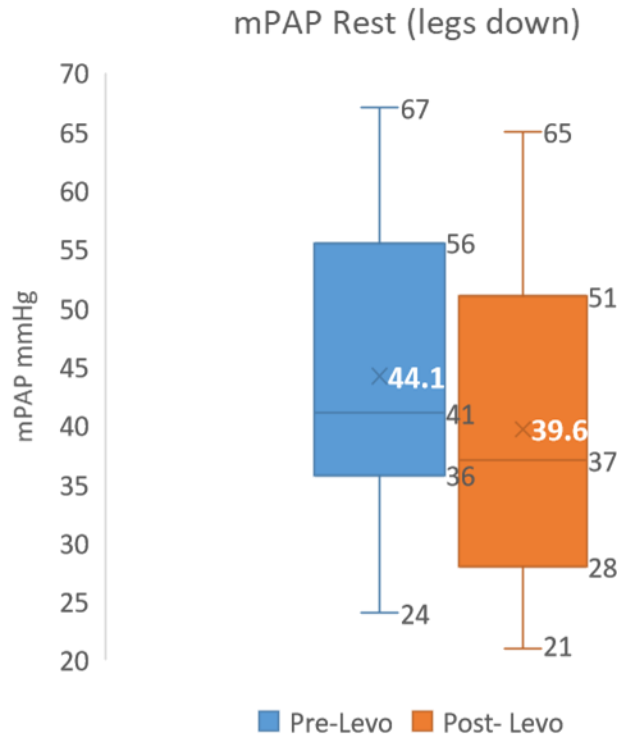


$P < 0.001$

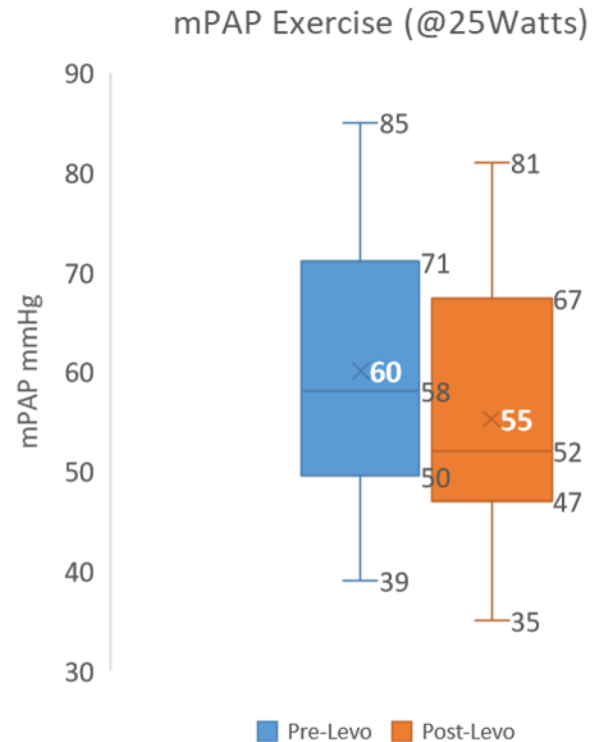
Data is from investigator reported hemodynamics during open-label lead in phase. Statistical analysis via Paired t-Test

mPAP – Pre vs Post Lead-in Infusion

Open-Label Levosimendan Responders (n=22)



$P < 0.007$

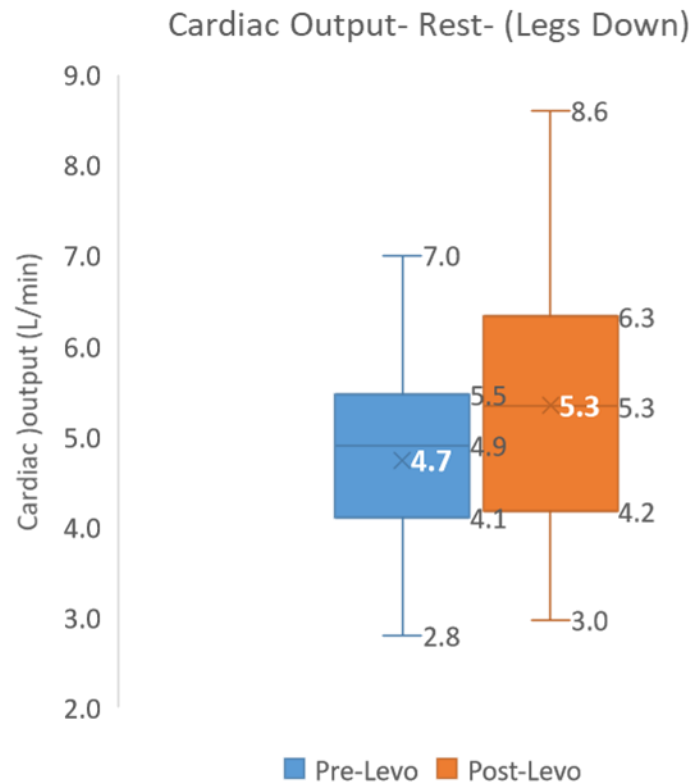


$P < 0.006$

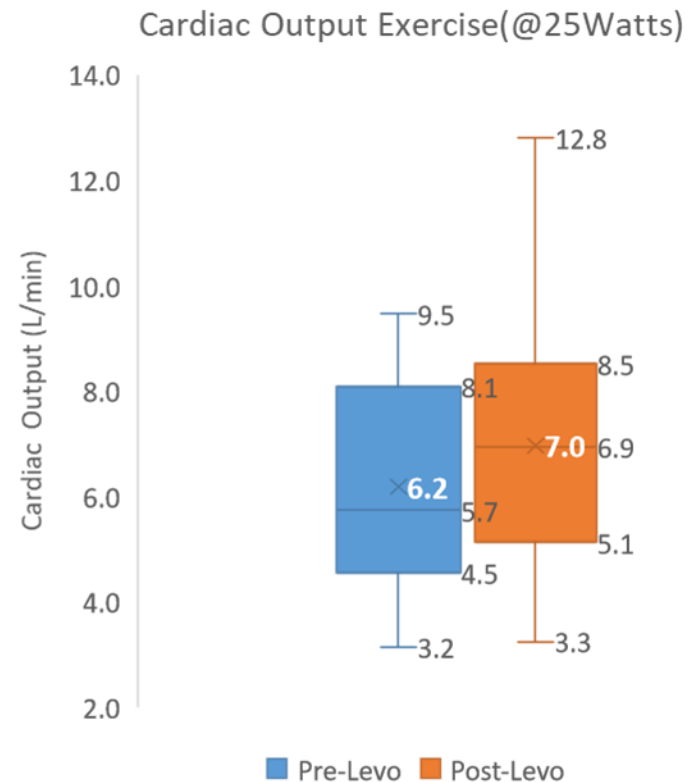
Data is from investigator reported hemodynamics during open-label lead in phase. Statistical analysis via Paired t-Test

Cardiac Output

Open-label Levosimendan Responders (n=22)



$P < 0.0005$



$P < 0.02$

Data is from investigator reported hemodynamics during open-label lead in phase. Statistical analysis via Paired t-Test

Summary:

The Opportunity for Levosimendan in PH-HFpEF

- **Area of high unmet medical need**
 - High mortality (up to 50% at 5 years)
 - Poor quality of life (poor exercise capacity)
 - No approved therapies in PH-HFpEF
- **Commercially attractive market**
 - Large potential market - Estimated PH-HFpEF prevalence in the US >2,000,000
 - High value chronic therapy that addresses a large unmet need
- **Mechanistic rationale for Levosimendan in PH-HFpEF**
 - Including mechanisms directed at right heart failure
- **Phase 2 trial is 65% enrolled, data expected in 2Q**
- **IV Levosimendan exclusivity as NCE**
- **Sub Q patent filed**