Corporate Update

May 2018

Tenax Therapeutics

Specialty pharmaceutical company focused on search, development, and commercialization of drugs that address diseases with high unmet medical need

- **Product - Levosimendan**
  - Calcium Sensitizer/K-ATP Channel Activator
  - Approved in 60+ countries
  - >1.4 million patients treated to date
  - US & Canadian rights
- **Levosimendan Clinical Development - Pulmonary Hypertension**
  - WHO Group 2- pulmonary hypertension associated with heart failure with preserved ejection fraction (PH-HFpEF)
  - Initiate Phase 2 Trial in Q3 2018
- **Ongoing search for assets and collaborations**

Levosimendan Clinical Development Strategy in Pulmonary Hypertension, WHO-Group 2

- **Leverage positive levosimendan clinical study data**
  - Positive levosimendan Phase 2 pulmonary hypertension study data
  - Positive levosimendan right heart failure data
- **Focus development in PH-HFpEF** (Pulmonary Hypertension in patients with Heart Failure and Preserved Ejection Fraction)
  - High unmet medical need
  - Large patient population with no approved drugs
- **Capitalize on PH-HFpEF advisors' expertise and advocacy**
  - Validate clinical development strategy with PH-HFpEF experts

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

Stuart Rich, M.D.
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

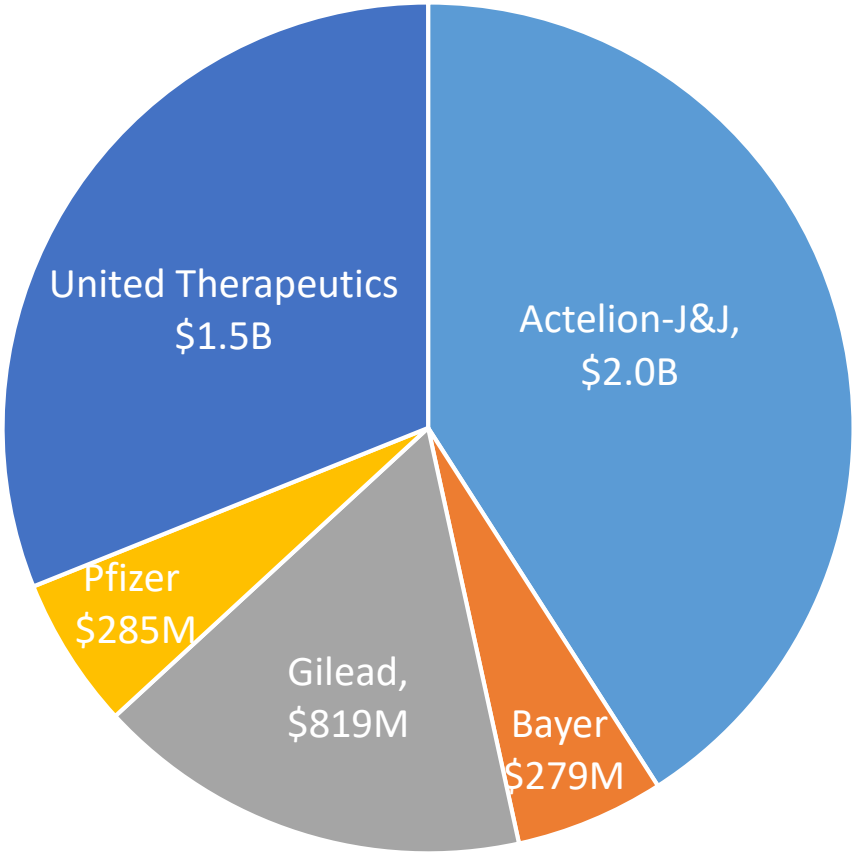
Director Heart Failure,
Hemodynamics and MCS Research at the
Cardiovascular Research Foundation
Adjunct Associate Professor of Medicine,
Columbia University

Sanjiv Shah, MD, FAHA, FACC, FASE
Professor of Medicine
Director, T1 Center for Cardiovascular Therapeutics
Director, Northwestern HFpEF Program
Division of Cardiology, Dept of Medicine
Northwestern University Feinberg School of Medicine

Rationale for Development of Levosimendan in PH-HFpEF

- **PH-HFpEF is an 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 >1,500,000
  - High value chronic therapy that addresses a large unmet need
- **Mechanistic rationale for Levosimendan in PH-HFpEF**
  - Including mechanisms directed at right heart failure
- **Existing preliminary positive Phase 2 clinical data in Pulmonary Hypertension**
- **Efficient and timely Phase 2 trial is planned**
- **IV Levosimendan exclusivity as NCE**

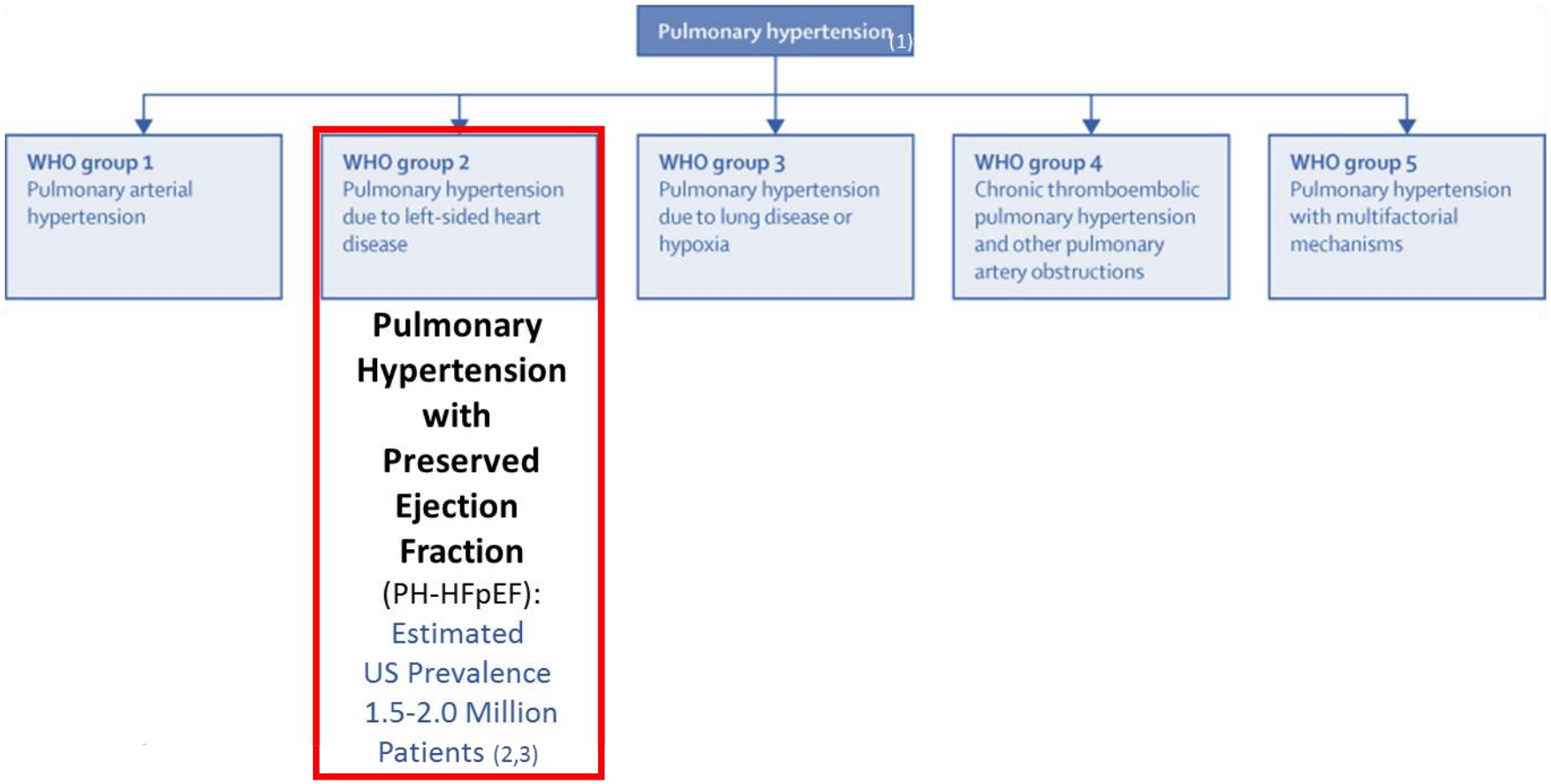
Global Pulmonary Hypertension Pharmaceutical Market > $5 Billion in 2016



Based on publicly reported sales from company annual reports

TENAX THERAPEUTICS

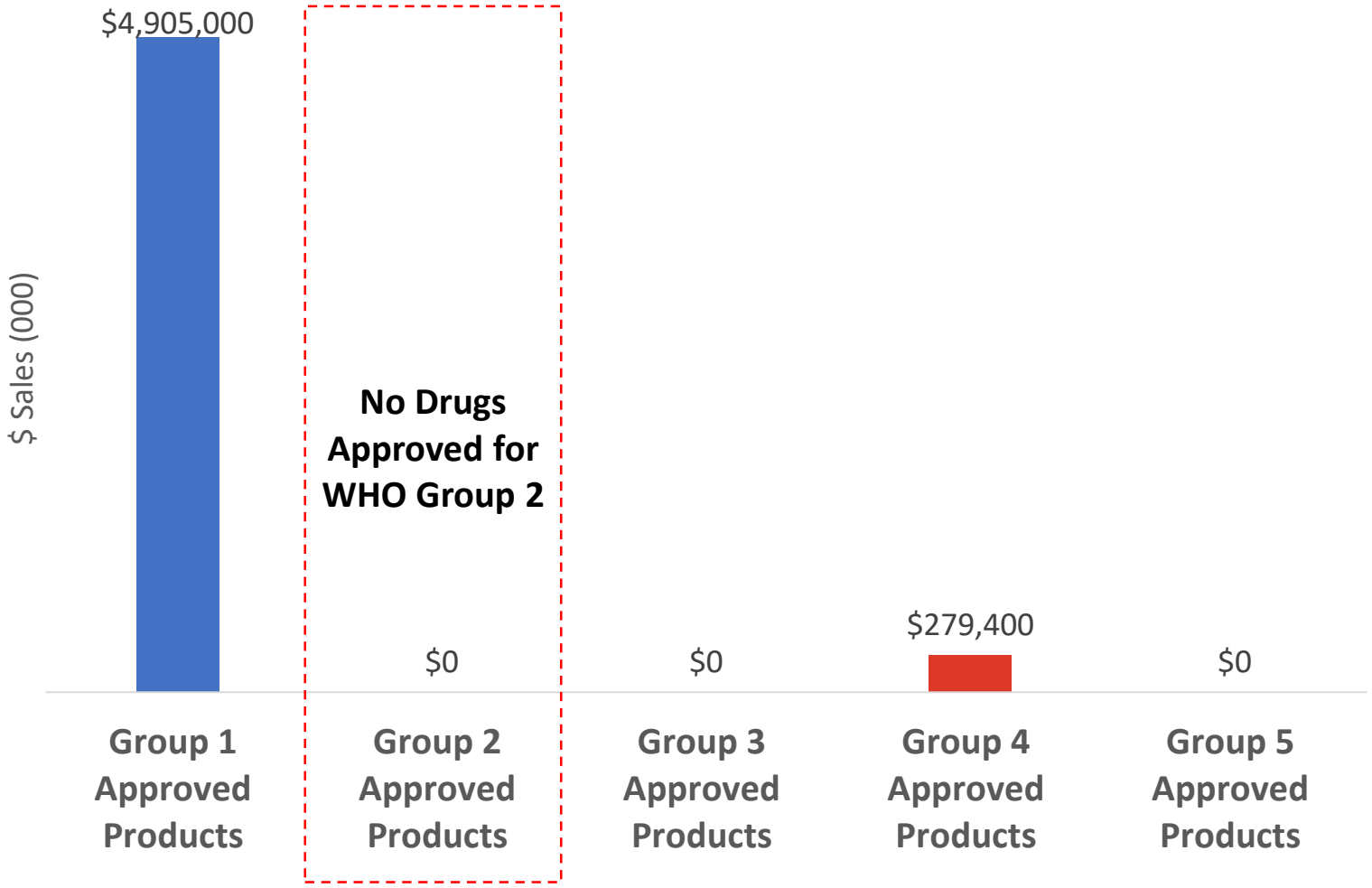
Pulmonary Hypertension WHO Classification Levosimendan Development Focused on Group 2



1) Hoeper, Marius M., et al. "A global view of pulmonary hypertension." *The Lancet Respiratory Medicine* 4.4 (2016): 306-322
2) Dixon, Debra D., Amar Trivedi, and Sanjiv J. Shah. "Combined post-and pre-capillary pulmonary hypertension in heart failure with preserved ejection fraction." *Heart failure reviews* 21.3 (2016): 285-297.(Estimates 2.2M PH-HFpEFpatiients
3) Guazzi, Marco. "Pulmonary hypertension in heart failure preserved ejection fraction: prevalence, pathophysiology, and clinical perspectives." *Circulation: Heart Failure* 7.2 (2014): 367-377.(PH-HFpEF =~50% of all US HFpEF patients)

TENAX THERAPEUTICS

Global Pulmonary Hypertension Product Sales -2016 Allocated by WHO Group Approved Indication



Excludes potential off-label uses

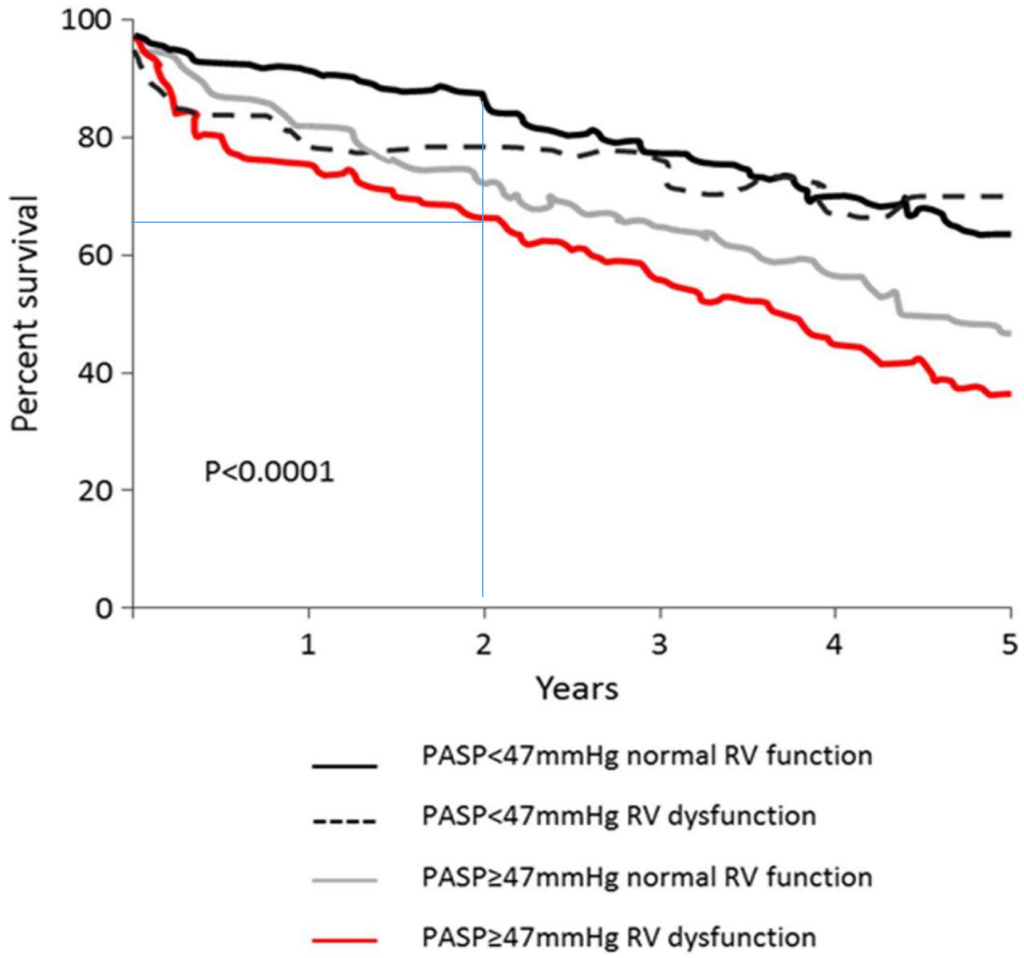
PH-HFpEF Unmet Need

Approved WHO Group 1 Drugs are **not Approved or Effective in** Group 2 Patients

Drug Class	Pulmonary Hypertension WHO Group 1 (PAH)	Pulmonary Hypertension WHO Group 2 (HFpEF)
PDE5 Inhibitors	**FDA Approved**	**Efficacy not established**
Endothelin Receptor Antagonists	**FDA Approved**	**Efficacy not established**
Soluble Guanylate Cyclase Stimulators	**FDA Approved**	**Efficacy not established**
Prostacyclins (IV/SC/Inhaled/Oral)	**FDA Approved**	**Efficacy not established**

PH-HFpEF Patients have Poor Outcomes

PH-HFpEF + RV Dysfunction is Associated with Highest Mortality



PH-HFpEF Patients Normal RV

PH-HFpEF Patients w/ RV Dysfunction

Mohammed, Selma F., et al. "Right ventricular systolic function in subjects with HFpEF: a community based study." (2011): A17407-A17407.

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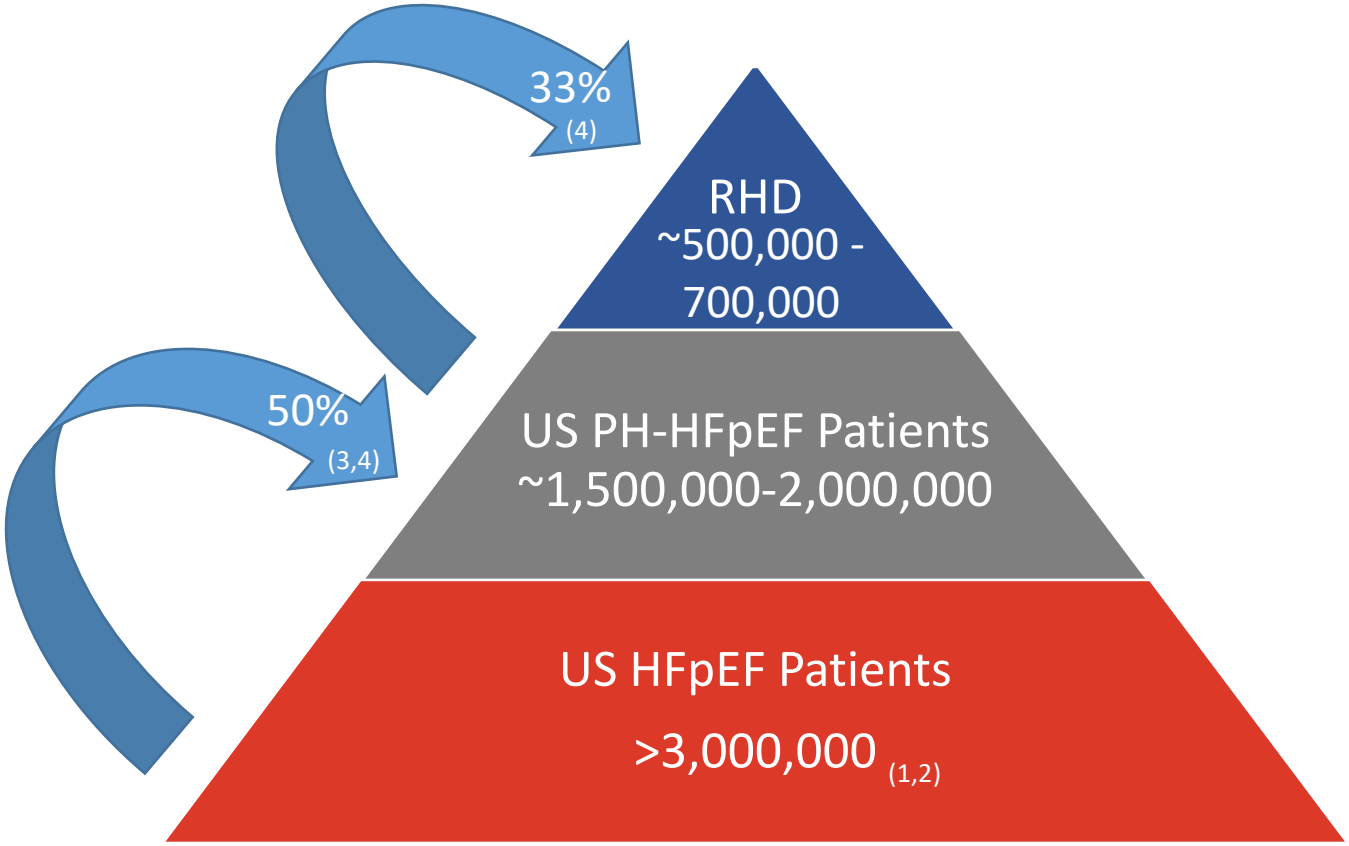
PH-HFpEF with Right Heart Dysfunction (RHD): Large Target Market with Very High Needs

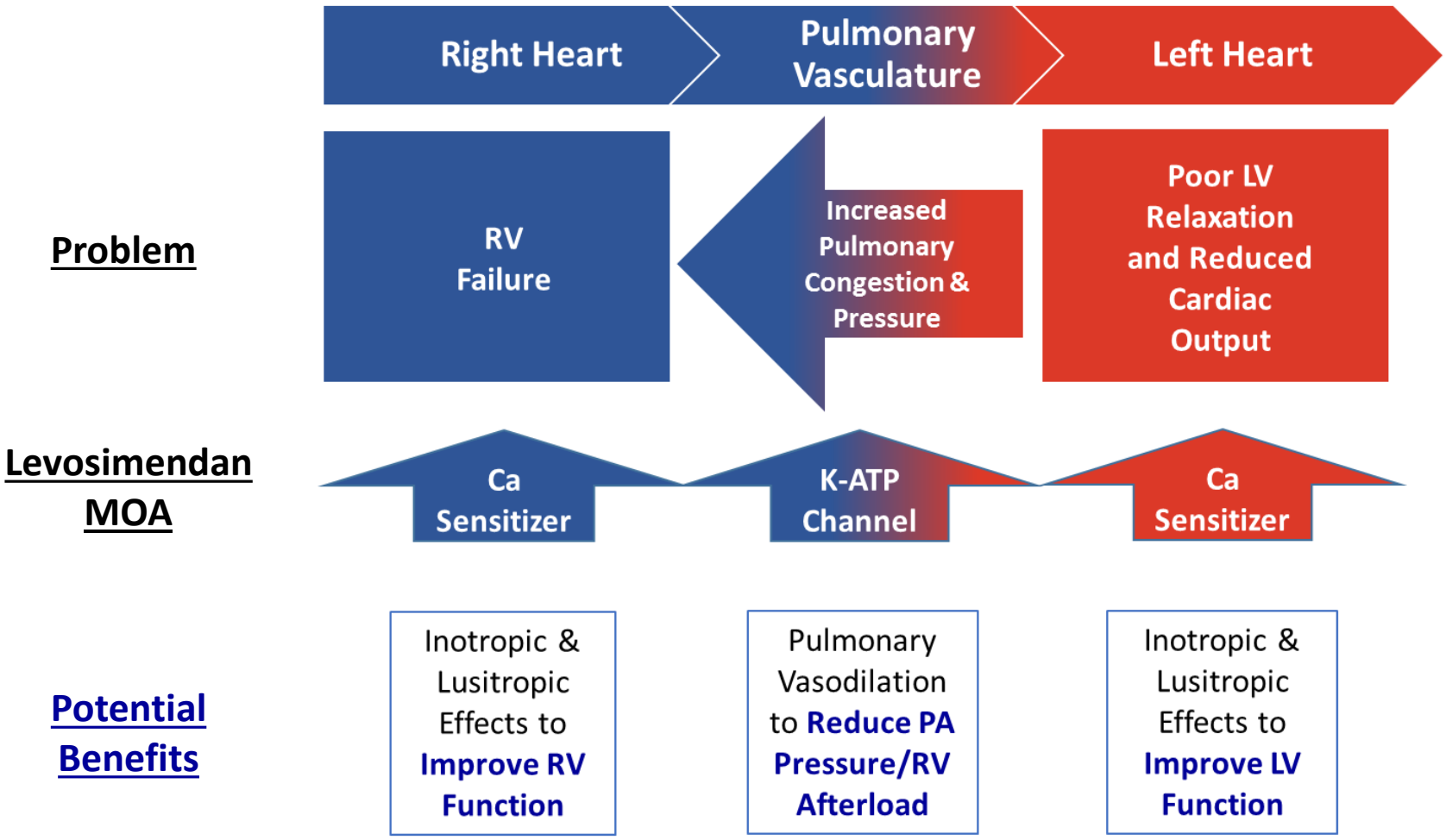


Estimates based on

1) Benjamin, Emelia J., et al. "Heart disease and stroke statistics—2017 update: a report from the American Heart Association." *Circulation* 135.10 (2017): e146-e603.
2) Steinberg, Benjamin A., et al. "Trends in Patients Hospitalized with Heart Failure and Preserved Left Ventricular Ejection Fraction-Prevalence, Therapies, and Outcomes." *Circulation*(2012): CIRCULATIONAHA-111.
3) Dixon, Debra D., Amar Trivedi, and Sanjiv J. Shah. "Combined post-and pre-capillary pulmonary hypertension in heart failure with preserved ejection fraction." *Heart failure reviews* 21.3 (2016): 285-297.(Estimates 2.2M PH-HFpEFpatiients
4) Guazzi, Marco. "Pulmonary hypertension in heart failure preserved ejection fraction: prevalence, pathophysiology, and clinical perspectives." *Circulation: Heart Failure* 7.2 (2014): 367-377.

TENAX THERAPEUTICS

Mechanistic Rationale for Levosimendan in PH-HFpEF – More than just a Vasodilator



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Increasing Number of Scientific Publications on Levosimendan in Pulmonary Hypertension

- **Clinical Studies**
  - **2017**- Jiang, Rong, et al. "Efficacy and Safety of a Calcium Sensitizer, Levosimendan, in Patients with Right Heart Failure due to Pulmonary Hypertension." *The Clinical Respiratory Journal* (2017).
  - **2016** -Guerrero-Orriach, José Luis, et al. "Cardiac, renal, and neurological benefits of preoperative levosimendan administration in patients with right ventricular dysfunction and pulmonary hypertension undergoing cardiac surgery: evaluation with two biomarkers neutrophil gelatinase-associated lipocalin and neuronal enolase." *Therapeutics and clinical risk management* 12 (2016): 623
  - **2012**- Martyniuk TV, Arkhipova OA, Kobal' EA, Danilov NM, Chazova IE. Possibilities of using levosimendan in patients with idiopathic pulmonary hypertension. Ter Arkh. 2012;84(9):83-8.
  - **2009** -Kleber, Franz X., et al. "Repetitive dosing of intravenous levosimendan improves pulmonary hemodynamics in patients with pulmonary hypertension: results of a pilot study." *The Journal of Clinical Pharmacology* 49.1 (2009): 109-115.
- **Preclinical Studies**
  - **2018-** Hansen, M. S., et al. "Levosimendan improves cardiac function and myocardial efficiency in rats with right ventricular failure." *Pulmonary circulation* 8.1 (2018): 2045893217743122-2045893217743122
  - **2017**- Hansen, Mona Sahlholdt, et al. "Levosimendan prevents and reverts right ventricular failure in experimental pulmonary arterial hypertension." *Journal of Cardiovascular Pharmacology* (2017).
  - **2017-** Tavares-Silva, Marta, et al. "Dose–Response Head-to-Head Comparison of Inodilators Dobutamine, Milrinone, and Levosimendan in Chronic Experimental Pulmonary Hypertension." *Journal of Cardiovascular Pharmacology and Therapeutics* (2017): 1074248417696818.
  - **2012**- Wiklund, Annaeva, David Kylhammar, and Göran Rådegran. "Levosimendan attenuates hypoxia-induced pulmonary hypertension in a porcine model." *Journal of cardiovascular pharmacology* 59.5 (2012): 441-449.
  - **2011**- Revermann, M., et al. "Levosimendan attenuates pulmonary vascular remodeling." *Intensive care medicine* 37.8 (2011): 1368-1377.

Results from a Multicenter, Randomized, Placebo Controlled, Pilot Study of Levosimendan in Pulmonary Hypertension Patients

Kleber, Franz X., et al. "Repetitive dosing of intravenous levosimendan improves pulmonary hemodynamics in patients with pulmonary hypertension: results of a pilot study." *The Journal of Clinical Pharmacology* 49.1 (2009): 109-115.

Kleber et al Patient Demographics

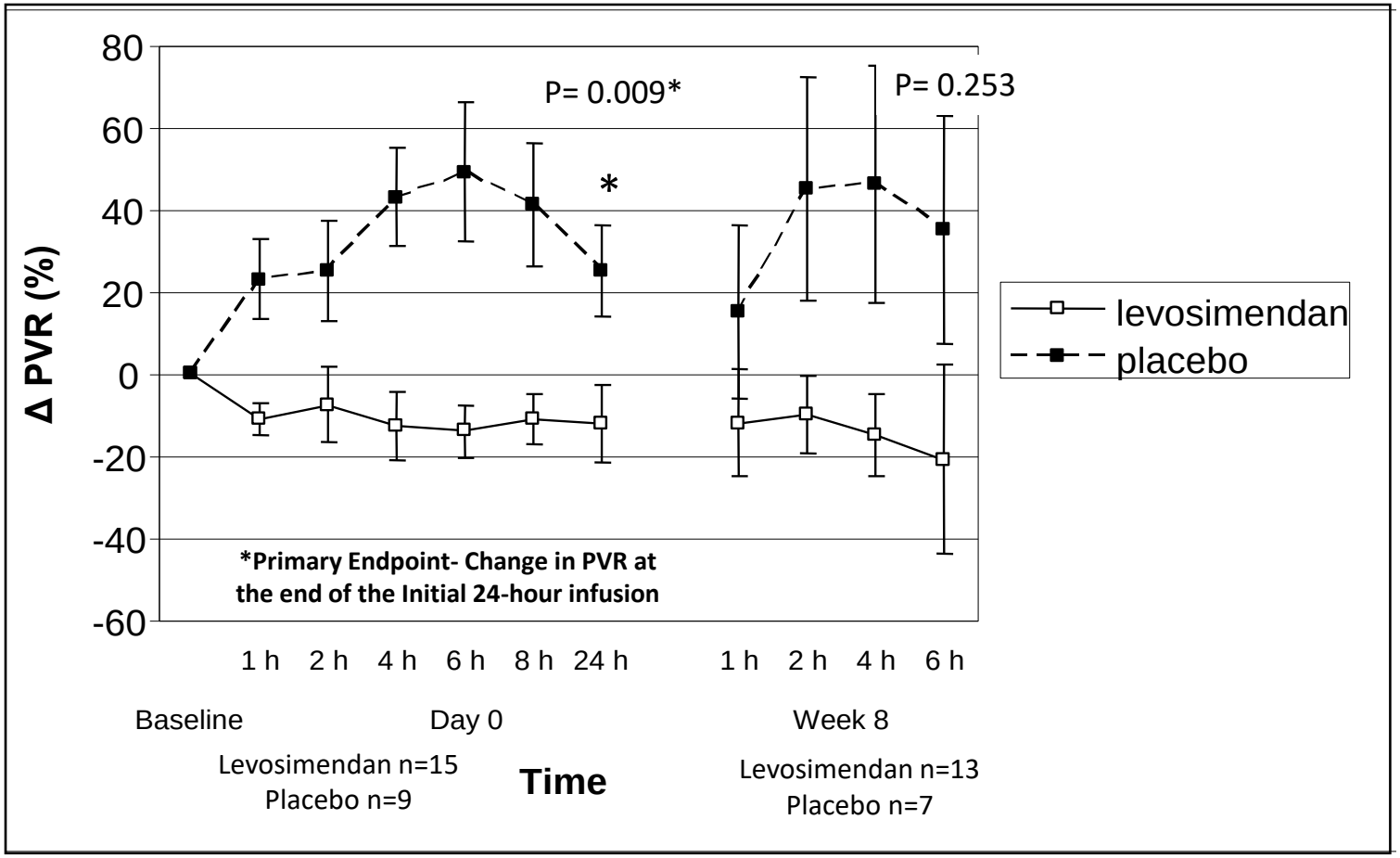
	Levosimendan (n = 18)	Placebo (n = 10)
Age, y	62 ± 11	58 ± 12
Sex, M/F	9/9	8/2
Etiology of pulmonary hypertension[a]		
Pulmonary arterial hypertension	7 (39)	4 (40)
Idiopathic	6	2
Portal hypertension	1	1
Congenital systemic to pulmonary shunts		1
Pulmonary venous hypertension due to left-sided heart disease	10 (56)	4 (40)
Pulmonary hypertension due to chronic thrombotic and/or embolic disease	1 (5)	2 (20)
Signs of right heart failure		
Jugular venous distension	12 (67)	7 (70)
Peripheral edema	14 (78)	8 (80)
Known response to vasodilator testing	18 (100)	10 (100)
Systemic hemodynamics		
Systolic blood pressure	121 ± 23	116 ± 15
Diastolic blood pressure	72 ± 10	75 ± 12
Heart rate	75 ± 18	70 ± 13
New York Heart Association class		
III	15 (83)	9 (90)
IV	3 (17)	1 (10)
mRAP		
Mean ± SD	12 ± 5.9 (n = 15)	14 ± 4.9 (n = 9)
Range	5-29	7-24
Use of vasoactive medication		
Diuretics	15 (83)	8 (80)
Angiotensin-converting enzyme inhibitor/ AT2-blocker	14 (78)	6 (60)
β-Blocker	10 (56)	7 (70)
Calcium channel blocker	6 (33)	4 (40)
Bosentan	3 (17)	2 (20)

Values are mean ± SD or n (%). Medication is expressed as the number of patients taking the drug (%).
a. According to the Venice classification.[24]

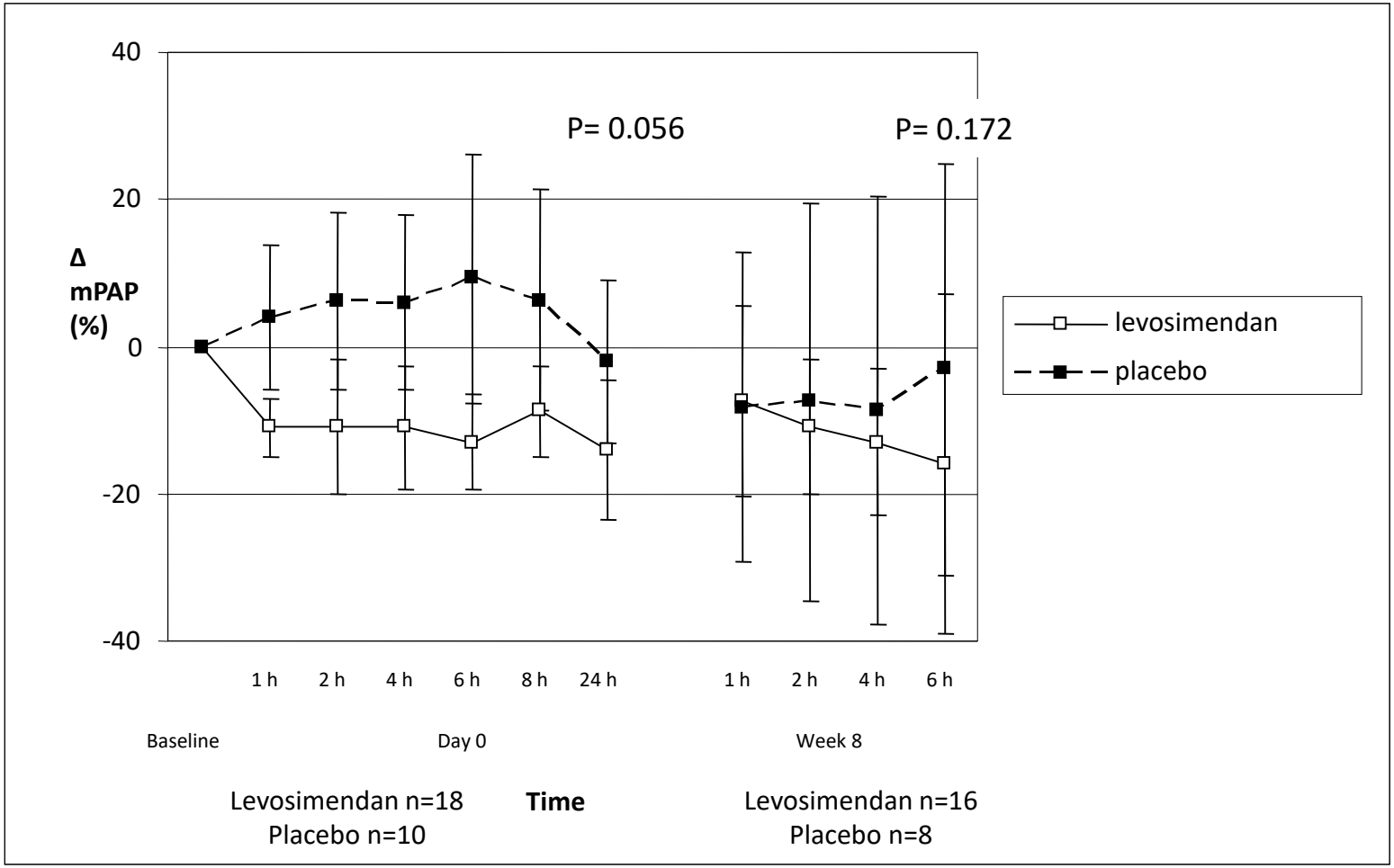
TENAX THERAPEUTICS

Kleber, Franz X., et al. "Repetitive dosing of intravenous levosimendan improves pulmonary hemodynamics in patients with pulmonary hypertension: results of a pilot study." *The Journal of Clinical Pharmacology* 49.1 (2009): 109-115.

Change in PVR (mean ± SEM) during 24-hour infusion and 6-hour infusion at week 8



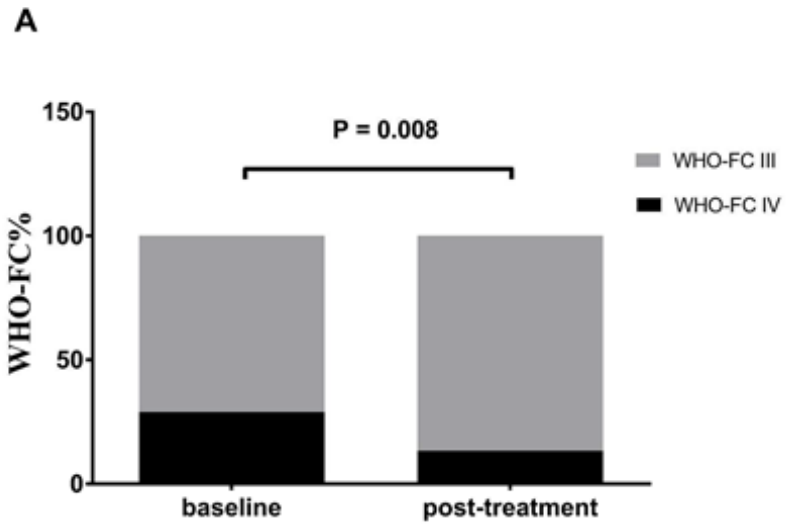
Change in mPAP (mean ± SEM) during 24-hour infusion and 6-hour infusion at week 8



Levosimendan in Pulmonary Hypertension

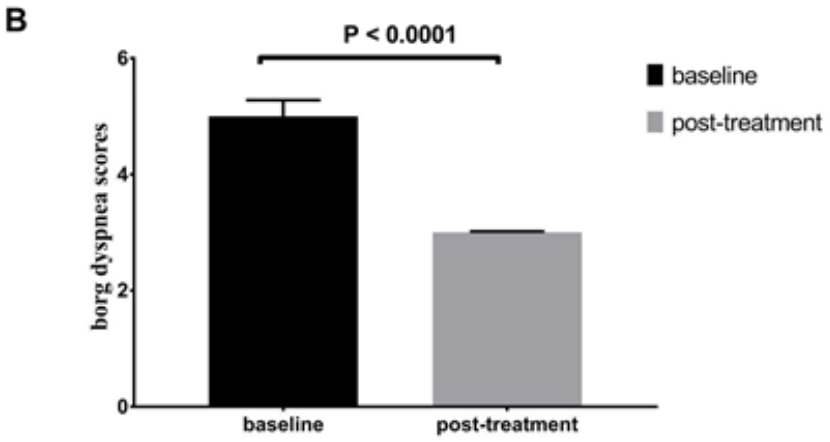
The Clinical Respiratory Journal (September 2017)

Primary endpoint-Change in WHO Functional Class



A. Change in WHO-FC after infusion of levosimendan from basement to post-treatment. World Health Organization Function Class: WHO-FC.

Primary Endpoint- Change in Dyspnea Scores



B. Change in Borg dyspnoea scores from basement to post-treatment

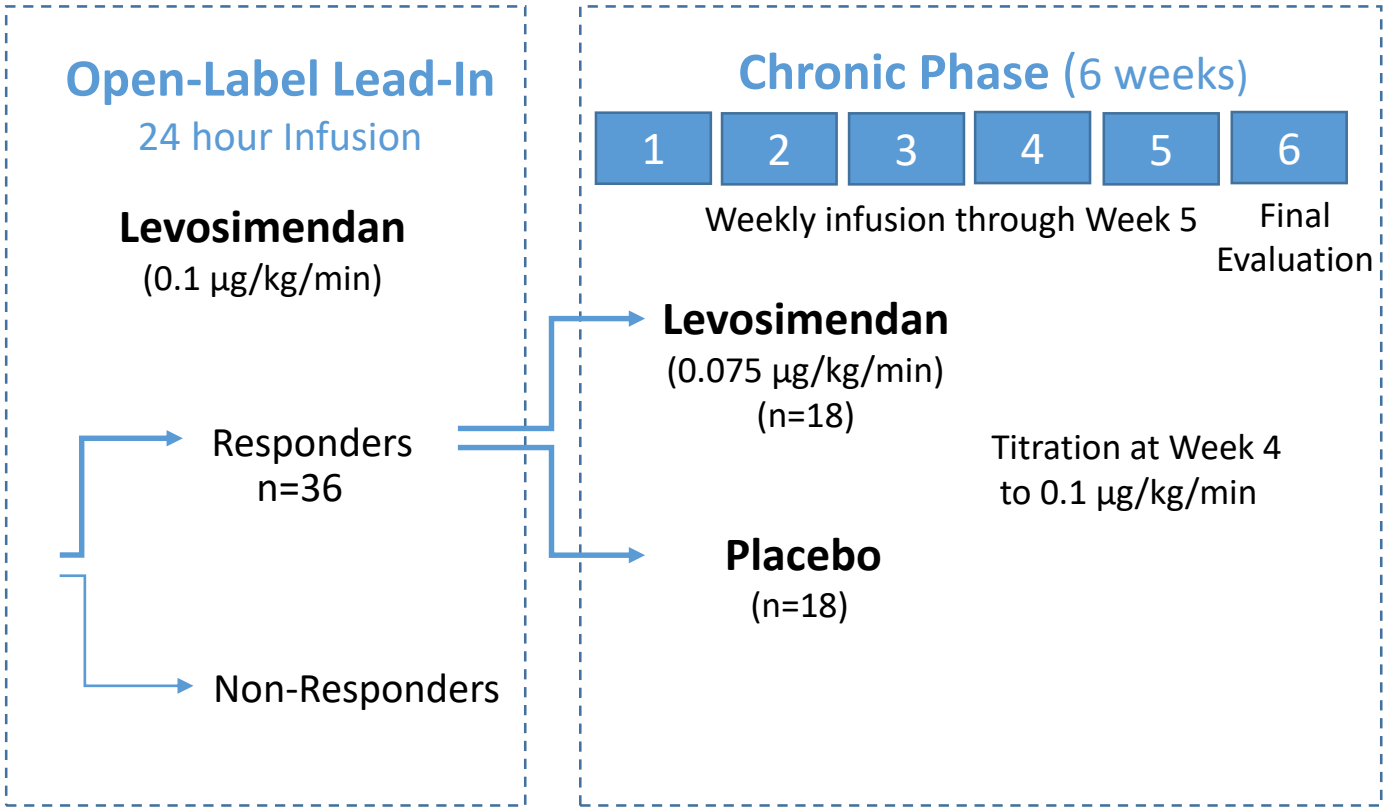
Jiang, Rong, et al. "Efficacy and Safety of a Calcium Sensitizer, Levosimendan, in Patients with Right Heart Failure due to Pulmonary Hypertension." *The Clinical Respiratory Journal* (2017).

TENAX THERAPEUTICS

Phase 2 Study Design

- **Double-blind study of PH-HFpEF Patients**
  - PAP ≥35, PCWP ≥20, NYHA Class IIb/III, LVEF ≥40%
- **36 Evaluable patients; 25 sites; 14-18 months**
- **Primary Endpoint:**
  - Change from baseline PCWP with bicycle exercise at Week 6
- **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 in PH-HFpEF
Phase 2 Study Design



Pre-IND Meeting in PH-HFpEF

- Meeting with FDA to review development of levosimendan in PH-HFpEF, March 2018
- FDA agreed nonclinical studies sufficient to support full development in PH-HFpEF
- Agreed with planned Phase 2 study design, entry criteria and endpoints
- Phase 2 study may be conducted under existing IND
- FDA acknowledged unmet medical need in PH-HFpEF could support limited Phase 3 program; topic to be discussed further at End-of-Phase 2 Meeting

Summary
The Opportunity for Levosimendan in PH-HFpEF

- **PH-HFpEF is an 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 >1,500,000
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- **Efficient and timely Phase 2 trial is planned**
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