

KOL Event on the Unmet Need in Group 2 PH-HFpEF (Pulmonary Hypertension due to Heart Failure with Preserved Ejection Fraction(PH-HFpEF) and TX45 as a Potential Treatment

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December 12, 2024

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Introduction

Alise Reicin, MD

CEO, Tectonic Therapeutic, Inc.

Agenda

	Time	Presenter	Agenda Item
01	4:00 PM	Alise Reicin	Welcome and introductions
02	4:05 PM	Raymond Benza	Review of Group 2 pulmonary hypertension (PH)
03	4:20 PM	John Teerlink	Review of relaxin physiology and use as a therapeutic
04	4:35 PM	Marcella Ruddy	Phase 1b and Phase 2 trial designs for TX45 in Group 2 PH
05	4:45 PM	Marcella Ruddy	Results of Phase 1b that may inform the outcome of Phase 2
06	4:50 PM	All	Q&A

KOL Event Expert Physicians in PH-HFpEF



Raymond Benza, MD, FACC, FAHA, FACP

Professor of Medicine, Icahn School of Medicine at Mount Sinai
Director of Pulmonary Hypertension, Mount Sinai Health System

John Teerlink, MD, FACC, FAHA, FESC, FHFSA

Professor of Medicine, University of California, San Francisco



Pulmonary Hypertension Due to Heart Failure with Preserved Ejection Fraction (PH-HFpEF)

Raymond Benza, MD, FACC, FAHA, FACP

TX45 Initial Indication: Group 2 Pulmonary Hypertension (PH)

Pulmonary Hypertension Consists of 5 Distinct Diseases

Group 2 PH is of Greatest Interest for TX45's Initial Indication

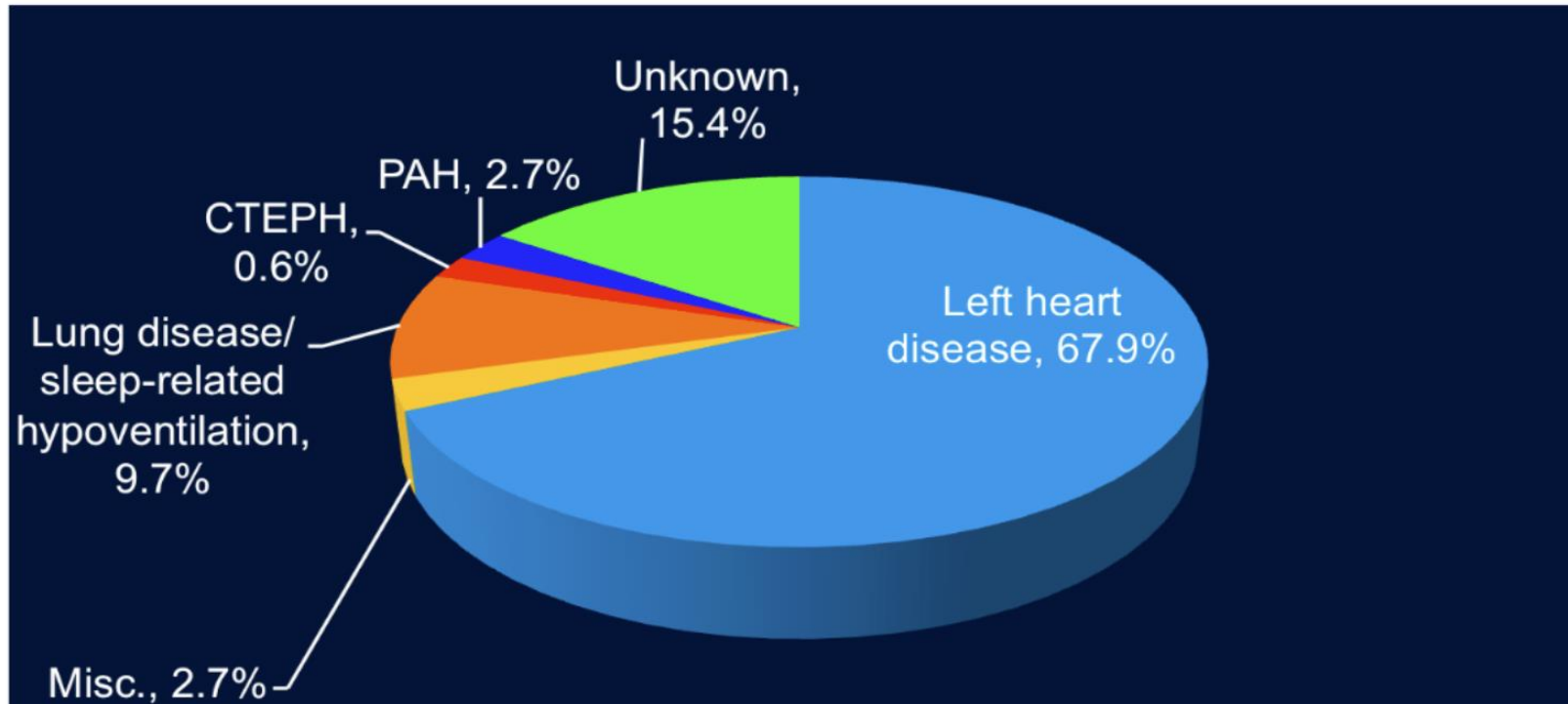


Group 1 ("PAH")	Group 2 Most common	Group 3	Group 4 ("CTEPH")	Group 5 (Misc.)
<ul style="list-style-type: none">• Idiopathic• Hereditary• Connective tissue disease-associated• Congenital heart disease-associated• Drug-induced	<ul style="list-style-type: none">• Due to left heart disease (HFpEF, HFrEF) or valvular heart disease• CAD, HTN, T2DM¹, high cholesterol are risk factors• Two Subtypes: CpcPH / lpcPH	<ul style="list-style-type: none">• Due to lung disease or hypoxia• May be due to COPD, interstitial lung disease (i.e., IPF) or obstructive sleep apnea	<ul style="list-style-type: none">• Chronic thrombo-embolic pulmonary hypertension –i.e., as a consequence of blood clots	<ul style="list-style-type: none">• Miscellaneous group with causes unclear or multiple underlying factors

1. CAD: Coronary Artery Disease, HTN: Hypertension, T2DM: Type 2 Diabetes Mellitus
Nat. Pul. Hypertension Unit, Ireland

Group 2 Pulmonary Hypertension (PH), the Largest Group of Patients with PH

- Single echocardiography lab; Australian community of 165,450; ~7,000 had echos; ~1,000 with PH
- **Etiology of PH noted on echo** (PAH = Group 1; Left heart disease = Group 2; Lung disease = Group 3; CTEPH = Group 4)



N=936 of 6994 patients with echo and sufficient TR to measure had PASP >40 mm Hg.
Strange G et al. *Heart* 2012;98:1806-1811.

Epidemiology of PH in HFrEF & HFpEF

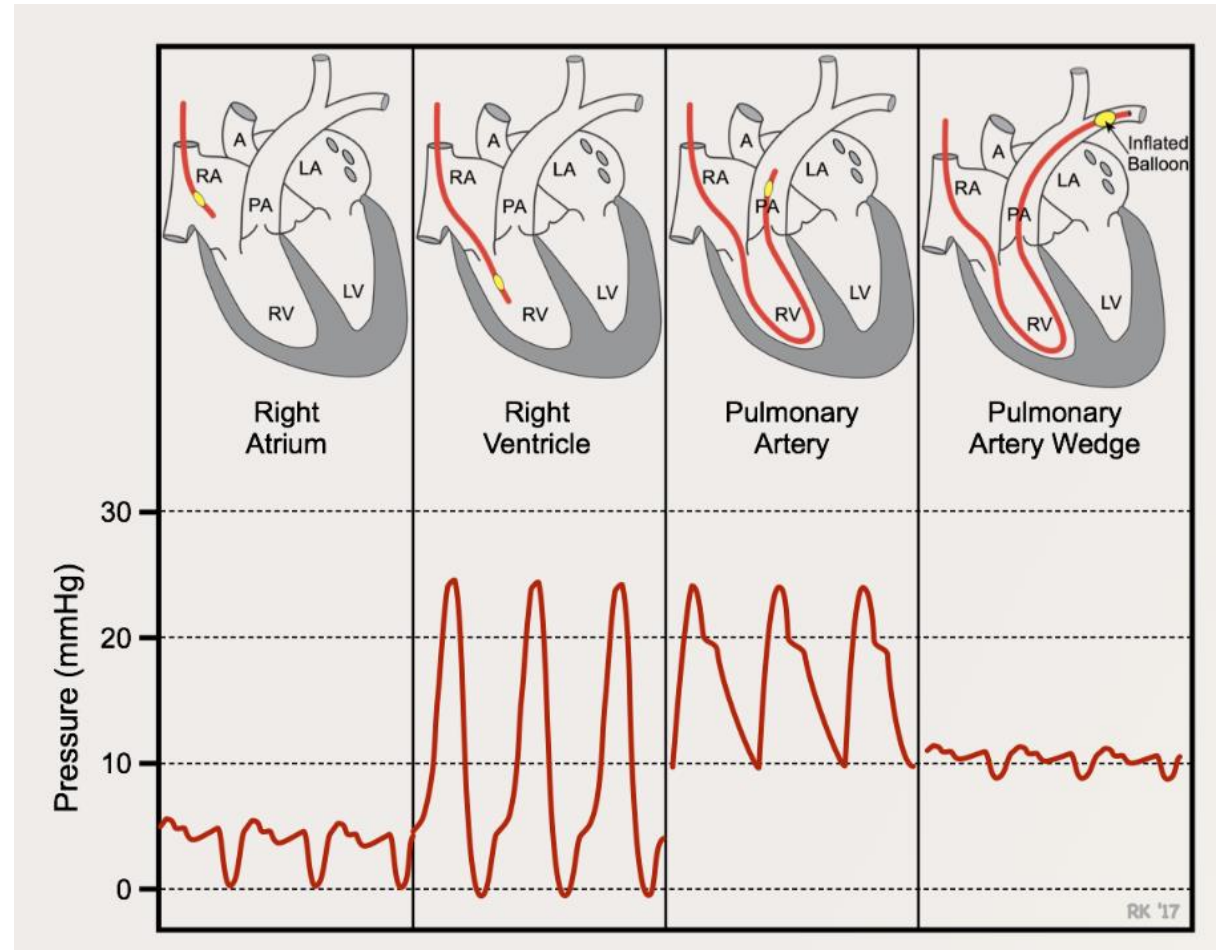
Study	N	Diagnosis	PH definition	HF type	PH prevalence
Khush KK ¹	171	Echo	mPAP \geq 25mmHg	HFrEF (only EF <30%)	47%
Shalaby A ²	270	Echo	sPAP \geq 35mmHg	HFrEF	79%
Ghio S ³	377	RHC	mPAP >20mmHg	HFrEF (only EF <35%)	62%
Grigioni F ⁴	196	RHC	mPAP >25mmHg	HFrEF	40%
Leung CC ⁵	455	RHC	mPAP \geq 25mmHg	HFpEF	52%
Gerges M ⁶	1063	RHC	mPAP \geq 25mmHg	SHF (664)	68%
Gerges M ⁷	391	RHC	mPAP \geq 25mmHg	SHF (172)	80%

40-80%

- 5 million people in US with HF; 2.7 million people with HFrEF and 2.3 million with HFpEF
- 62% of all HFrEF and 52% of all HFpEF patients have PH
- ~1.7 million US citizens with HFrEF and ~1.2 million US citizens with HFpEF have Group PH
- \uparrow PH = \downarrow survival
- A significant number of patients with HF have an even higher risk of dying beyond that, related to their PH

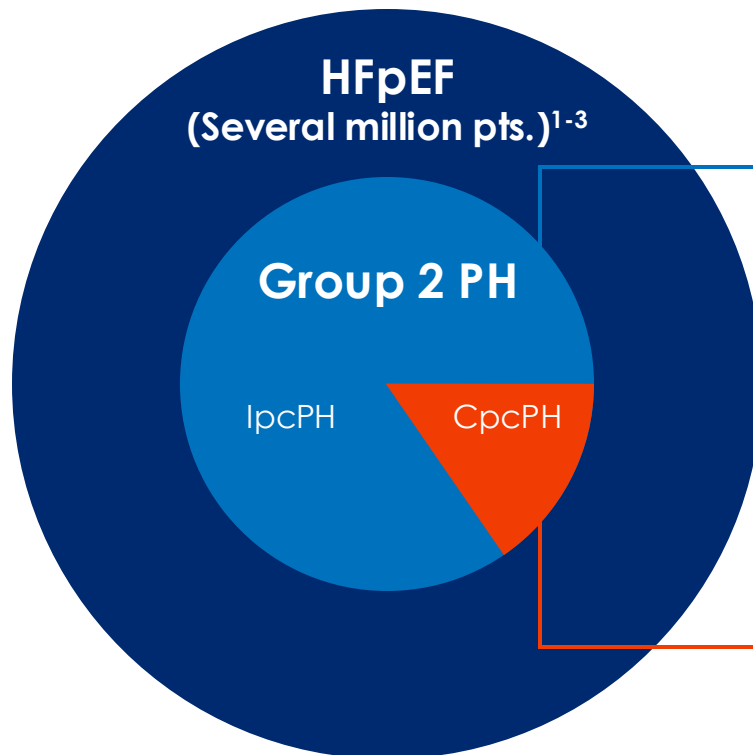
Key Hemodynamic Endpoints in PH-HFpEF: PCWP, mPAP, PVR

- 1. PCWP** (pulmonary capillary wedge pressure) - measure of left atrial pressure, the pressure required to fill the left ventricle in diastole, a key marker of LV diastolic function:
 - Heart failure if PCWP > 15 mmHg
- 2. mPAP** (mean pulmonary artery pressure) – mean of systolic and diastolic pulmonary artery pressures:
 - Pulmonary hypertension if mPAP ≥ 20 mmHg
- 3. PVR** (pulmonary vascular resistance) - measure of resistance to blood flow in pulmonary arteries and arterioles:
 - $PVR = (mPAP - PCWP) / CO$
 - Combined pre- and post-capillary PH (CpcPH) if PVR > 3 Wood Units (>2 new definition)
- 4. TPR** (Total pulmonary resistance) = mPAP/CO; useful for following lpcPH. Provides an assessment for the combined lpcPH and CpcPH patients on their right ventricular afterload.



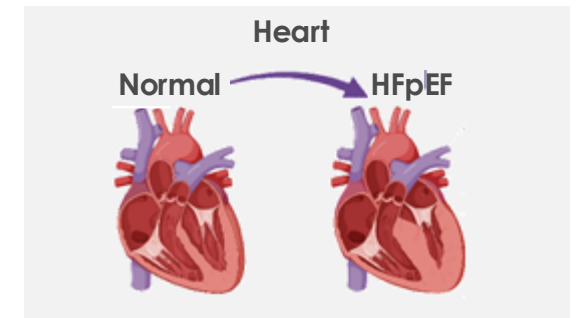
Subtypes of Group 2 PH: IpcPh and CpcPH

CpcPH is a more severe form of Group 2 PH



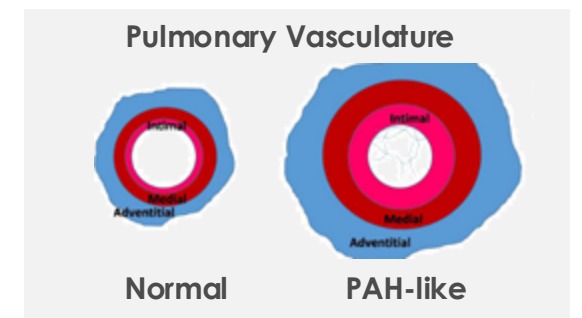
IpcPH (I)solated, **p**ost **c**apillary **PH**

Increased Left Ventricle Filling Pressures
 ↓
 Increased Pulmonary Venous Pressures
 ↓
 Passive Pressure Backflow
 ↓
 Pulmonary Hypertension



CpcPH (C)ombined, **p**re- and post **c**apillary **PH**

Chronic PH and/or Other Drivers
 ↓
 Permanent Vascular Changes, e.g. Pulmonary Artery Remodeling
 ↓
 Increased Vascular Resistance
 ↓
 Right Heart Failure



1. US prevalence numbers. Estimates based on data from
2. Kapelios, C. et al. Cardiac Failure Review 2023;9:e14
3. Sera F. et al. Heart 2023;109:626–633

2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension*

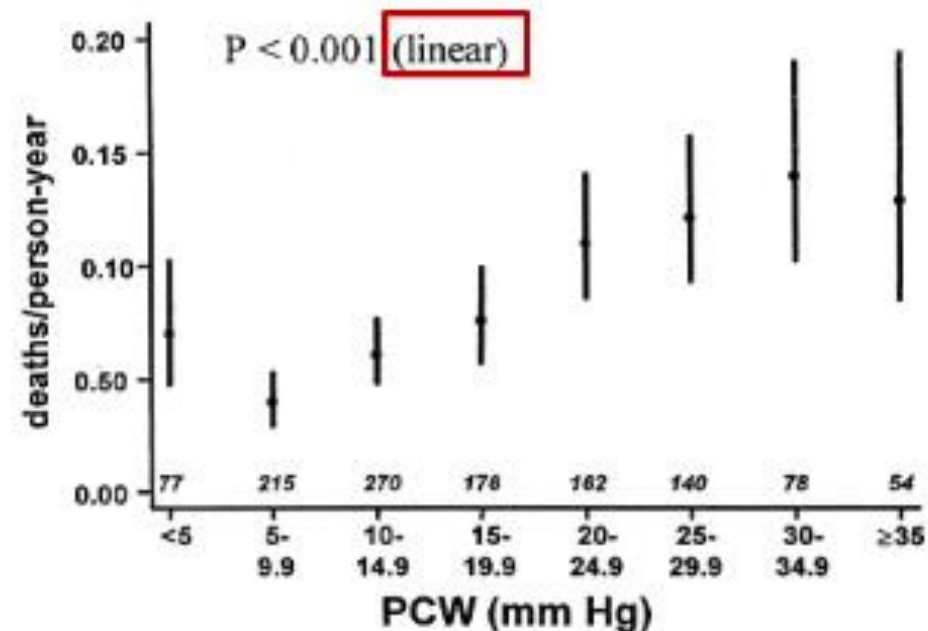
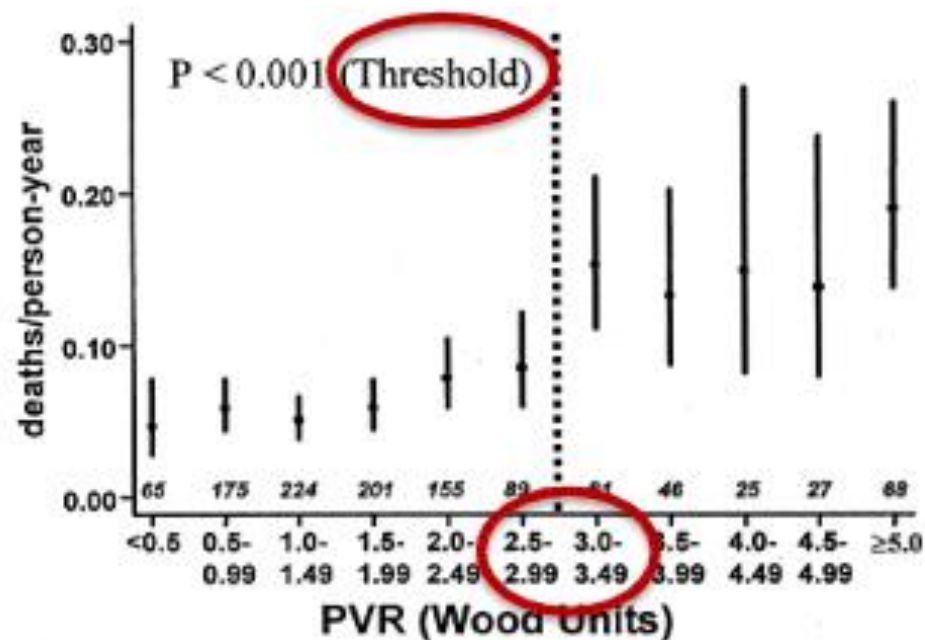
Updated hemodynamic definitions of PH

Definition	Hemodynamic Characteristics
PH	mPAP \geq 20 mmHg
Isolated post-capillary PH (IpcPH)	mPAP \geq 20 mmHg PCWP $>$ 15 mmHg PVR \leq 2 Wood Units
Combined pre- and post-capillary PH (CpcPH)	mPAP \geq 20 mmHg PCWP $>$ 15 mmHg PVR $>$ 2 Wood Units

*Some physicians still consider PVR $>$ 3 to be the definition of CpcPH

Mortality Rates Within Strata of PVR and PCWP in HFrEF¹:

Higher PVR and Higher PCWP are associated with increased mortality risk

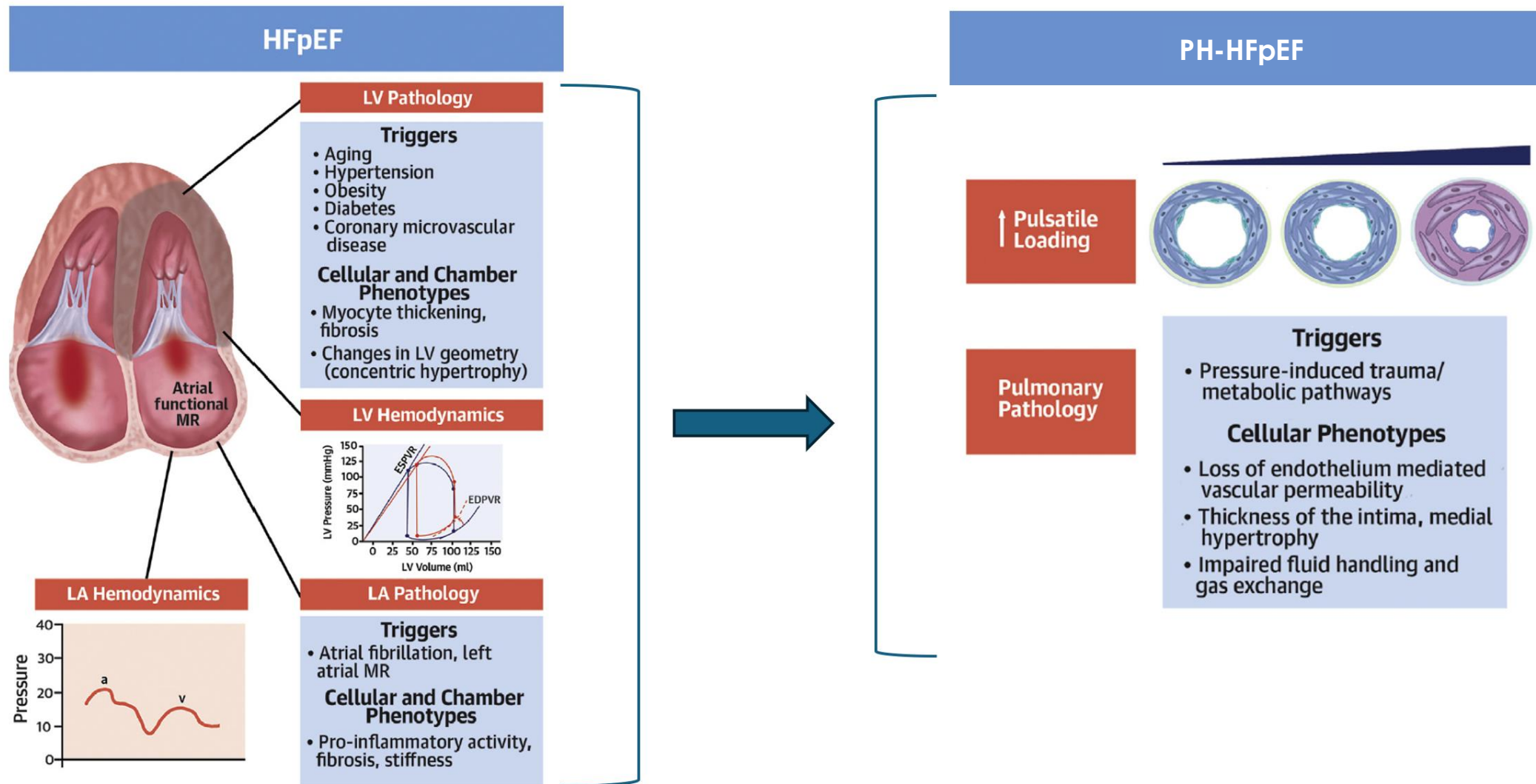


- In large retrospective cohort study, HF in 58%, PVR>2.2 was associated with increased risk of mortality²

¹Cappola TP et al. Circulation 2002

²Maron BA et al. Lancet Respir. 2020

PH-HFpEF: LV Pathology Can Lead to Pulmonary Hypertension¹



¹Modified from Guazzi M. et al. JACC 2020; 76: 1102

Patient Journey in PH-HFpEF

Patient presents to caregiver with symptoms:

- Shortness of breath (dyspnea) with exercise or at rest
- Swelling of legs or abdomen (edema)



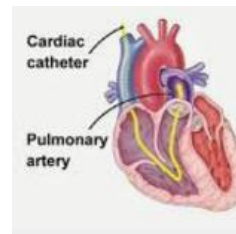
Caregiver orders echocardiogram:

- LV ejection fraction $\geq 50\%$
- Thickened LV
- Left atrial enlargement
- Systolic pulmonary artery pressure high
- *Diagnosis: possible PH-HFpEF, recommend RHC*



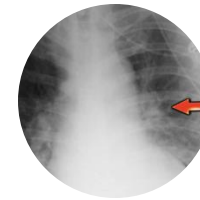
Initiate Rx for HFpEF (none for PH):

- SGLT2 inhibitor
- Mineralocorticoid receptor antagonist
- Consider ARNI, diuretics



Caregiver evaluates patient:

- Chest X-ray shows mild pulmonary vascular redistribution, perihilar haze
- Elevated NTproBNP
- *Diagnosis: possible heart failure, recommend echo*



Right heart catheterization:

- Cardiac output mildly reduced
- mPAP high (≥ 20 mmHg)
- PCWP high (> 15 mmHg)
- PVR high (> 3 WU)
- *Diagnosis: CpcPH due to HFpEF*

Management Principles of Group 2 PH

Manage Left Atrial Pressure (PCWP)



Manage Underlying Substrate



Induce Vascular Remodeling

Long term phase must emphasize simultaneous management



Relaxin-RXFP1 Signaling in Cardiovascular Physiology

**John Teerlink, MD, FACC, FAHA, FESC,
FHSA**

Relaxin Hemodynamic and Anti-fibrotic Properties Are Demonstrated by its Role in Pregnancy

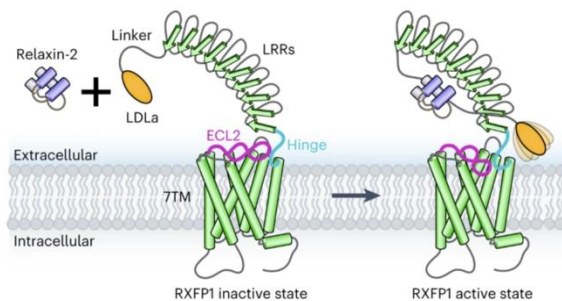
Pharmacology

AGONIST

Natural Ligand of RXFP1 Receptor

No RXFP1 internalization from relaxin agonism → no desensitization with chronic therapy

Relaxin upregulated in pregnancy



Facilitates Gestation

PULMONARY AND SYSTEMIC VASODILATOR

Increases cardiac output to accommodate the increased demand from developing fetus

ANTIFIBROTIC

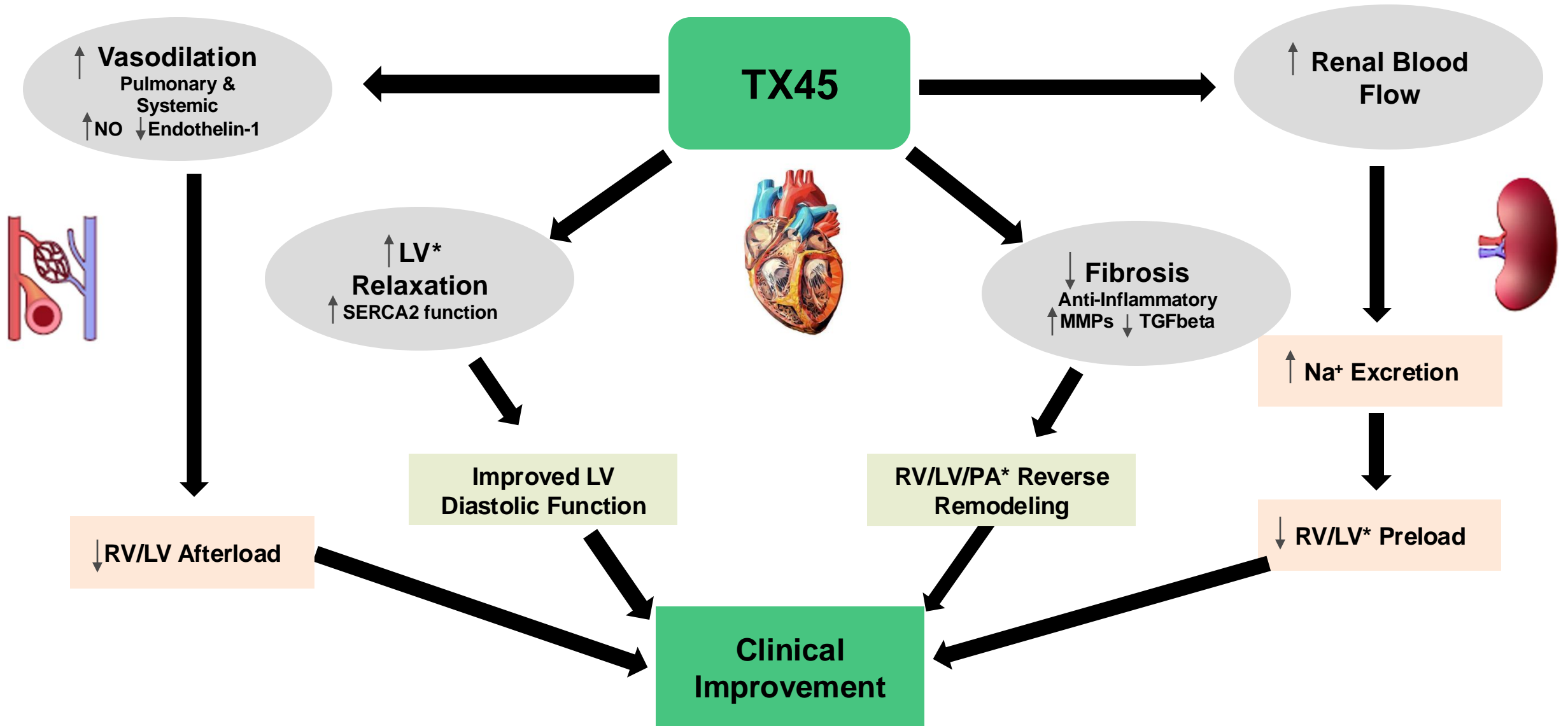
Prepares musculoskeletal tissues for pregnancy and childbirth

ORGAN PROTECTION

Protects heart, liver and kidney in pregnancy



Beneficial Effects of TX45 in PH-HFpEF



*RV: right ventricle; LV: left ventricle; PA, pulmonary arteries

Relaxation and Anti-Fibrotic Effects of Relaxin Have Potential for Disease Modification in PH-HFpEF

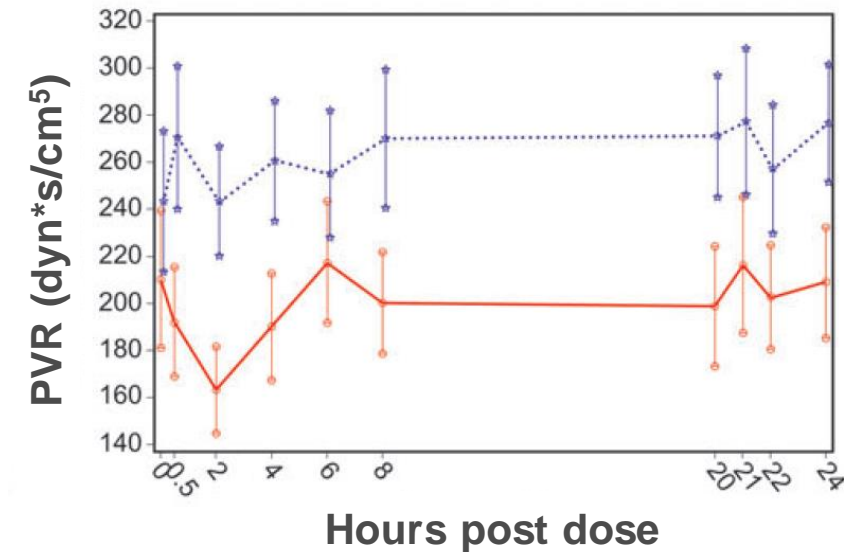
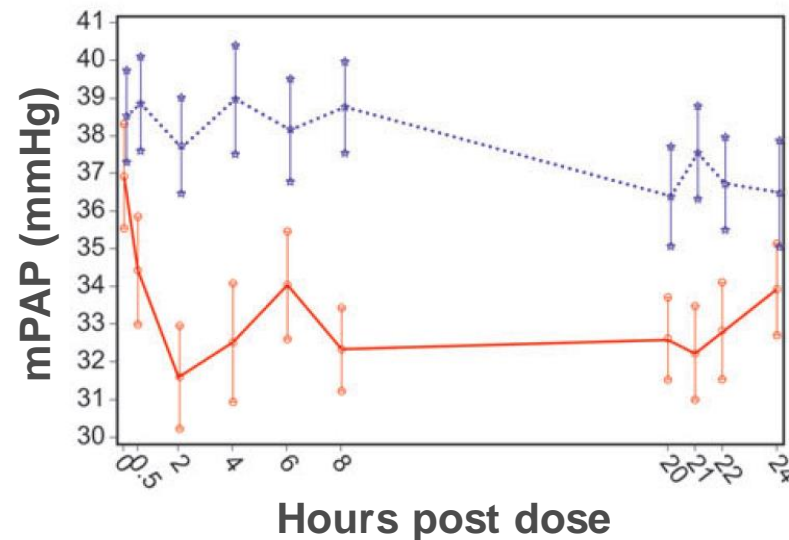
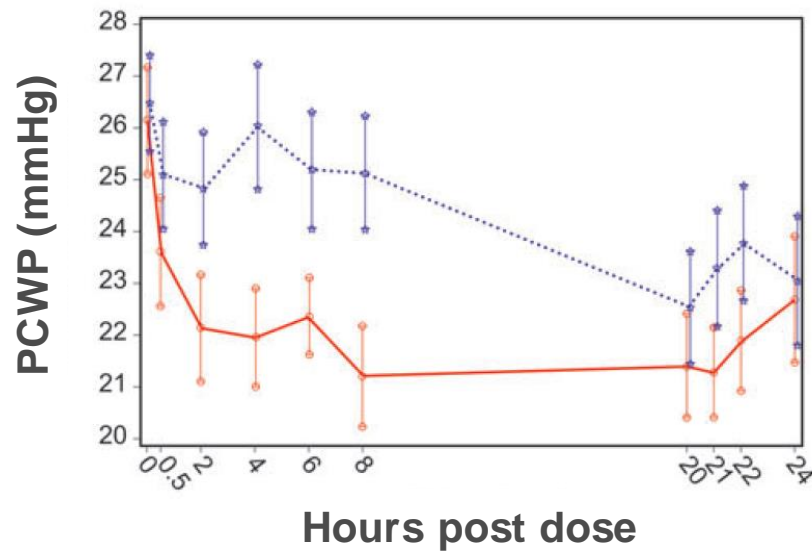
- Heart, and vascular dysfunction contribute to disease pathology
- Renal dysfunction also present in many of these patients

CHARACTERISTICS OF PH-HFpEF	ANTICIPATED RELAXIN EFFECTS
Pulmonary artery narrowing, thickening, stiffening, fibrotic remodeling	Pulmonary Vasodilation Anti-inflammatory, anti-fibrotic
Thickening and stiffening of Left Ventricle	Peripheral vasodilation, improved cardiac relaxation, left ventricular remodeling
Compromised kidney function	Improvement in kidney function, natriuresis

Combined Decrease in Pulmonary Pressure and Increased Cardiac Function Are Expected to be Needed for Efficacy in PH-HFpEF

In Acute Heart Failure (AHF), Serelaxin Improves LV Function (Lowering PCWP), and Lowers Pulmonary Pressures and Resistance (mPAP, PVR)¹

Furosemide given 4h prior to serelaxin infusion, and 8h after initiation of serelaxin



Treatment group —○— Serelaxin -☆- Placebo

¹Ponikowski P. et al. Eur. Heart J. 2014

Serelaxin Reduced Worsening Heart Failure at Day 5 in AHF¹

-Note: trials only included a two-day serelaxin infusion in AHF patients

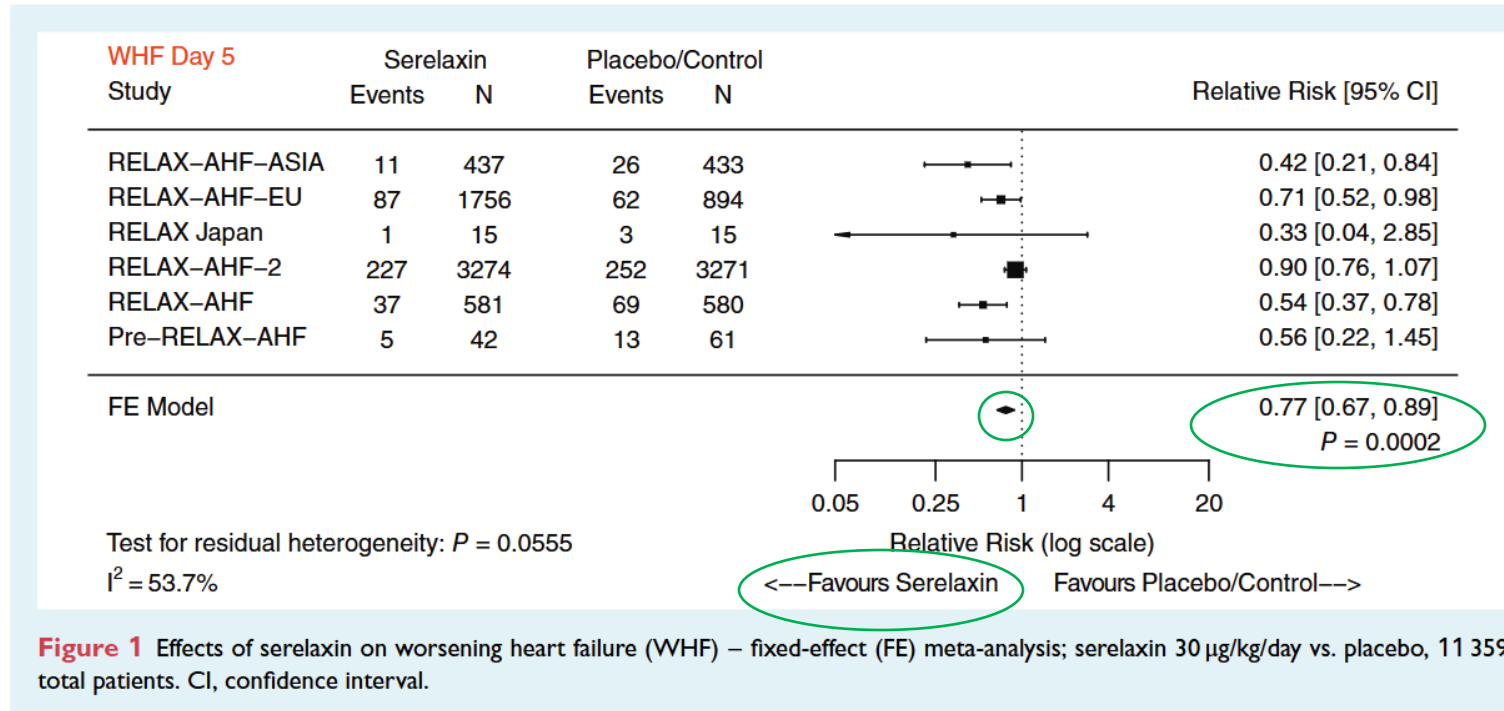


Figure 1 Effects of serelaxin on worsening heart failure (WHF) – fixed-effect (FE) meta-analysis; serelaxin 30 µg/kg/day vs. placebo, 11 359 total patients. CI, confidence interval.

- One of two pivotal studies included in meta-analysis, RELAX-AHF-2, failed to achieve the co-primary endpoints, and we believe that two factors contributed to this outcome
 - Operational challenges and site selection

¹Teerlink J.R. et al. Eur. J. Heart Fail. 2019; 22: 315-329

Serelaxin Improved Renal Function in AHF: Reduced Creatinine at D2 & D5; Mainly Seen in CKD Patients¹

-Note: trials only included a two-day serelaxin infusion in AHF patients

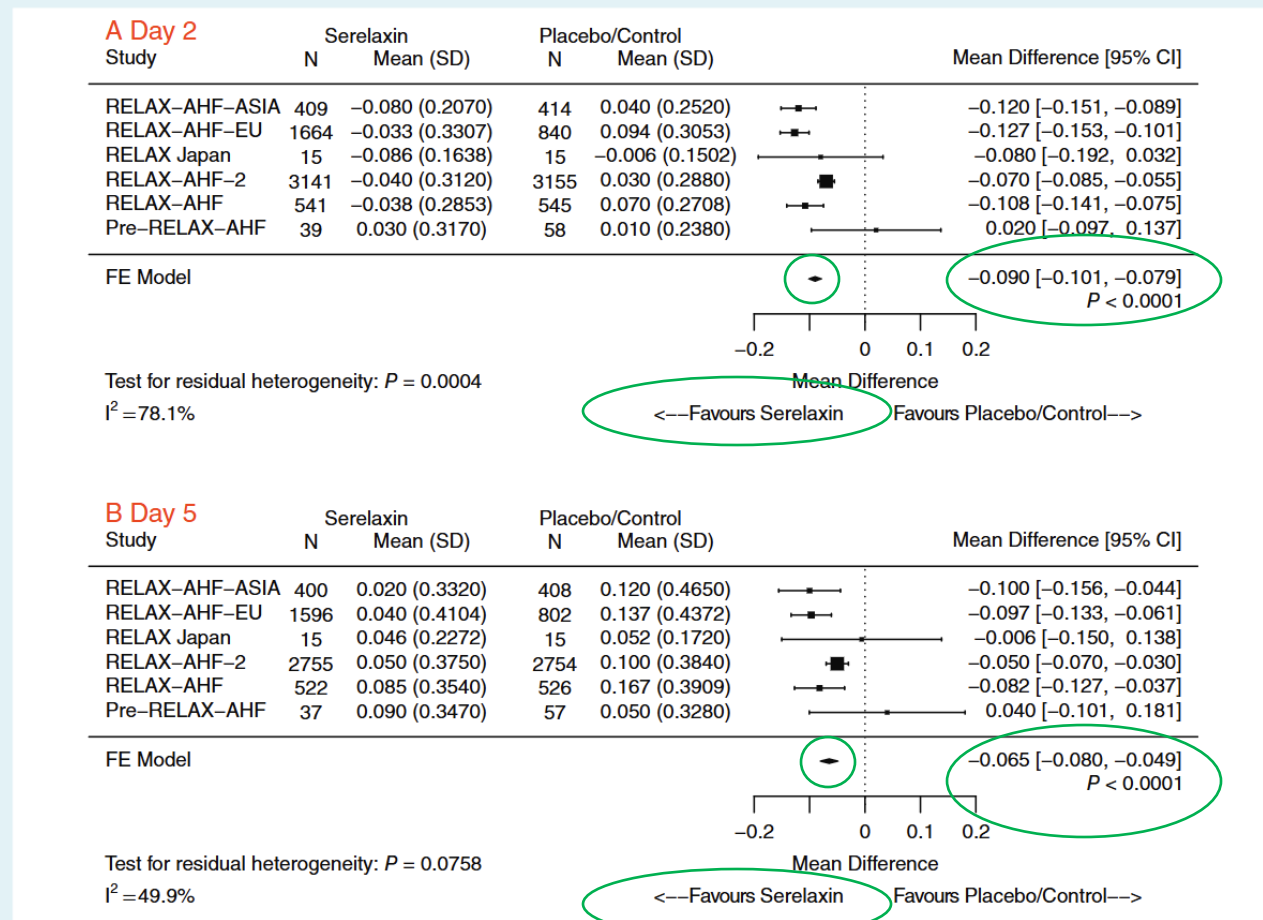


Figure 5 Effects of serelaxin on changes in creatinine (mg/dL) from baseline to (A) day 2 and (B) day 5 – fixed-effect (FE) meta-analysis; serelaxin 30 µg/kg/day vs. placebo; 10 836 total patients. CI, confidence interval; SD, standard deviation.

Serelaxin Reduced All-Cause Death in AHF Patients¹

-Note: trials only included a two-day serelaxin infusion in AHF patients

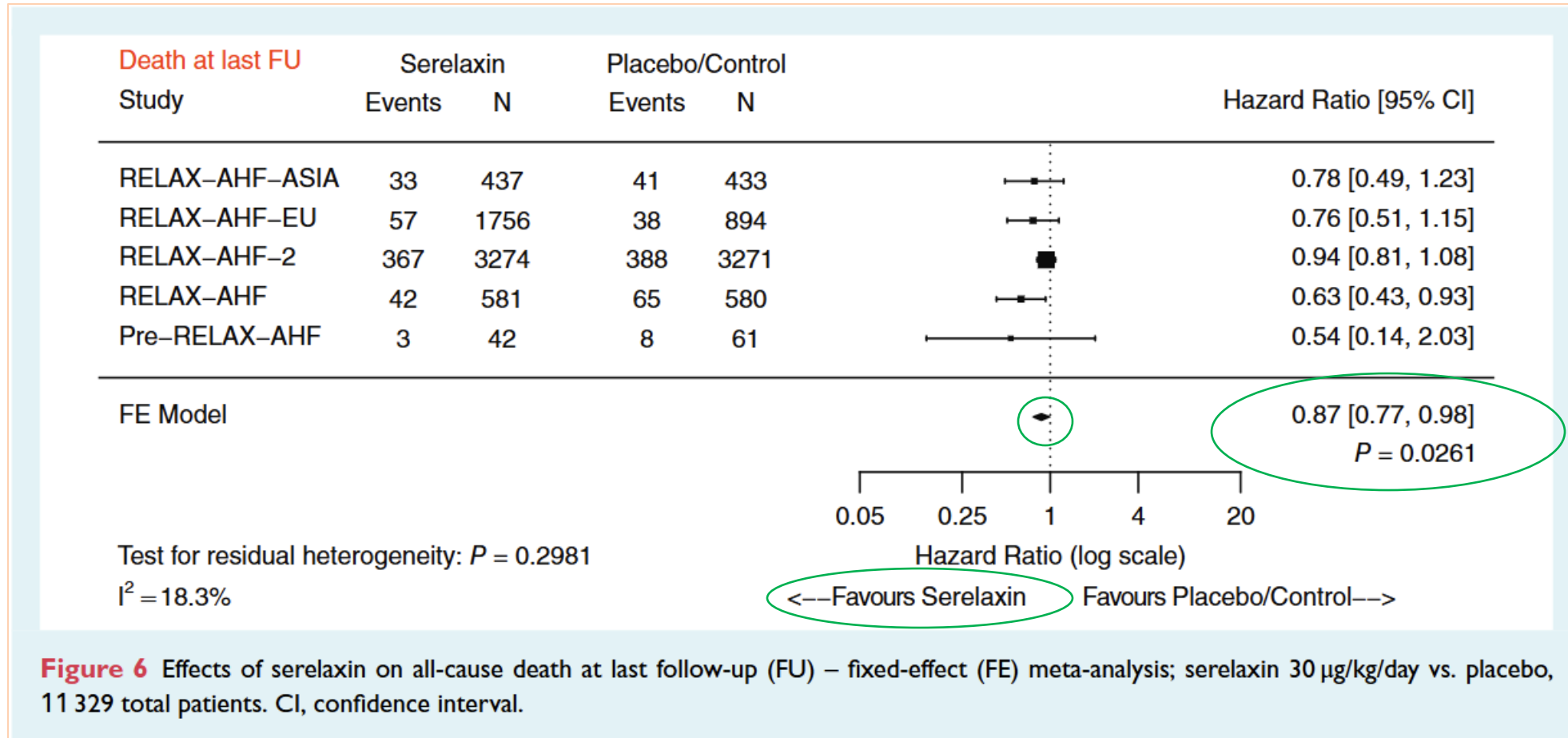


Figure 6 Effects of serelaxin on all-cause death at last follow-up (FU) – fixed-effect (FE) meta-analysis; serelaxin 30 µg/kg/day vs. placebo, 11 329 total patients. CI, confidence interval.

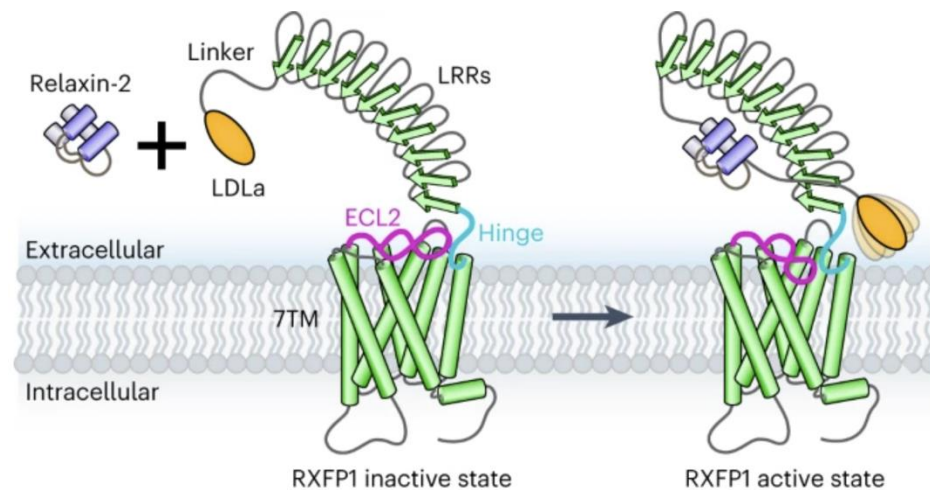
Summary: Pleiotropic Effects of Relaxin Increase Odds of Success in PH-HFrEF

TX45, a long-acting relaxin-Fc fusion protein, is predicted to have the following effects in PH-HFrEF:

- Pulmonary and systemic vasodilator
- Directly improves LV diastolic function
- Anti-fibrotic activity
- Anti-inflammatory activity

TX45 could also be evaluated in:

- PH-HFrEF
- HFpEF
- HFrEF
- Chronic Kidney Disease (glomerular protection)





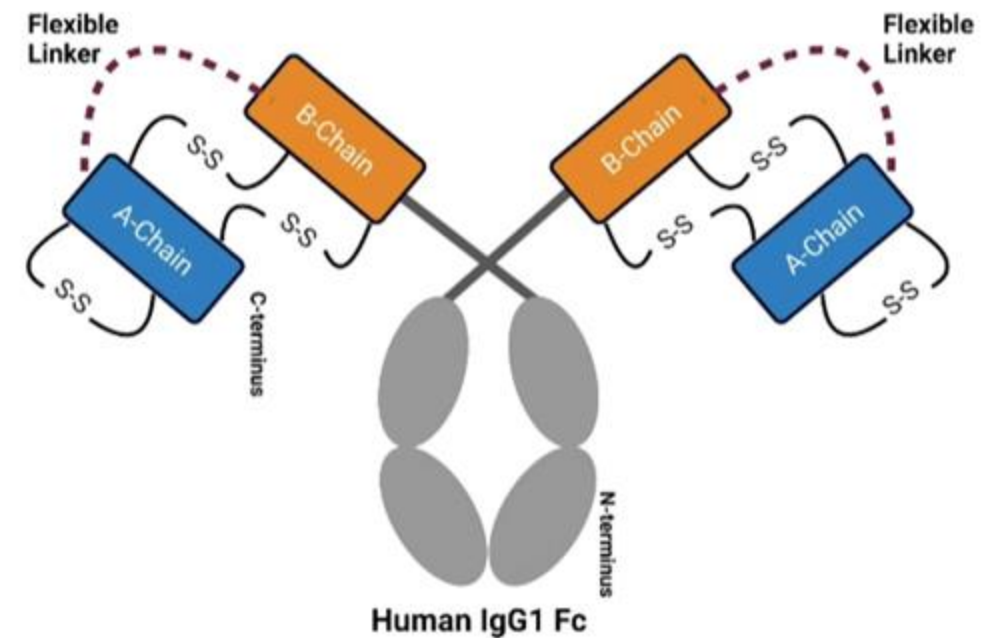
TX45 Clinical Development Program

Marcie Ruddy, MD

CMO, Tectonic Therapeutic

What is TX45?

- TX45 is a human relaxin-2-Fc fusion protein designed to prolong its half-life
 - TX-45 has a half life on the order of 2-3 weeks in contrast to serelaxin which had a half-life on the order of hours
- TX45 formulation is 150mg/mL, suitable for subcutaneous administration
- TX45 is being developed by Tectonic Therapeutic for the treatment of PH-HFpEF



TX45 Development Program

Tectonic Has a Potential Best-In-Class Molecule



Phase 1a
Safety, tolerability, PK/PD

Healthy Volunteers

Expected Q3'24
Safety, PK, PD (Renal Blood Flow)

Phase 1b
RHC study to establish hemodynamic proof of concept

Group 2 PH with HFpEF

Expected 2025
mPAP, PVR, PCWP, CO

Phase 2
Randomized, 6-month study

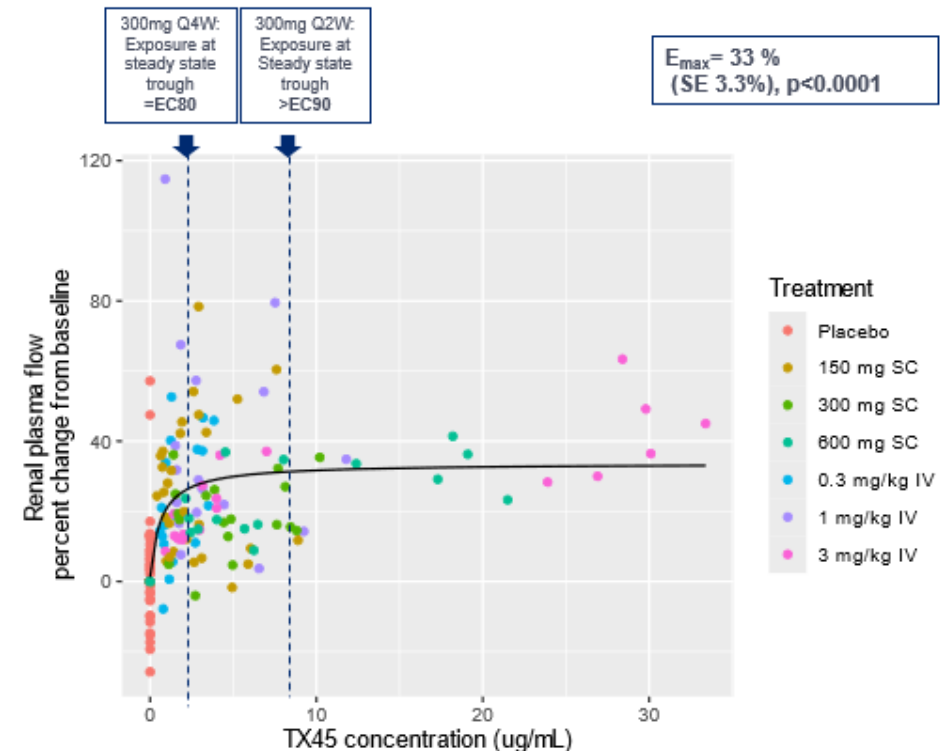
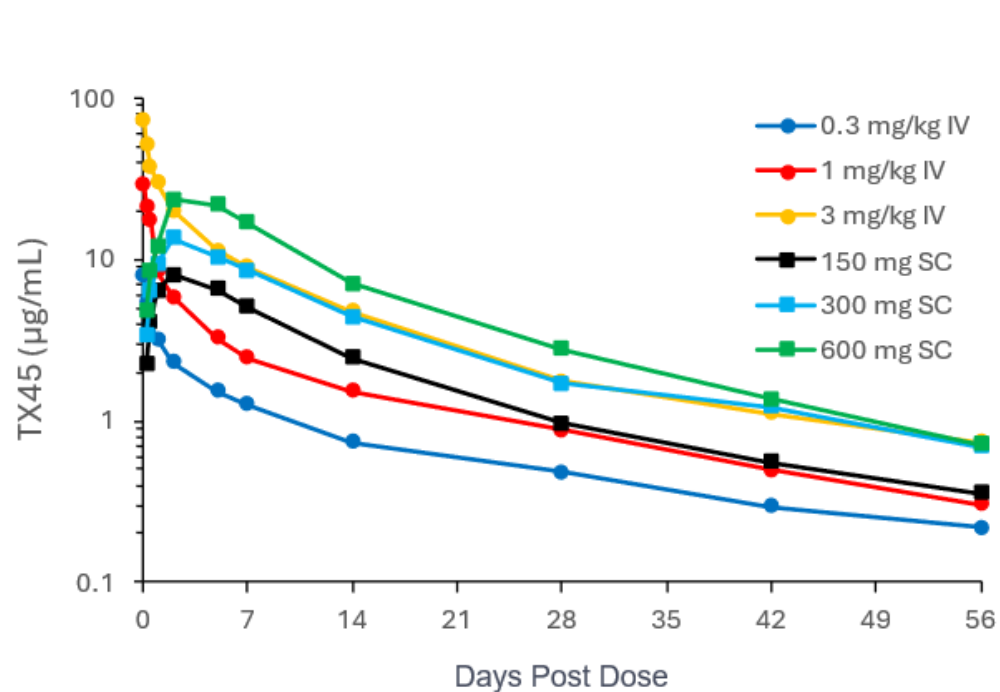
Group 2 PH with HFpEF (enriched for CpcPH)

Expected 2026
PVR, SV, mPAP, 6MWT

RHC: Right Heart Catheter
mPAP: Mean Pulmonary Arterial Pressure
PVR: Pulmonary Vascular Resistance
CO: Cardiac Output

Phase 1a Trial In Healthy Volunteers: Pharmacokinetic and Pharmacodynamic (Renal Plasma Flow) Results

- TX45 was demonstrated to be well-tolerated with no discontinuations, drug-related SAEs, injection-site reactions or ADA; most common AE of orthostatic tachycardia was transient and not associated with change in BP
- TX45 terminal half-life of 2-3 weeks
- TX45 increased renal plasma flow consistent with relaxin mechanism, E_{max} =33% increase in RPF ($p=0.0001$)
- Phase 2 dose selection based on exposure-response relationship: 300 mg Q4W SC achieves EC_{80} at trough, 300 mg Q2W SC achieves $>EC_{90}$ at trough: preclinical data suggest maximal efficacy at exposures $\geq EC_{70}$ RPF

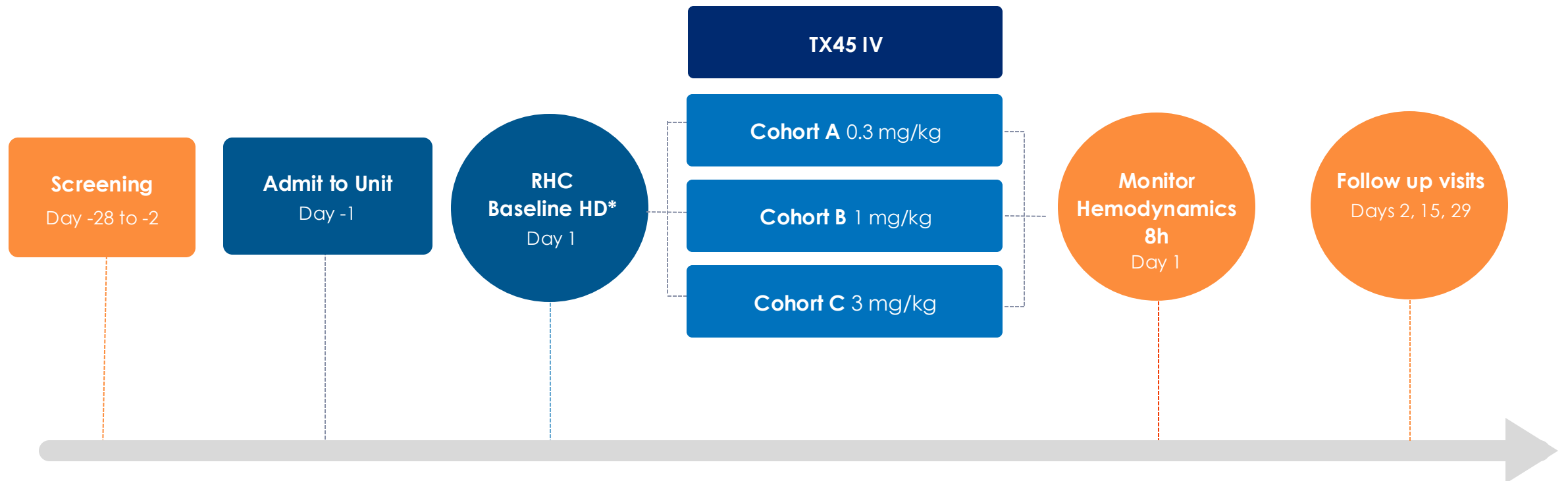


TX45 Phase 1b Trial Design

Open Label Safety and Hemodynamics Trial in PH-HFpEF

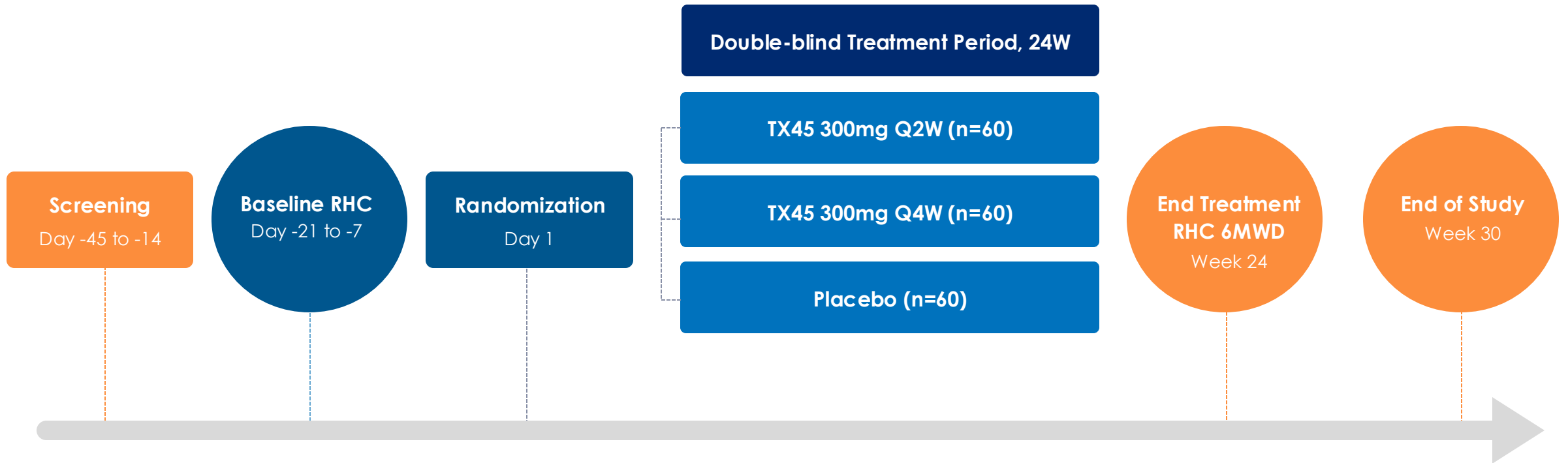
Goal of this study:

- Establish single dose safety
- Demonstrate relevant acute hemodynamic changes consistent with improvement in **both** LV function as well as pulmonary vascular dysfunction



*HD = Hemodynamics

APEX Trial = A Phase 2 Efficacy Study of RelaXin Trial Design



- 1° Endpoint: Change from baseline in PVR
- 2° Endpoints: Change from baseline in PCWP, 6MWD, KCCQ

Positive TX45 Phase 1b Trial Expected to Improve Probability of Success of TX45 in Later Stage Development

GOAL: Treatment for PH-HFpEF needs to **both** increase LV function and improve pulmonary vascular component of the disease

- **Decrease in pulmonary capillary wedge pressure (PCWP)** (~15-20%)
 - PCWP provides insight into left ventricular function and correlates with exercise capacity in HFpEF and HFrEF¹
- **Decrease in pulmonary vascular resistance (PVR)** in patients with CpcPH (~15-20%)
 - PVR is normal in lpcPH, so a floor effect is likely in this subgroup
 - In PAH, a lowering of PVR is associated with improvement in 6MWD²
- **Reduction in total pulmonary resistance (TPR)** in the overall patient population

¹ Wolsk E et al. Eur. J. Heart Fail. 2018

² www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209279Orig1s000MedR.pdf

PCWP has been correlated with 6MWD in HFpEF

- At rest, the only hemodynamic parameter that predicts 6MWD in HFpEF patients is PCWP¹

Table 2 Association of haemodynamic variables with six-minute walk test at rest (n = 64)

	Univariate		Multivariable ($r^2=0.07$, $P=0.03$)	
	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
CVP, mmHg	-5.4 (-12.7, 1.8)	0.14		
mPAP, mmHg	-3.1 (-7.1, 1.0)	0.13		
PCWP, mmHg	-5.4 (-10.4, -0.5)	0.033	-5.4 (-10.4, -0.5)	0.033
CI, L/min/m ²	2.7 (-37.8, 43.2)	0.89		
PVR, Wood units	4.8 (-34.3, 43.9)	0.81		
SVR, dyn x s/cm ⁵	0.0 (-0.1, 0.1)	0.74		
SvO ₂ , %	1.0 (-3.6, 5.5)	0.68		
PCWP/CI, mmHg/L/min/m ²	-9.2 (-20.0, 1.7)	0.097		

CI, cardiac index/confidence interval; CVP, central venous pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SvO₂, mixed venous oxygen; SVR, systemic vascular resistance.

- Elevated PCWP is associated with worse outcomes in HFpEF²
- SGLT2 inhibitors lower wedge and increase 6MWD in HFpEF^{3,4}
 - Improvement with SGLT2 have demonstrated ~20m increase in 6MWD with ~20% decrease in PCWP

¹Wolsk E et al. Eur. J. Heart Fail. 2018

²Mascherbauer J et al., J. Am. Coll. Cardiol. H.F. 2017

³Borlaug BA et al. Circulation 2023

⁴Nassif ME et al. Nat. Med. 2021

PCWP and PVR Correlated with 6MWD in PH-HFpEF

- **Several hemodynamic parameters, including PCWP and PVR, correlated with 6MWD in a PH-HFpEF registry¹**
 - PCWP was highly correlated with 6MWD ($P < 0.001$)
 - PVR and mPAP were also highly correlated with 6MWD ($P < 0.001$)
- **6MWD is also a key predictor of outcomes in PH-HFpEF¹**
 - Outcomes included CV death and HF hospitalization
 - Most significant factor in predicting outcomes for PH-HFpEF was 6MWD
- **Concomitant decreases in both PCWP and PVR were associated with marked improvement in 6MWD in CpcPH patients undergoing surgical Pulmonary Artery Denervation (PADN)²**

¹Zotter-Tufaro C et al. J. Am. Coll. Cardiol. H.F. 2015

²Zhang H et al. JACC Cardiovasc. Interv. 2019

Summary: TX45 is a Potentially Best-in-Class, Long-Acting Relaxin

- TX45 is a long-acting relaxin-Fc fusion protein that has optimized biophysical properties
- TX45 has demonstrated biologic activity with a significant effect on renal plasma flow (RPF) in healthy volunteers
- Phase 1b acute hemodynamic data expected in late 1Q'25 / early 2Q'25
 - Data demonstrating a reduction in PCWP and PVR (in CpcPH patients) should improve the likelihood of success in later stage development
- Phase 2 APEX study is ongoing; aiming to deliver data in 2026



Q&A

All Speakers