

## TENAX THERAPEUTICS

**Corporate Presentation** 

November 2023

#### **Safe Harbor Statement**

#### Disclaimer

Except for historical information, all the statements, expectations and assumptions contained in this presentation are forward-looking statements. 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: our ability to raise additional money to fund our operations for at least the next 12 months as a going concern; risks related to our business strategy, including the prioritization of product candidates; risks of our clinical trials, including, but not limited to, the timing, delays, costs, design, initiation, enrollment, and results of such trials; any delays in regulatory review and approval of product candidates in development; 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; the potential advantages of our product candidates; our estimates regarding the potential market opportunity for our product candidates; intellectual property risks; our competitive position; risks related to our continued listing on Nasdaq; our ability to maintain our culture and recruit, integrate and retain qualified personnel and advisors, including on our Scientific Advisory Boards and Board of Directors; volatility and uncertainty in the global economy and financial markets in light of the COVID-19 pandemic or similar health epidemics and geopolitical uncertainties such as in 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.

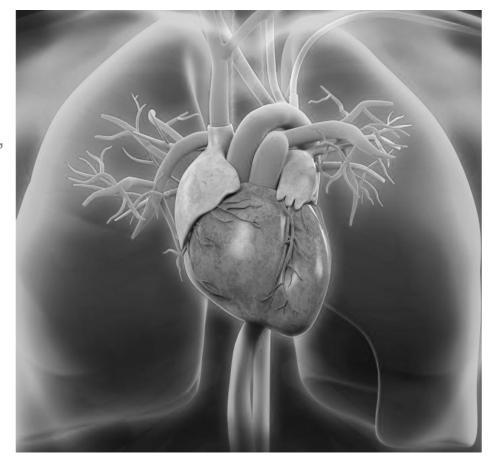


#### **Mission Statement**

Specialty pharmaceutical company focused on identifying, developing, and commercializing products that address cardiovascular and pulmonary diseases with high unmet medical need.

Our current therapeutic focus is on pulmonary hypertension and the development of two products:

- TNX-103 for Treatment of PH-HFpEF (WHO Group 2 PH)
- TNX-201 for Treatment of PAH (WHO Group 1 PH)





#### **Lead Product: TNX-103**

#### TNX-103

- NCE, oral, small molecule (levosimendan)
- Unique K-ATP mechanism relevant in pulmonary hypertension and HFpEF (PH-HFpEF)
- Levosimendan is not available for oral administration anywhere in the world

#### Clinical - Positive Phase 2b data

- 6MWD +29 meters (p=0.03) and well tolerated in PH-HFpEF patients\*
- First and only drug to show a benefit in PH-HFpEF

#### Regulatory

- Large safety database with >1.9M patient exposures via IV administration
- Positive FDA feedback on efficient Phase 3 trial design (<500pts)</li>
- Potential for FDA Approval with a single trial (p≤0.01), or 2 trials (p≤0.05)

#### Manufacturing

- Produced at scale in FDA approved facility
- 5-year shelf life

#### IP

U.S. patent protection to 2040+ via multiple method of use patents for treatment of PH-HFpEF

#### Commercial

Large market (U.S. prevalence approaching 2M\*) with no approved therapies



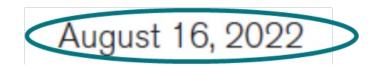
# American Heart Association: Call to Action PH-HFpEF Represents a Large Unmet Medical Need

#### **AHA SCIENCE ADVISORY**

Elucidating the Clinical Implications and Pathophysiology of Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction: A Call to Action: A Science Advisory From the American Heart Association

Evan L. Brittain, MD, MSc, FAHA, Chair; Thenappan Thenappan, MD, Vice Chair; Jessica H. Huston, MD; Vineet Agrawal, MD, PhD; Yen-Chun Lai, PhD; Debra Dixon, MD, MS; John J. Ryan, MD, FAHA; Eldrin F. Lewis, MD, MPH, FAHA; Margaret M. Redfield, MD; Sanjiv J. Shah, MD, FAHA; Bradley A. Maron, MD; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; and Stroke Council

Circulation. 2022;146:e73-e88.

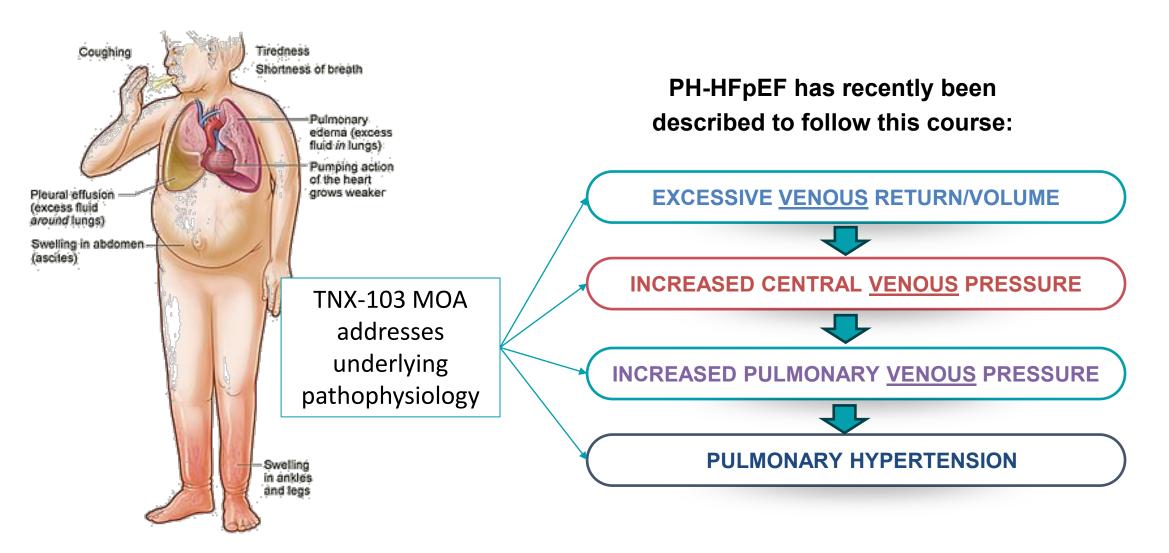


eart failure (HF) with preserved ejection fraction (HFpEF) is one of the leading causes of pulmonary hypertension (PH) in the world. The development of PH and particularly pulmonary vascular disease (which distinguishes functional pressure elevation from vascular dysfunction or remodeling) is among the strongest risk factors for adverse outcomes in HFpEF.<sup>2</sup> Despite this recognition, no evidencebased therapies exist for PH attributable to HFpEF (PH-HFpEF), in part because the pathophysiology is poorly understood. In this call to action, we encourage the scientific community to prioritize the study of PH-HFpEF, which has implications for collaboration, data sharing, and clinical trial design, among other considerations. The goal of this science advisory is to clarify key knowledge gaps in PH-HFpEF and to suggest scientific directions for addressing such gaps, which we synthesize in Table 1.



## Overview: Pathophysiology of PH with HFpEF

The venous circulation has now been discovered to be the source of the problem





## TNX-103: Mechanism of Action in PH-HFpEF is Unique

01

TNX-103 (oral levosimendan) is a **unique K+ATP** channel activator and calcium sensitizer.\* **No other drug** shares these properties

02

Strong vasodilatory effects on **venous beds**\*\*

Causes a marked reduction in central venous pressure (CVP)

Causes a marked reduction in pulmonary venous pressure (PCWP)

03

Recent clinical science has **confirmed** that reducing the **elevated CVP and PCWP are critical targets** for left heart failure\*\*\*

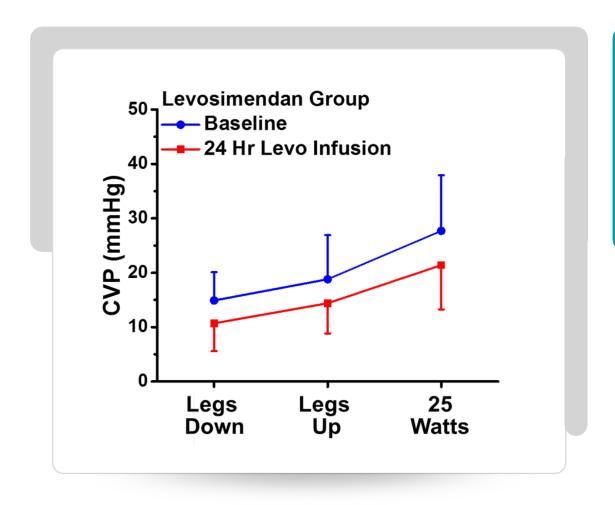
<sup>\*\*\*</sup> Fudim, Marat, et al. "Splanchnic Nerve Block for Chronic Heart Failure." Heart Failure 8.9 (2020): 742-752.

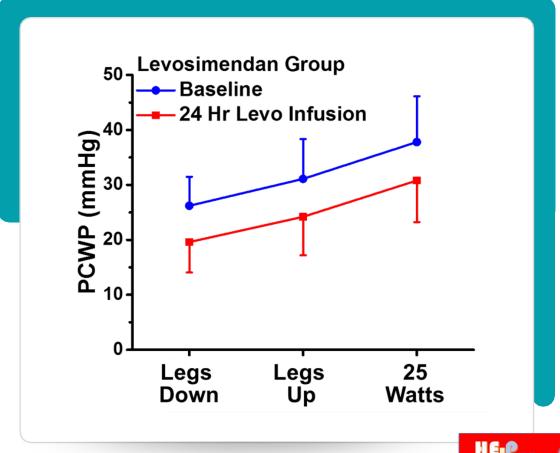


<sup>\*</sup> Rich, Stuart, Burkhoff, Daniel, Pollesello, Piero, Papp, Zoltan. "Levosimendan-induced vendilation is mediated by opening of potassium channels." ESC Heart Failure. 10.1002 (2021)

<sup>\*\*</sup> Brener, Michael I., et al. "Changes in stressed blood volume with levosimendan in pulmonary hypertension from heart failure with preserved ejection fraction: insights regarding mechanism of action from the HELP trial." Journal of Cardiac Failure 27.9 (2021): 1023-1026

# Levosimendan improves CVP and PCWP <u>at rest</u> and <u>with exercise</u> in PH-HFpEF Patients



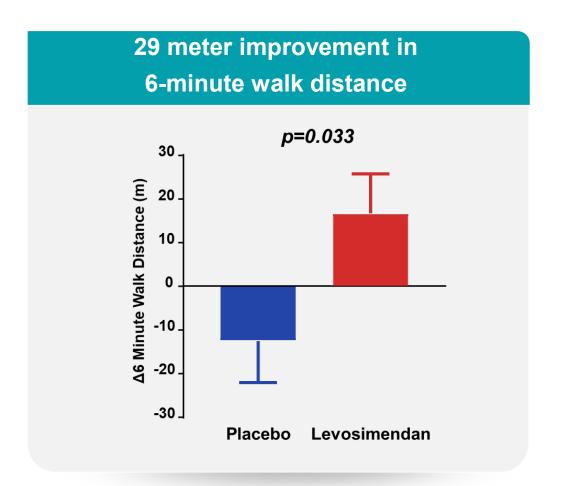


Burkhoff D, Rich S, et. al. Levosimendan Improves Hemodynamics and Exercise Tolerance in PH-HFpEF. JACC Heart Fail. 2021; 9:360-370



## **HELP Study: Six Minute Walk Distance**

Levosimendan Improves Exercise Capacity in PH-HFpEF Patients after 6 Weeks



#### **Dr Barry Borlaug, Mayo Clinic:**

"...this is the first medicine that has actually improved 6-minute walk distance in any patient population with HFpEF...",



https://www.medscape.com/viewarticle/938671



# Patients in the Open Label Extension stage of HELP were transitioned from IV to Oral Levosimendan (TNX-103)

Previous IV Infusion	Week 0 (Office)	Week 2 (Home)	Week 4 (Home)	Week 6 (Office)	
0.10 μg/kg/min	1mg QD	1mg BID	1mg TID	Datiant	
	(1mg total daily dose)	(2mg total daily dose)	(3mg total daily dose)	Patient evaluated for further	
	Morning	Every 12 hrs.	Every 8 hrs.	titration	

**6 Week Transition Period** 



# Improvements in Efficacy Measures in Patients Transitioned from IV to Oral Levosimendan (TNX-103)

- 6MWD (exercise capacity)
  - Improved a further 7 meters
- BNP/NT-pro-BNP (measure of cardiac function)
  - Improved further by 23%
- KCCQ (patient reported symptoms)
  - Improved *further* in 6 of 7 different domains



## Levosimendan Efficacy and Safety in PH-HFpEF Is Unprecedented

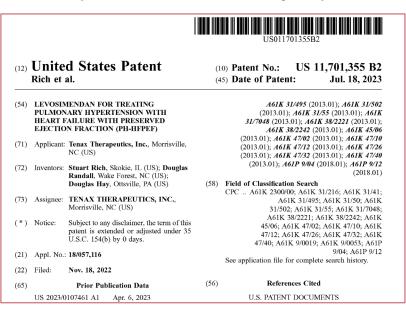
#### All PAH approved drugs studied in PH-HFpEF have failed

- Bosentan (BADDHY Trial₁) FAILED in PH-HFpEF
  - "Six-minute walk distance (6MWD) did not change in the Bosentan group"
- Macitentan (MELODY Trial<sub>2</sub>) FAILED in PH-HFpEF
  - "The mean treatment effect (6MWD) for macitentan versus placebo was negative 14.3 meters"
- Riociguat (DYNAMIC Trial₃) FAILED in PH-HFpEF
  - "The observed haemodynamic changes were <u>not</u> accompanied by significant improvements of NT-proBNP serum levels, WHO-FC, exercise capacity, or QoL."
    - 1) Koller, B., et al. "Pilot study of endothelin receptor blockade in heart failure with diastolic dysfunction and pulmonary hypertension (BADDHY-Trial)." Heart, Lung and Circulation 26.5 (2017): 433-441
    - 2) Mascherbauer, Julia, et al. "Evaluation of the pharmacoDYNAMIC effects of riociguat in subjects with pulmonary hypertension and heart failure with preserved ejection fraction: study protocol for a randomized controlled trial." Wiener Klinische Wochenschrift 128 (2016): 882-889.
    - 3) Vachiéry, Jean-Luc, et al. "Macitentan in pulmonary hypertension due to left ventricular dysfunction." European Respiratory Journal 51.2 (2018)

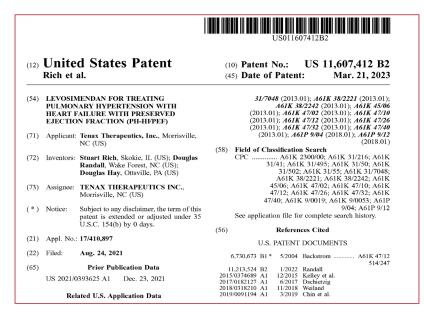


## Recently Issued Method of Use Patents Cover Levosimendan Use in PH-HFpEF and Expire in December 2040

## TNX-103 (Oral Use in PH-HFpEF)



## TNX-101 (IV Use in PH-HFpEF)



## TNX-102 (SC Use in PH-HFpEF)



Expires **December 2040** 

Expires December 2040

Expires **December 2039** 



## TNX-103 Phase 3 Development Plans in PH-HFpEF

- Phase 3 clinical trial design guided by:
  - Phase 2 (HELP) trial results
  - FDA feedback
  - Our scientific advisors' input:
    - Sanjiv Shah, MD
    - Daniel Burkhoff, MD, PhD
    - Barry Borlaug, MD
    - Javed Butler, MD, MPH, MBA



## Tenax's PH-HFpEF Scientific Advisors

#### World Recognized Experts in Pulmonary Hypertension and Heart Failure

#### Sanjiv Shah, MD

Professor of Medicine, Northwestern University Feinberg School of Medicine Director, Northwestern HFpEF Program, Bluhm Cardiovascular Institute



#### Daniel Burkhoff, MD, PhD

Director Heart Failure, Hemodynamics and MCS Research at the Cardiovascular Research Foundation

Adjunct Associate Professor of Medicine, Columbia University

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

#### **Barry Borlaug, MD**

Professor of Medicine and Director, Circulatory Failure Research, Mayo Clinic Chair for Research, Division of Circulatory Failure



#### Javed Butler, MD, MPH, MBA

President of the Baylor Scott and White Research Institute

Chair of Medicine, Chair of CV Research, Distinguished Professor of Medicine, Univ. of Mississippi





### FDA Guidance: Phase 3 TNX-103 Development in PH-HFpEF

#### FDA meeting minutes record agreements on key details of potential Phase 3 program:

• Two phase 3 trials (p<0.05) with 6MWD as the primary endpoint would be sufficient

<u>or</u>

• Single phase 3 trial (p<0.01) with 6MWD as the primary endpoint would be sufficient

<u>and</u>

 Safety database requirement: 300 patients followed for 6 months, and 100 patients followed for 12 months (ICH minimum requirement)



## Phase 3 Development Guided by Phase 2b Results

### Leverage Phase2b (HELP) Study Results to Design Phase 3 IV-to-Oral Transition: improvement in Hemodynamic Entry Criteria 85% responder rate 6MWD, 29m, p=0.03 BNP, KCCQ, 6MWD **Initial Phase 3 PH-HFpEF Study** ~152 patients, 90% Power, p<0.05 Hemodynamic Entry Criteria Primary Endpoint = 6MWD 2<sup>nd</sup> Phase 3 PH-HFpEF Study Provides additional data required for NDA filing Results of Initial Phase 3 trial de-risks 2<sup>nd</sup> Phase 3 Trial (FDA has confirmed minimum ICH requirement for safety database)



## The LEVEL Study: Projected Timelines

The LEVEL Study	2023		2024		2025	
Phase 3 PH-HFpEF oral levosimendan	H1	H2	H1	H2	H1	H2
Phase 3 Initiation		<b>\rightarrow</b>				
First Patient Enrolled			<b>♦</b>			
Last Patient Enrolled					<b>\rightarrow</b>	
Topline						<b>♦</b>



### **PH-HFpEF Market Assumptions**

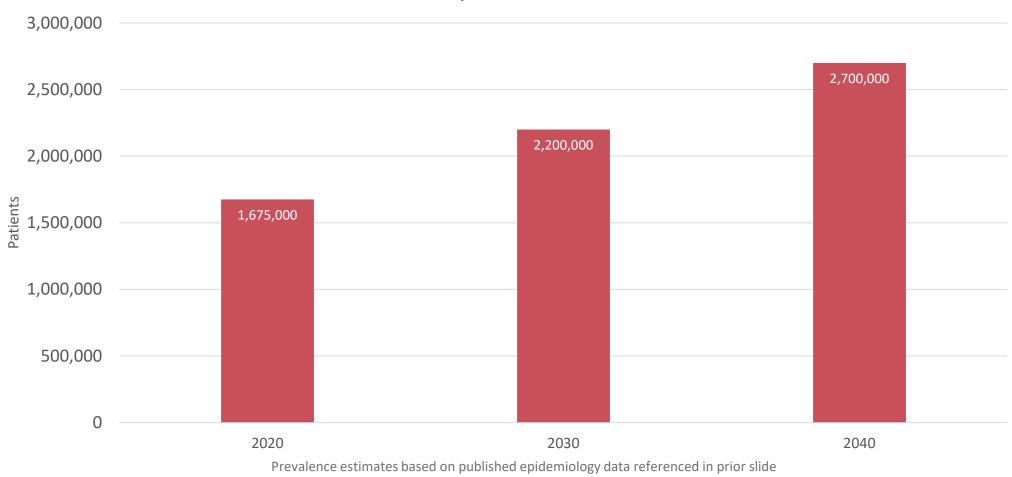
#### PH-HFpEF Prevalence

- 6,700,000 Heart Failure patients in U.S. (1)
- 2% Annual Growth Rate (1)
- 54% is HFpEF, with HFpEF proportion increasing to 60% by 2040 (1,2,3,4)
- 50% of HFpEF is PH-HFpEF (2,5,6)
- 1) Tsao, Connie W., et al. "Heart disease and stroke statistics—2023 update: a report from the American Heart Association." Circulation 147.8 (2023): e93-e621.
- 2) Lai, Yen-Chun, Longfei Wang, and Mark T. Gladwin. "Insights into the pulmonary vascular complications of heart failure with preserved ejection fraction." The Journal of physiology 597.4 (2019): 1143-1156.
- 3) Pfeffer, Marc A., Amil M. Shah, and Barry A. Borlaug. "Heart failure with preserved ejection fraction in perspective." Circulation research 124.11 (2019): 1598-1617.
- 4) Steinberg, Benjamin A., et al. "Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes." Circulation 126.1 (2012): 65-75.
- 5) Brittain, Evan L., et al. "Elucidating the Clinical Implications and Pathophysiology of Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction: A Call to Action: Circulation 146.7 (2022): e73-e88.
- 6) Guazzi, Marco. "Pulmonary hypertension in heart failure preserved ejection fraction: prevalence, pathophysiology, and clinical perspectives." Circulation: Heart Failure 7.2 (2014): 367-377.



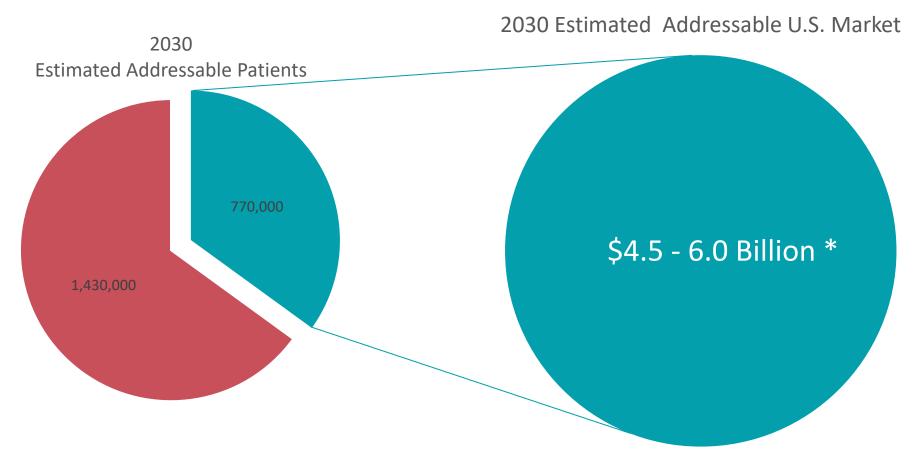
## **PH-HFpEF Market is Large and Growing**

Estimated PH-HFpEF Prevalence in the U.S.





### Estimated Total Addressable PH-HFpEF U.S. Market in 2030



\*Assumes only 35% of patients are addressable and the estimated Annual Value = \$6-8K/patient (1)

<sup>1)</sup> Drugs.com. March 2023 Annual cost/patient branded for ANRI or SGLT2 inhibitors approved in HF. Assumes similar pricing for a PH-HFpEF drug



## **Multiple Levels of Derisking**

Risk Considerations	Questions	De-risking Factors		
	DILLIEREE Efficacy Data (DhOb)	Hemodynamic improvements		
Clinical Development	PH-HFpEF Efficacy Data (Ph2b)	29M+ 6MWD , P=0.03		
	Safety Database	>1,900,000 patient exposures (IV)		
		6MWD primary endpoint accepted		
Regulatory	FDA Feedback	ICH minimum safety database		
	. 27 . 7 . 2 . 3 . 3 . 3 . 3	Single Study, p≤0.01 Two Studies, p ≤0.05		
	Facility Inspection	FDA inspected facility that produces other FDA approved products		
Manufacturing	Production at Scale	1.5M capsules produced		
	Shelf -life	5 years		
	Clinical Supply	Produced and available		
	Market	Approaching 2.0M U.S. patient prevalence		
Commercial-IP	Competitors	No approved or effective therapies		
	IP	Multiple granted patents to 2040+		



## **New Value Proposition for Investors**

#### **Short-term and Long-term catalysts**

- Short-term potential events
  - First Phase 3 trial sites initiated
  - First patient enrolled

#### Long-term

- Phase 3 trial results
- Potential IP protection beyond 2040
- Estimated \$4.5 to \$6.0 billion addressable market potential in 2030

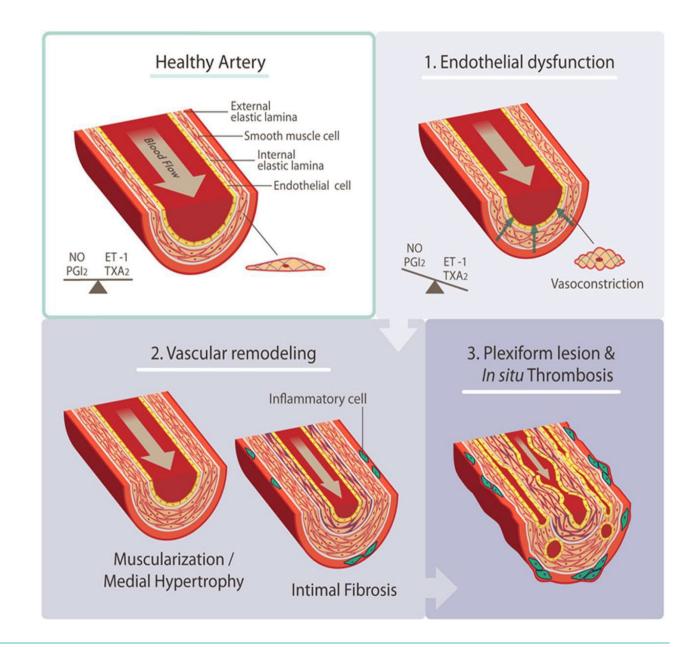




#### **Overview of PAH:**

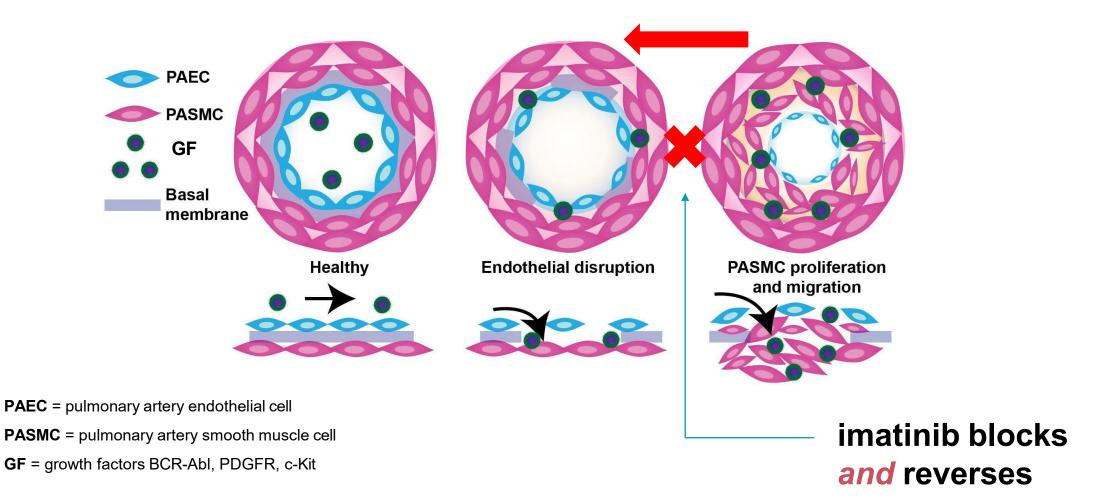
#### The Pathology

As the pulmonary artery narrows, the pulmonary pressure increases.





#### **Imatinib Targets the Pathophysiology of PAH**





#### **Proof of Concept IMPRES STUDY**

Imatinib is Proven Effective in Treating PAH

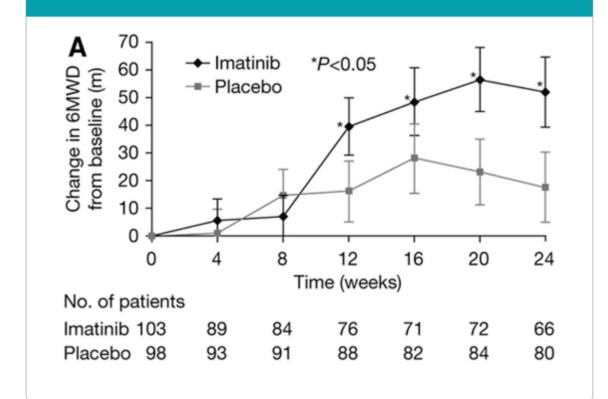
#### **Phase 3 Clinical Trial:**

Imatinib Mesylate as Add-On Therapy for Pulmonary Arterial Hypertension: Results of the Randomized IMPRES Study

**Results:** After 24 weeks, the mean placebo-corrected treatment effect on 6-minute walk distance was 32 meters (95% confidence interval, 12–52; **P=0.002**)

**Conclusions:** Imatinib improved exercise capacity and hemodynamics in patients with advanced PAH, but frequent dropout events prevented approval.

## The primary endpoint was change in 6-minute walk distance



Circulation. 2013;127:1128-1138.



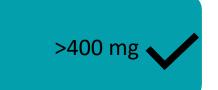
#### **Key Learnings from IMPRES Study Informed Phase 3 IMPROVE**

**IMPROVE** 

Efficacy was established in PAH

PAH 🔦

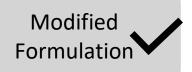
1 Adequate dose is critical (400mg) to achieve clinical efficacy



**Avoid excessive dropouts**, mostly related to <u>early-onset</u> side effects



Gastrointestinal side effects are most the common, novel formulation to reduce





04

# Imatinib-MR Remains a Very Attractive Therapy When Compared to Sotatercept and/or Seralutinib

## Sotatercept (STELLAR) vs. Oral Imatinib (IMPRES)

#### 6-minute walk test

- Sotatercept increased by 8.5%
- Imatinib increased by 8.2%
- Hemodynamics (PVR)
  - Sotatercept reduced by 2 Wood units
  - Imatinib reduced by 4 Wood units

## Seralutinib-inhaled (TORREY) vs. Oral Imatinib (IMPRES)

- 6-minute walk test
  - Seralutinib increased by 1.6%
  - Imatinib increased by 8.2%
- Hemodynamics (PVR)
  - Seralutinib reduced by 1 Wood unit
  - Imatinib reduced by 4 Wood units

STELLAR: Hoeper, Marius M., et al. "Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension." NEJM (2023).

IMPRES: Hoeper, Marius M., et al. "Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study." Circulation 127.10 (2013): 1128-1138.

TORREY: <a href="https://ir.gossamerbio.com/news-releases/news-release-details/gossamer-bio-announces-seralutinib-meets-primary-endpoint-phase5">https://ir.gossamerbio.com/news-releases/news-release-details/gossamer-bio-announces-seralutinib-meets-primary-endpoint-phase5</a>.



### **Execution Led by a Highly Experienced Team**

#### Management Team

Chris Giordano - President & CEO, Board Director

Previous President of IQVIA Biotech 20+ years of clinical trial expertise

Stuart Rich, MD - CMO, Board Director

Globally recognized expert in Pulmonary Hypertension 40+ Years clinical experience in PH and HF Former FDA Cardio Renal Advisory Panel Member

Doug Hay, PhD - EVP, Regulatory

Experienced senior pharmaceutical regulatory expert 35+ years regulatory experience, including founder

**Doug Randall - EVP, Business Development and Operations** 

Experienced BD and Commercial expert 40+ years BD commercial roles, including founder

#### **Board of Directors**

**Gerry Proehl - Chairman** 

President, CEO and Chairman, Dermata Therapeutics Previously CEO, Santarus

June Almenoff, MD

CMO, Redhill Biopharma
Previously President and CMO, Furiex Pharmaceuticals

Declan Doogan, MD

CMO, Juvenescence Previously Head of Global Drug Development, Pfizer Previously Chairman/Co-Founder, Biohaven Pharmaceuticals

Michael Davidson, MD

CEO, New Amsterdam Pharma Previously CSO, Corvidia Therapeutics

**Robyn Hunter** 

CFO, Sotio Biotech Business Previously CFO, Fortress Biotech



### **Tenax Investment Opportunity**

- Therapeutic Focus Pulmonary Hypertension
  - PH-HFpEF (approaching 2.0M U.S. patients, no approved therapies)
  - PAH (Orphan)
- Pipeline Two Phase 3-Ready Products
  - TNX-103: Levosimendan oral (First in class oral KATP Activator/Ca++ Sensitizer) for PH-HFpEF
  - TNX-201: Imatinib (Modified Release/Modified Dose) for PAH
- Positive Phase 2 & Phase 3 Data
  - HELP Study- Levosimendan in PH-HFpEF
  - IMPRES Study Imatinib in PAH
- Efficient Clinical Development Pathway
  - Small Phase 3 trials required (FDA confirmed)
- Significant Exclusivity
  - Levosimendan
    - 3 U.S. method of use patents granted: Oral, IV, SC
  - Imatinib orphan exclusivity
- Large Commercial Potential
  - TNX-103: \$4.5-\$6.0B market in 2030
  - TNX-201: >\$5B market, currently

