Hemodynamic effects of TX45, a long-acting Fc-relaxin fusion, in Group 2 pulmonary hypertension (PH) patients

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Relaxin is a peptide hormone that activates the G protein coupled receptor RXFP1

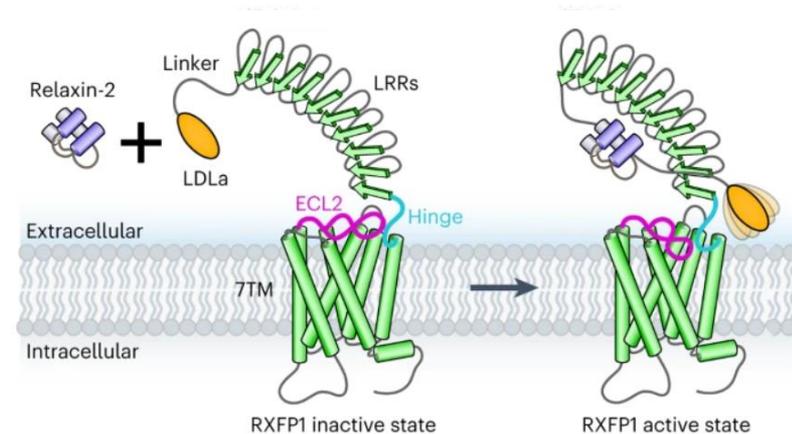- TX45 is a long-acting Fc domain of IgG_1-relaxin fusion protein

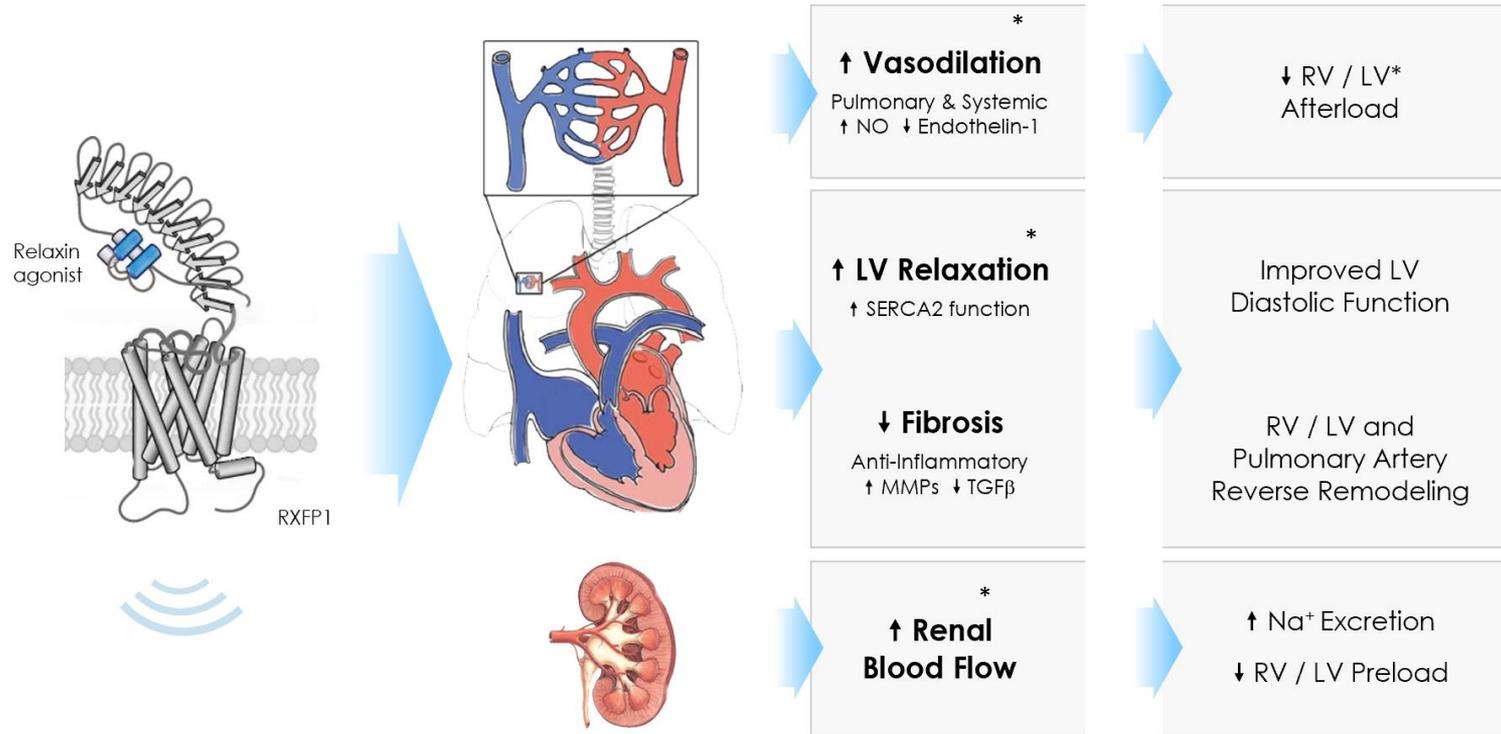## Pharmacology

AGONIST

Natural ligand of RXFP1 receptor

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

Relaxin upregulated in pregnancy

Relaxin is a pulmonary and systemic vasodilator with lusitropic, anti-fibrotic and anti-inflammatory activity

Relaxin agonist

RXFP1

↑ Vasodilation *
Pulmonary & Systemic
↑ NO ↓ Endothelin-1

↓ RV / LV* Afterload

↑ LV Relaxation *
↑ SERCA2 function

Improved LV Diastolic Function

↓ Fibrosis
Anti-Inflammatory
↑ MMPs ↓ TGFβ

RV / LV and Pulmonary Artery Reverse Remodeling

↑ Renal Blood Flow *

↑ Na^+ Excretion
↓ RV / LV Preload

* Acute onset of effect

Phase 1b single ascending dose, open-label acute hemodynamic trial in PH-HF (LVEF>40%, NYHA II/III)

- Pure intention to treat (ITT) analysis performed: all data points included in the analysis.

- Hemodynamic data prespecified to be pooled across all doses. After IV administration, all doses resulted in exposures in the efficacious range throughout the 8-hour assessment period (trough exposure >2 μg/mL).
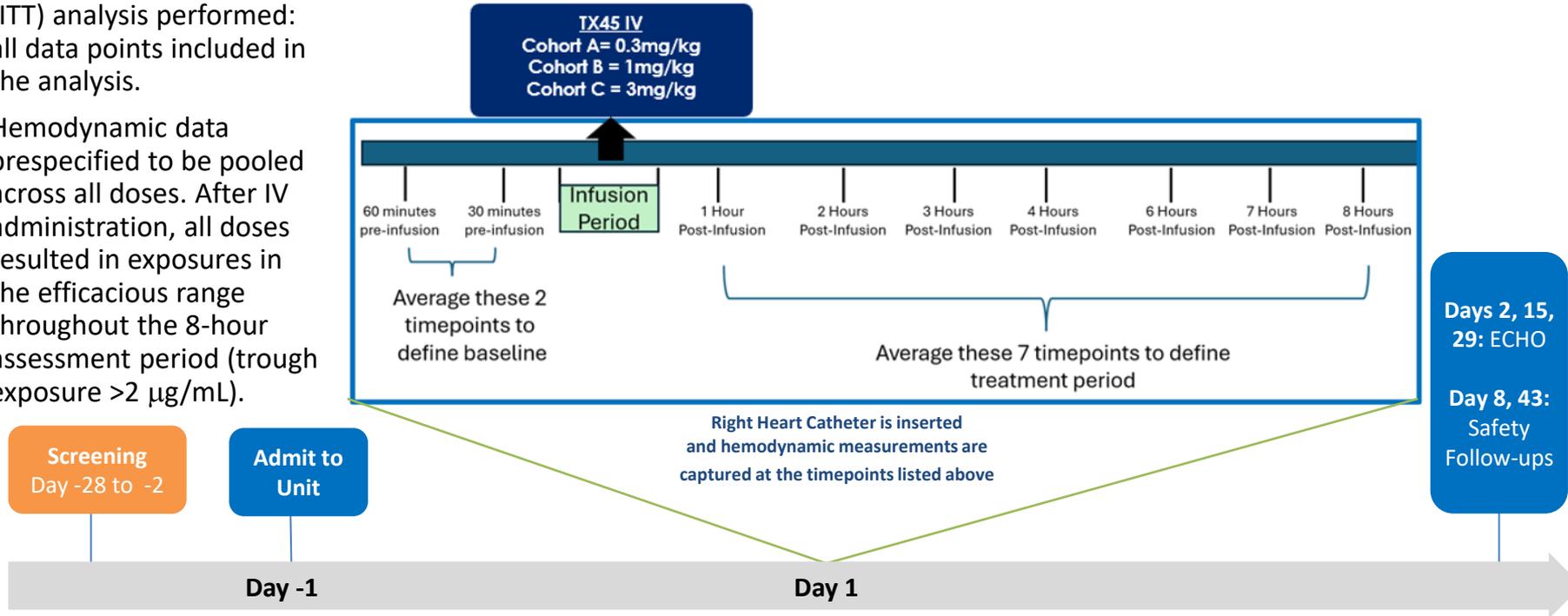
Phase 1b demographics and medical history were consistent with PH-HFpEF/PH-HFmrEF

	All Subjects N = 19
Age (mean, SD)	65.1 (8.7)
Females [n (%)]	7 (36.8%)
BMI (mean, SD)	28.9 (3.6)
Creatinine (uMol/L; mean, SD)	82.7 (18.9)
NT-proBNP (pg/mL)	1347 (1115)
Comorbidities	
Hypertension [n (%)]	16 (84.2%)
Atrial fibrillation [n (%)]	12 (63.2%)
Diabetes mellitus [n (%)]	7 (36.8%)
Coronary artery disease [n (%)]	12 (63.2%)
NYHA Class [n (%)]	
NYHA Class II	12 (63.2%)
NYHA Class III	7 (36.8%)

Key Concomitant Medications	All Subjects N = 19
ACEi/ARB [n (%)]	10 (52.6 %)
MRA [n (%)]	16 (84.2 %)
SGLT2i [n (%)]	8 (42.1 %)
Loop Diuretic [n (%)]	13 (68.4 %)
Beta-blocker	15 (78.9 %)
Digoxin [n (%)]	6 (31.6 %)

Phase 1b - Summary of baseline hemodynamics were consistent with PH-HFpEF/PH-HFmrEF

Parameter	Baseline Value mean (SD)
Heart Rate (bpm)	68.9 (11.4)
Systolic Blood Pressure (mm Hg)	127.8 (11.5)
Diastolic Blood Pressure (mm Hg)	79.0 (6.1)
Right Atrial Pressure (mm Hg)	11.7 (4.6)
Mean Pulmonary Artery Pressure (mm Hg)	27.0 (4.4)
Pulmonary Capillary Wedge Pressure (mm Hg)	17.2 (3.6)
Pulmonary Vascular Resistance (Wood Units)	2.33 (1.06)
Cardiac Output (L/min)	4.48 (1.06)
Stroke Volume mL	66.8 (19.3)
Total Pulmonary Resistance (Wood Units)	6.4 (1.7)
Systemic Vascular Resistance (Wood Units)	20.3 (6.0)

PVR < 2WU	2 WU ≤ PVR < 3WU	PVR ≥3 WU
10	4	5

CpcPH defined as PVR ≥ 2 WU:
IpcPH = 10
CpcPH = 9

CpcPH defined as PVR ≥ 3 WU:
IpcPH = 14
CpcPH = 5

Phase 1b - TX45 was well-tolerated

- There were 10 treatment-emergent adverse events (TEAEs) in 8 patients – all mild/moderate and self-limited

- There were no serious or severe adverse events, discontinuations, infusion reactions or drug related adverse events

- There were no clinically significant changes in vital signs, ECG or safety laboratory values, including hemoglobin

- Transient effects on blood pressure:
  - Mild acute drop of systemic blood pressure (5-10 mmHg) on D1 were similar across a 10-fold dose range
  - Systemic blood pressure was at baseline on Day 8 follow up visit in all subjects

Treatment-emergent adverse events (# of subjects)				
Preferred Term	Cohort A 0.3 mg/kg (n=3)	Cohort B 1 mg/kg (n=7)	Cohort C 3 mg/kg (n=9)	Total N=19
Fatigue	0	0	4	4 (21.1%)
Back pain	0	1	1	2 (10.5%)
Nasopharyngitis	0	0	1	1 (5.3%)
Gout (worsening)	0	1	0	1 (5.3%)
Viral infection	0	0	1	1 (5.3%)
Procedural pain	0	0	1	1 (5.3%)

- TEAE of fatigue:
  - All occurred in the evening of D1 (<3 hr duration)
  - Investigator reported as "non-drug related"
  - No fatigue after D1 despite high drug levels

TX45 improved hemodynamics in PH-HF patients

Secondary Endpoints	CFB^ mean [95% CI]	Average % CFB^ mean [95% CI, P-value^]
Hemodynamics (Key 2°) (N = 19)		
Mean Δ PCWP in all participants	- 3.2 [-4.3 to -2.1,***]mm Hg	**-19.0% [-26.1 to -11.9%,***]**
Mean Δ PVR in CpcPH (PVR ≥ 2 WU) (n= 9)	- 1.06 [-1.34 to -0.78,***]WU	**-32.0% [-35.9 to -28.1%,***]**
Mean Δ PVR in CpcPH (PVR ≥ 3 WU) (n= 5)	- 1.35 [-1.55 to -1.15,***]WU	**-35.5% [-38.6 to -32.5%,***]**
Other Hemodynamic Effects		
Mean Δ Cardiac Output in all participants	+0.73 [0.39 to 1.08,***]L/min	**+18.54% [10.2 to 26.9%,***]**
Mean Δ Stroke Volume in all participants	+7.4 [2.9 to 11.9,**]mL	**+14.3% [6.0 to 22.7%,**]**
Mean Δ TPR in all participants	-1.89 [-2.42 to -1.36,***]WU	**-28.7% [-34.1 to -22.1%,***]**
Mean Δ mPAP in all participants	-4.63 [-5.77 to -3.48,***]WU	**-16.8% [-20.8 to -12.8%,***]**
Mean Δ SVR in all participants	-3.95 [-5.82 to -2.08,***]WU	**-16.6% [-24.4 to -8.83%,***]**

^, CFB = Change from Baseline = (Average of Hours 1-8) – Baseline. Nominal P-Values were determined by T-Test (*, P<0.05; **, P<0.01; ***, P<0.001).
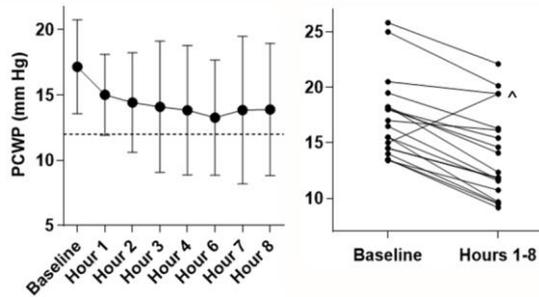
Phase 1b results

TX45 reduced PCWP in both IpcPh and CpcPH patients; TX45 improved PVR in CpcPH patients

Change in PCWP All Subjects*

PCWP in All Subjects (N=19)
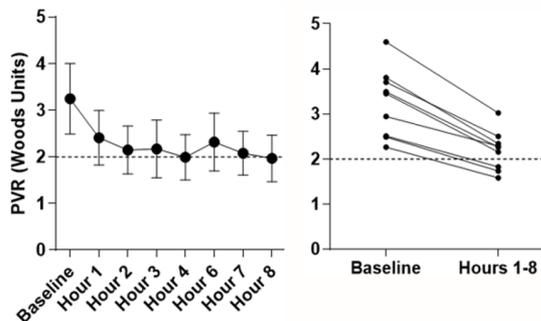Mean ΔPCWP = -3.2 [-4.3 to -2.1] mmHg
Average % CFB = -19.0 [-26.1 to -11.9]

^The only patient with increased PCWP post treatment had a PCWP greater than dPAP suggesting a technical issue

Change in PVR by baseline PVR*

PVR in Subjects with Baseline PVR≥2 WU (N=9
Mean ΔPVR = -1.06 [-1.34 to -0.78] WU
Average % CFB = -32.0 [-35.9 to -28.1]

PVR≥2 (CpcPH): All subjects had decreased PVR w/ TX45

PVR in Subjects with Baseline PVR<2 WU (N=10)
Mean ΔPVR = -0.18 [-0.64 to +0.27] WU
Average % CFB = -0.3 [-43.4 to +42.8]
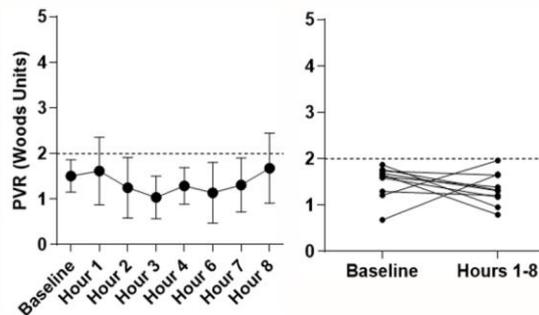
PVR<2 (IpcPH): No change in PVR w/ TX45

Group averages reported as mean [95% CI]. Parameter vs. time plots show mean ± SD. Spaghetti plots show average baseline values and average of Hours 1-8 for each participant.

Phase 1b results

TX45 increased cardiac output; enhanced in patients with higher baseline PVR

Cardiac Output				
	Baseline (L/min) mean (SD)	Treatment Period (L/min) mean (SD)	Absolute CFB (L/min) mean [95% CI]	Average % CFB mean [95% CI]
All subjects (N = 19)	4.48 (1.06)	5.21(1.04)	+0.73 [0.39 to 0.72]	+18.5% [10.2 to 26.9%]
Baseline PVR < 2 WU (N=10)	4.83 (0.84)	5.59 (1.03)	+0.76 [0.12 to 1.40]	+16.8% [3.7 to 29.9%]
Baseline PVR ≥ 2 WU (N = 9)	4.08 (1.19)	4.79 (0.93)	+0.70 [0.30 to 1.10]	+20.5% [7.3 to 33.6%]
Baseline PVR ≥ 3 WU (N = 5)	3.62 (0.94)	4.46 (1.00)	+0.84 [0.35 to 1.32]	+24.5% [7.4 to 41.5%]

TX45 hemodynamic effects were similar in subjects with HFmrEF and HFpEF

|	CFB* mean [95% CI]	Average % CFB* mean [95% CI]
PCWP (N = 19)		
Mean Δ PCWP in all participants	- 3.2 [-4.3 to -2.1] mm Hg	**-19.0% [-26.1 to -11.9%]**
Mean Δ PCWP in HFpEF (LVEF ≥ 50%) (N = 9)	- 3.6 [-4.3 to -3.0] mm Hg	**-19.7% [-23.9 to -15.5%]**
Mean Δ PCWP in HFmrEF (LVEF 41-49%) (N = 10)	- 2.8 [-4.2 to -1.4] mmHg	**-18.4% [-27.5 to -9.4%]**
Cardiac Output (N=19)		
Mean Δ Cardiac CO in all participants	+0.73 [0.4 to 1.1] L/min	**+18.5% [10.2 to 26.9%]**
Mean Δ CO in HFpEF (N = 9)	+0.73 [0.3 to 1.2] L/min	**+18.3% [9.1 to 27.5%]**
Mean Δ CO in HFmrEF (N = 10)	+0.74 [0.43 to 1.1] L/min	**+18.7% [11.0 to 26.4%]**

CFB = Change from Baseline = (Average of Hours 1-8) - Baseline

- Changes in pulmonary hemodynamics similar in PH-HFmrEF vs. PH-HFpEF

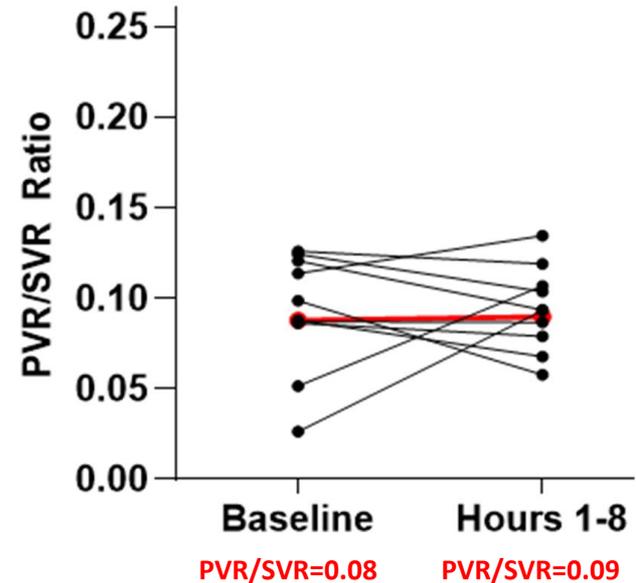Heart Failure 2025
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Phase 1b results

PVR/SVR ratio: TX45 preferentially dilates pulmonary vessels in CpcPH, is a balanced vasodilator in IpcPH

PVR/SVR Ratio in Subjects with Baseline* PVR ≥ 2 WU (n= 9)

PVR/SVR Ratio in Subjects with Baseline* PVR < 2 WU (n= 10)
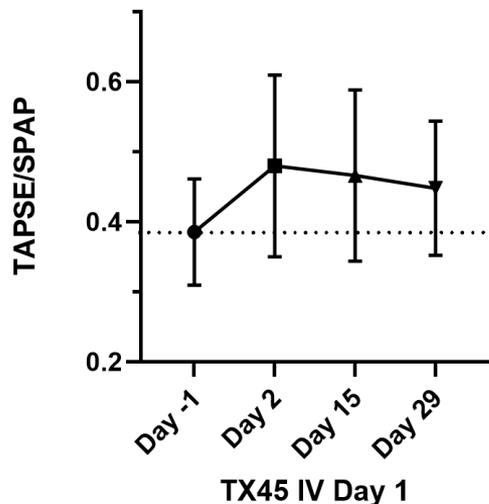
PVR/SVR=0.15   PVR/SVR=0.12

PVR/SVR=0.08   PVR/SVR=0.09
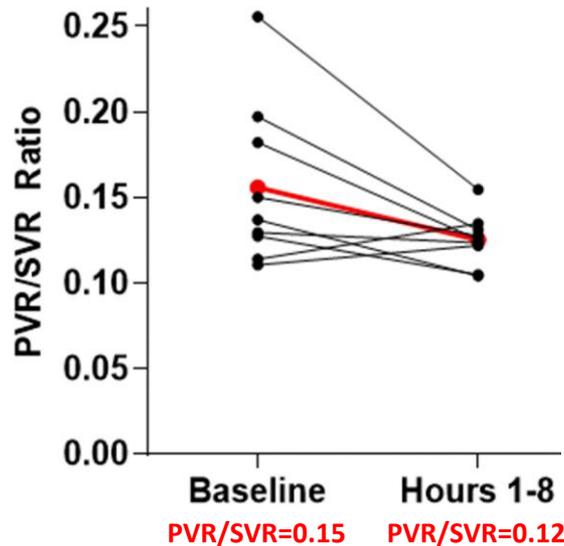
Mean PVR/SVR at baseline and at Hours 1-8 is in red

Echo results suggest sustained improvement in hemodynamics with TX45

- TX45 administration increased tricuspid annular plane systolic excursion/systolic pulmonary artery pressure (TAPSE/SPAP) and RV fractional area of change (RVFAC)
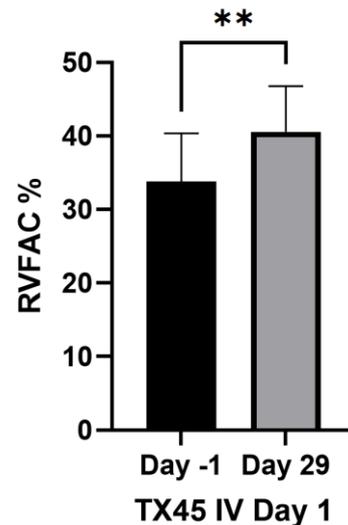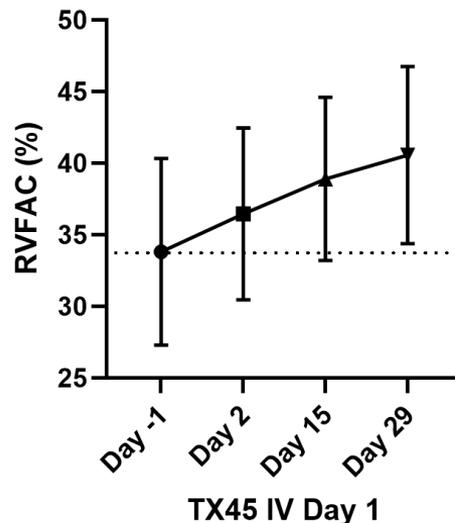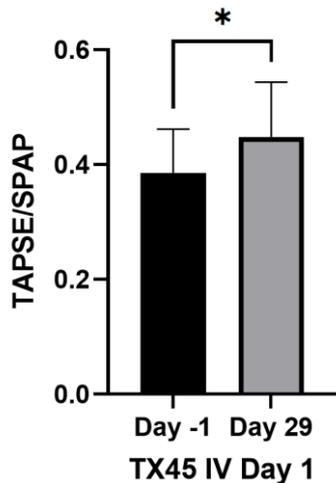
*Nominal P<0.05, **Nominal P<0.01 for treated (Day 29) versus baseline (Day -1)*

Conclusions

- In this open-label single ascending dose study, TX45 was well-tolerated in Group 2 PH patients with HF (LVEF>40%)

- TX45 administration resulted in acute hemodynamic improvement, including decreased PCWP, mPAP, and TPR, and increased CO and SV in entire cohort

- TX45 decreased PVR in CpcPH patients, but not IpcPH patients where PVR is normal

- Echocardiographic analysis suggested sustained improvements in hemodynamics with single dose TX45

- A randomized, placebo-controlled, double-blind Phase 2 study in PH-HF (LVEF>40%) with TX45 is ongoing (APEX trial)