Transforming the Discovery of Novel GPCR-Targeted Therapies

JANUARY 2024

TECTONIC Therapeutic

AVROBIO

DISCLAIMER

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Additional Information and Where to Find It

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Transforming the Discovery of Novel GPCR-Targeted Therapies

JANUARY 2024

TECTONIC Therapeutic

Merger of Tectonic Therapeutic and AVROBIO

OVERVIEW

- Tectonic Therapeutic, a privately-held biotechnology company focused on discovering and developing GPCR-targeted therapies, intends to merge with AVROBIO, Inc. (Nasdaq: AVRO)
- Supported by the Board of Directors of both companies and subject to stockholder approval and other customary closing conditions

TRANSACTION SUMMARY

- Planned $130.7 million private financing from new and existing leading life sciences investors, together with existing cash from both companies at closing, expected to be approximately $165 million and provide cash runway into mid-2027
- Expected pro forma ownership is approximately 40% pre-merger Tectonic shareholders, 22% pre-merger AVROBIO shareholders, and 38% purchasers in the private financing
- Merger and financing expected to close in Q2 2024

MANAGEMENT

- Existing Tectonic management to lead the combined company
- Board of Directors of combined company will include one director from the AVROBIO BOD

Tectonic Therapeutic – Transforming the Discovery of Novel GPCR-Targeted Therapies, Innovating in Their Development

- Validated platform to discover and optimize biologics that target GPCRs
- Prioritizing high value GPCR targets, where small molecules are not the right modality
- First two assets address indications with no approved therapy
  1. RXFP1 agonist - potential therapy for Group 2 PH[1] in HFpEF[2]
     - >600,000 Patients in US alone (>20 times PAH)
     - Initial Phase 1A PK/PD data demonstrated activity and favorable PK with potential for monthly dosing; full data set from this study expected by mid 2024
     - Phase 1B hemodynamic proof of concept expected in 2025, randomized Phase 2 data expected in 2026
  2. GPCR antagonist antibody addressing hereditary hemorrhagic telangiectasia (HHT)
- Team with extensive track record of drug discovery and development success, resulting in 20 first approvals across multiple therapeutic areas
- Well capitalized by a syndicate of leading institutional funds
- **Transaction expected to provide runway into mid-2027**

1. Pulmonary Hypertension
2. Heart Failure with Preserved Ejection Fraction

TECTONIC Therapeutic

Our Team Has Delivered for Patients and Investors

Alise Reicin, M.D.
CEO, Director

Celgene · MERCK · EMD SERONO · Columbia University · Harvard

Christian Cortis, Ph.D.
COO

agenus · SYNTA PHARMACEUTICALS · GEMINX · ATV Advanced Technology Ventures · Booz | Allen | Hamilton · Columbia University

Peter McNamara, Ph.D.
CSO

NOVARTIS · GNF · Penn University of Pennsylvania · Harvard

Anthony Muslin, M.D.
CDO

NOVARTIS · SANOFI · Washington University in St. Louis School of Medicine · Harvard

Marcella Ruddy, M.D.
CMO

REGENERON · MERCK · Alnylam Pharmaceuticals · Washington University in St. Louis School of Medicine · Harvard

Marc Schwabish, Ph.D.
CBO

Fusion Pharmaceuticals · BAYER · Eisai · LEERINK SWANN · RBS · Harvard

Timothy Springer, Ph.D.
Co-Founder

FOUNDED MULTIPLE SUCCESSFUL COMPANIES

LeukoSite · moderna · MORPHIC THERAPEUTIC · SEISMIC THERAPEUTIC · Scholar Rock

2022 Lasker Award

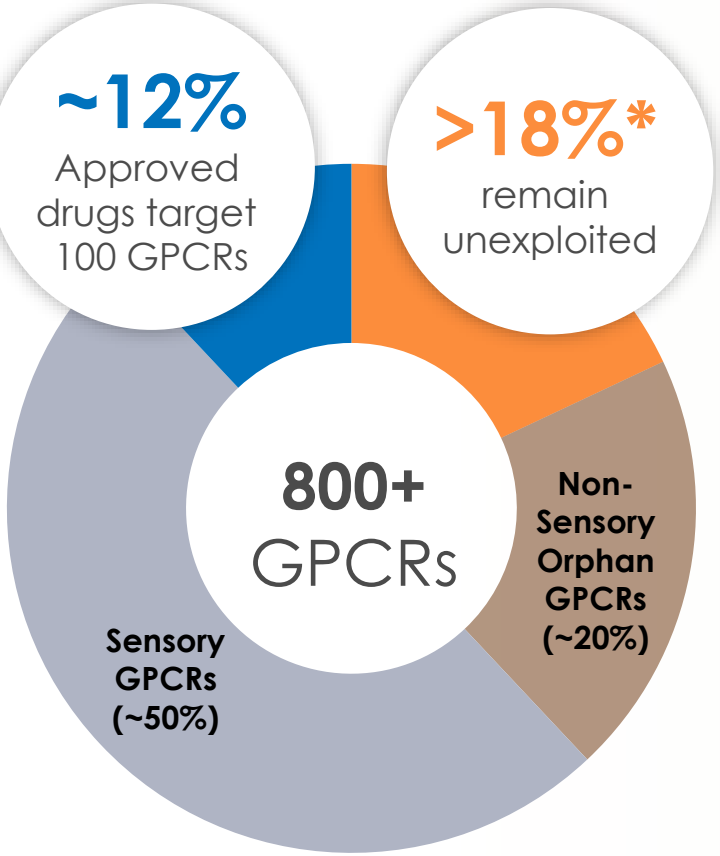
Andrew Kruse, Ph.D.
Co-Founder

GPCR EXPERT, FORBES "30 under 30"

HARVARD MEDICAL SCHOOL · SEISMIC THERAPEUTIC

Multiple Awards and Fellowships
(Biomedical Research, NIH, Amgen, Sloan Research)

Biologics Offer Advantages Over Small Molecules in Targeting GPCRs in Multiple Settings



- **>470 Approved drugs (~33% of all)**
- **>$180B in annual sales**
- **Predominantly small molecules**
- **Address broad range of therapeutic areas**
- **Only 3 are antibodies**

→ **When difficult to drug with small molecules**
Biologic captures complexity of ligand / receptor engagement

→ **If target site similar to domains of different proteins**
Biologic minimizes off target binding to improve safety / tolerability

→ **If use case requires tissue /compartment targeting**
Engineer biologic to target or exclude compartment as needed

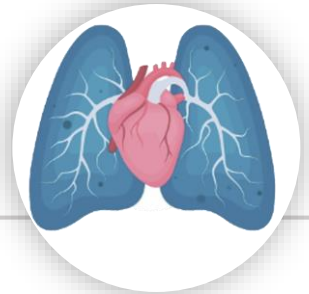
→ **When multi-modal action needed**
Bispecific approach enables dual target engagement

(*) Hauser, A.S. et al., Cell. 2018 Jan 11; 172(1-2): 41–54.e19.

* 18% = 100% - 12% (approved drug targets) – 50% (sensory) – 20% (non-sensory, orphan)

TECTONIC Therapeutic

Our Unique Pipeline Opportunities are Enabled by Biologic Targeting of GPCRs

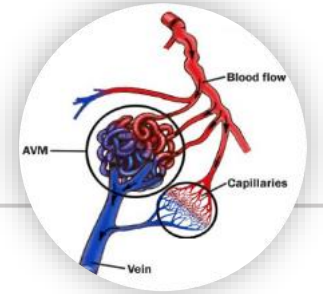


GROUP 2 PULMONARY HYPERTENSION (Group 2 PH)

Potential Best-in-Class

RXFP1 Agonist[1]

Supporting clinical data

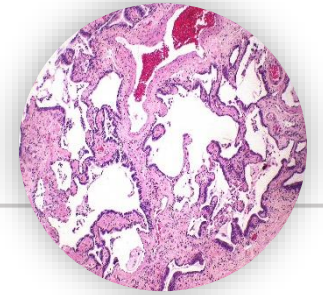


HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

First in Class & Indication

GPCR Antagonist[2] (anti-angiogenic)

Target pathway linked to disease genetics



FIBROSIS

Bi-specific Approach

GPCR Antagonist[2] (anti-fibrotic)

Supporting clinical data for one component of bispecific

Scale of POC studies: ~50-200 patients per indication
3-6 months treatment

1. Fusion protein – lead molecule in-licensed from Harvard U., optimized using GEODe platform
2. GPCR targeted mAbs discovered internally using GEODe platform

TECTONIC Therapeutic

Post Close Cash to Support Pipeline Progression Into Mid-2027 and Several Key Inflection Points

Tectonic Pipeline and Expected Readouts

RXFP1 Agonist (TX45 – Fc-relaxin)	Phase 1a	• Complete PK/PD Data: mid 2024 • Ph 1b hemodynamic proof of concept data: 2025 • Randomized Ph 2 data: 2026
GPCR Antagonist (HHT Program)	Development Candidate Selection	• Start of Ph 1: Q4 2025 / Q1 2026 • Start of randomized studies: ~Q4 2026
GPCR Antagonist (Fibrosis Program)	Discovery	• Develop internally or partner
GPCR Modulators (Undisclosed)	Discovery	• Develop internally or partner

[1]Includes in vivo HHT validation

TECTONIC Therapeutic

GEODe Designed to Solve Key Challenges in GPCR Targeted Biologics Discovery

Challenges

RETAIN
endogenous GPCR structure to enable screening against relevant form of receptor

PURIFY
target in sufficient quantities to power screening campaign

INDUCE
immune response to human GPCR in animals if immunization strategy is pursued

STABILIZE
receptor in active conformation to enable agonist discovery

GEODe™ Platform Features Designed for Success

1.
Receptor Engineering, and Purification Technology
delivers abundant receptor reagent in native conformation

2.
In-vitro Yeast Display Libraries
provide high-diversity, without immune editing

3.
Protein Engineering
Optimize protein pharmacology
Engineer antigen formats to enable screening for agonists or antagonists as needed

TX45: Fc-RELAXIN FUSION PROTEIN

RXFP1 agonist with differentiated profile

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

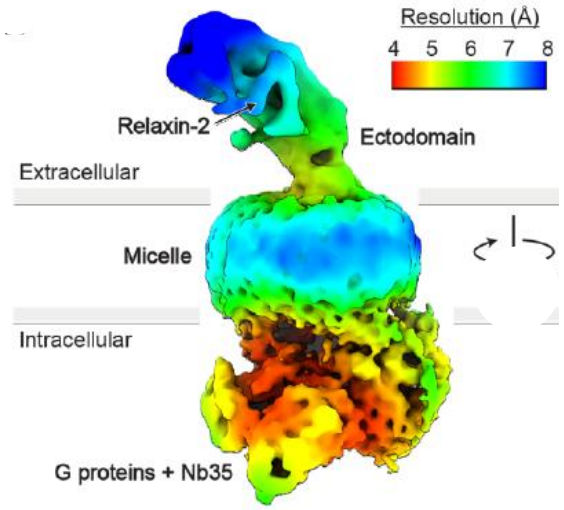
Pharmacology

AGONIST

Natural Ligand of RXPF1 Receptor

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

Relaxin upregulated in pregnancy



Local resolution cryo-EM map of full-length RXFP1–Gs complex
BioRxiv: https://doi.org/10.1101/2022.01.22.477343

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

Pharmacologic properties of relaxin hold promise as a potential treatment for cardio-pulmonary and renal disease, but its short half-life has impeded its development

Evidence of Serelaxin's Safety and Benefit in Acute Heart Failure (AHF)

- A meta-analysis of 6 studies and >11,000 patients demonstrated that **a 2-day infusion of serelaxin was safe and resulted in a 23% decrease in 5-day worsening heart failure**

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

  - It was ambitious to expect that a two-day infusion of serelaxin, with its short half-life and mechanism of action, would demonstrate clinical benefit at day 5 and, more puzzlingly at 6 months
  - Operational challenges with patient enrollment may also have had an impact

- Limitations of serelaxin's PK inhibited further development, but **its clinical performance supports advancement of TX45 whose PK profile permits chronic dosing for chronic diseases** such as pulmonary hypertension and heart failure

*Teerlink J.R. et al. Eur. J. Heart Fail. 2019; 22: 315-329; patients from RELAX-AHF-JP (N=30 total) not listed in table

TX45 is Engineered to Solve a Critical PK Problem Observed with Other Relaxin Molecules

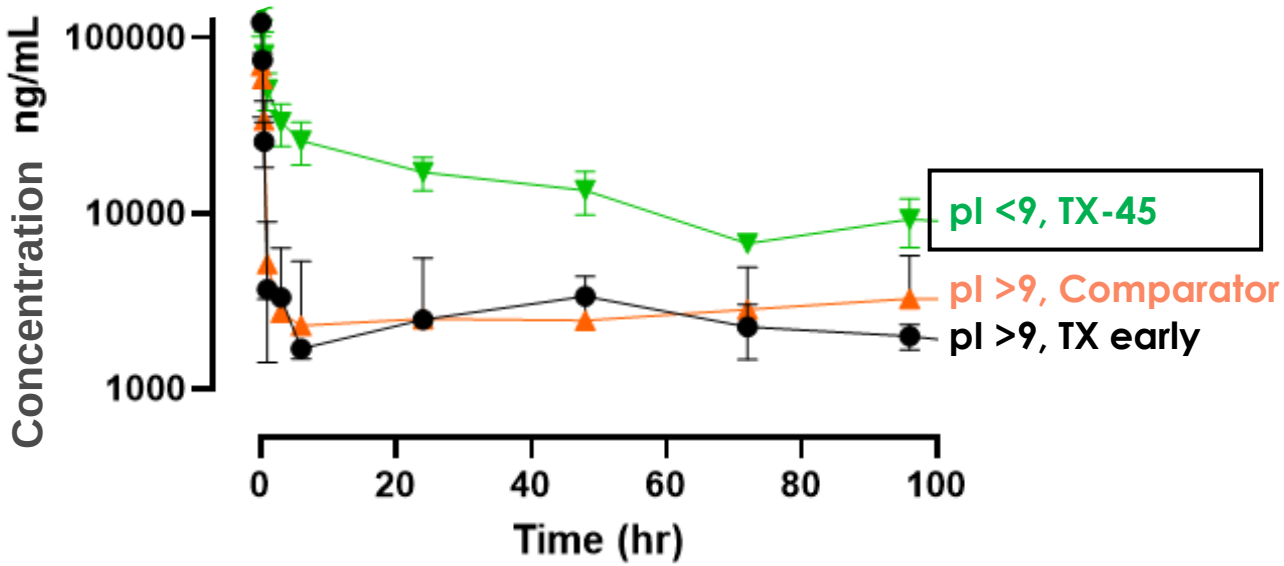
Relaxin has **very short *in vivo* half-life** Fc-fusion needed to improve PK

Relaxin Fc-fusions **have steep decline in exposure after dosing** (>90%) because of glycocalyx binding due to high pI[1]

Engineering TX45 to **reduce net positive charge (and lower pI) prevents rapid clearance**

TX45 EXHIBITS SUPERIOR PROFILE vs. PARENT COMPOUND AND COMPARATOR[2] MOLECULE[3]

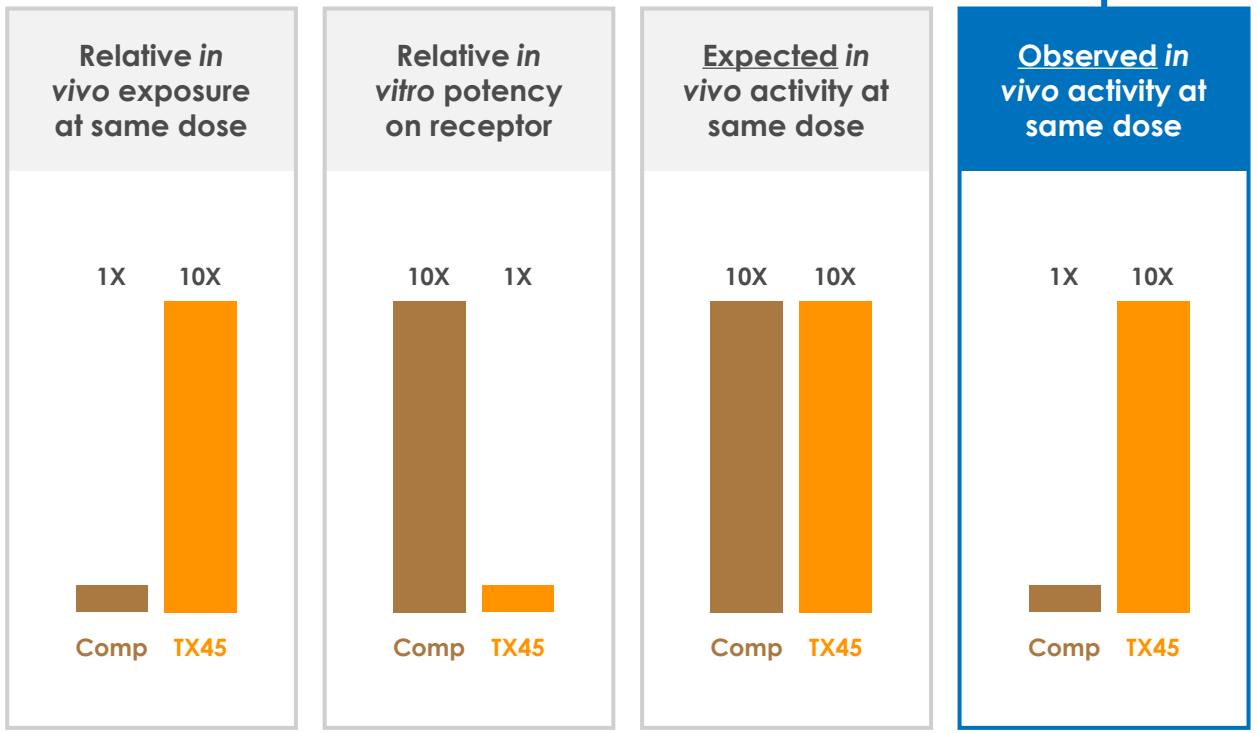
Preclinical Rat Pharmacokinetic Data

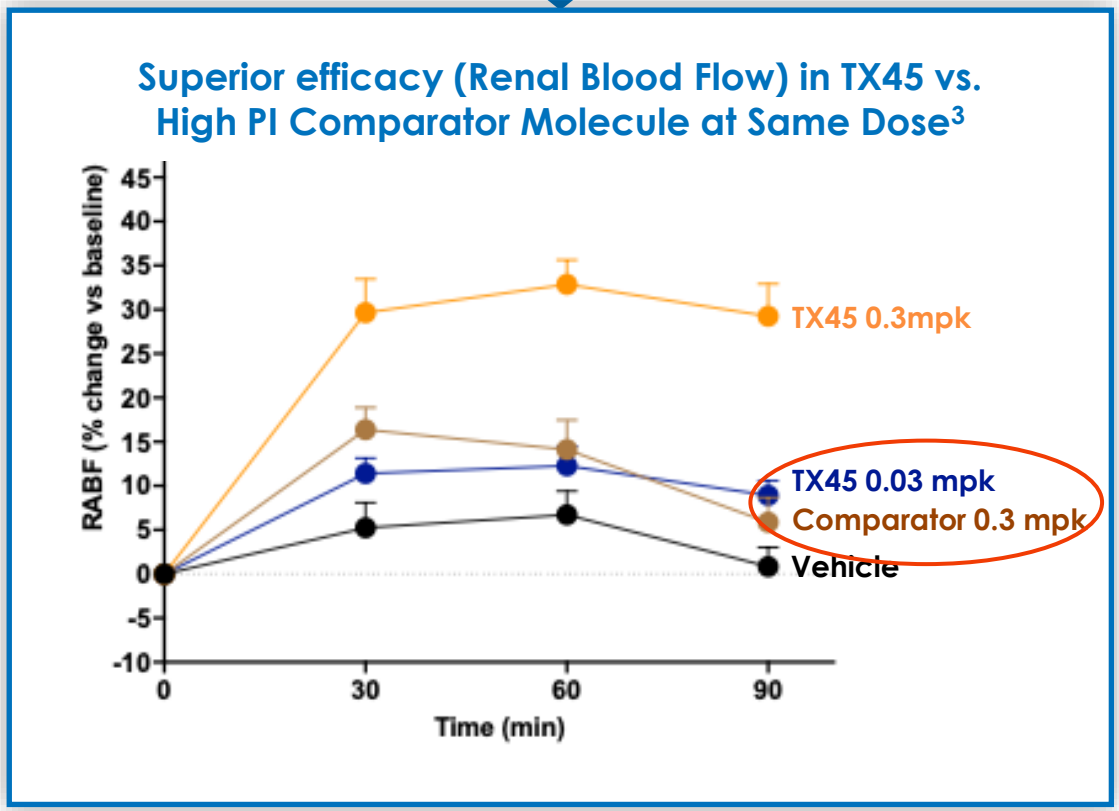


1. Isoelectric Point
2. High pI Fc-relaxin fusion protein described in literature
3. Source: Tectonic internal data

TX45 Reflects Significant Protein Engineering to Optimize Its Pharmacology

TX45 results in ~10x greater *in vivo* potency over comparator[1] molecule than predicted based on PK and *in vitro* activity[2] – potentially from reduced trapping of drug in glycocalyx, resulting in increased free drug available to activate RXFP1 in tissues





1. High pI Fc-relaxin fusion protein described in literature

2. ~0.03 mpk of TX45 has similar efficacy as 0.3 mpk of Comparator

3. Source: Tectonic internal data

TECTONIC Therapeutic

TX45 – Optimized RXFP1Agonist for Group 2 PH in HFpEF

✓ **Potential Best-in-Class Relaxin Agonist with Optimized PK**	• Protein engineering has extended pharmacologic half-life to support monthly dosing
✓ **High Unmet Need in Group 2 PH with HFpEF[1]**	• No approved therapy • >600,000 patients in US • High 5-year high mortality
✓ **Mechanism may be Ideal to Address Group 2 PH**	• Pulmonary + systemic vasodilation, cardiac relaxation • Reversal of fibrosis in pulmonary vasculature and heart • Anti-inflammatory
✓ **Supporting Clinical and Pre-clinical Data**	• Hemodynamic benefit in studies of serelaxin in AHF • Clear benefit observed with TX45 in rodent PH and CHF models
✓ **Streamlined Development Strategy**	• No outcome study needed • Enrichment strategy for CpcPH where there is greatest unmet need • Enables potential early launch relative to congestive heart failure
✓ **Potential to Expand Indications**	• Other PH Groups, Heart failure, renal disease

1. Heart Failure with preserved Ejection Fraction

Pulmonary Hypertension Consists of 5 Distinct Diseases

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

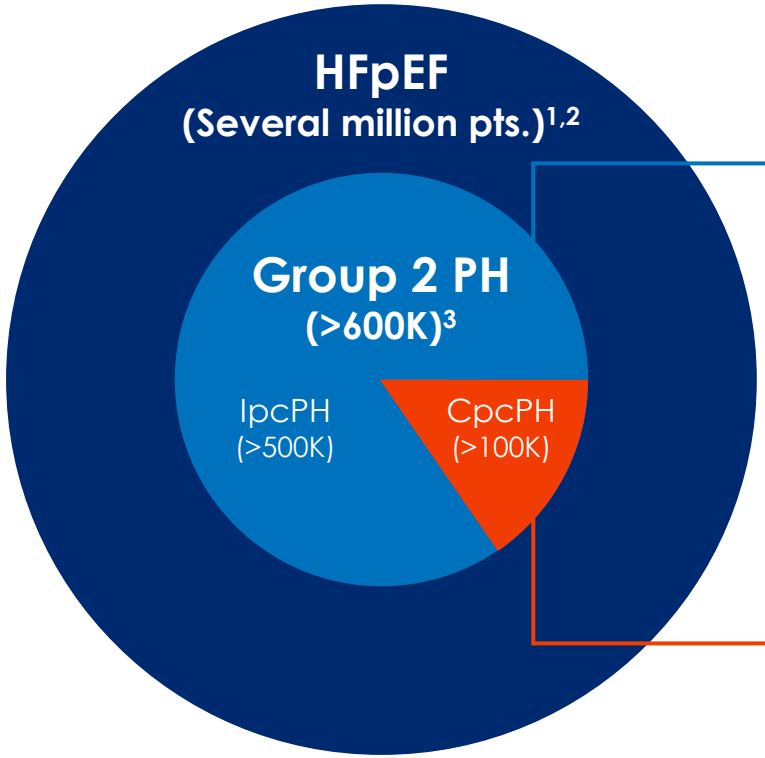
Group 1 ("PAH") (~25,000[1])	Group 2 (>600,000[1])	Group 3	Group 4 ("CTEPH")	Group 5 (Misc.)
• Idiopathic • Hereditary • Connective tissue disease-associated • Congenital heart disease-associated • Drug-induced	• **Due to left heart disease (HFpEF, HFrEF) or valvular heart disease** • **CAD, HTN, T2DM[2], high cholesterol are risk factors** • **Two Subtypes: CpcPH / IpcPH**	• Due to lung disease or hypoxia • May be due to COPD, interstitial lung disease (i.e., IPF) or obstructive sleep apnea	• Chronic thrombo-embolic pulmonary hypertension –i.e., as a consequence of blood clots	• Miscellaneous group with causes unclear or multiple underlying factors

1. US Prevalence
2. CAD: Coronary Artery Disease, HTN: Hypertension, T2DM: Type 2 Diabetes Mellitus

Nat. Pul. Hypertension Unit, Ireland

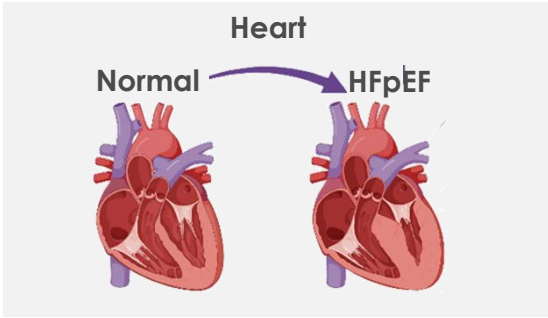
Our Focus is on the Group 2 PH Subset of Heart Failure with Preserved EF (HFpEF)

Clinical Program Designed to Enable Evaluation of Efficacy in Each Subgroup



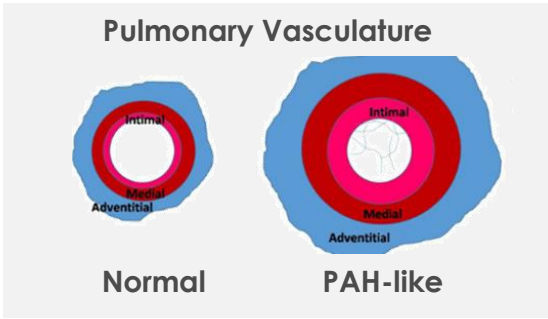
IpcPH (**I**solated, **p**ost **c**apillary **PH**)

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

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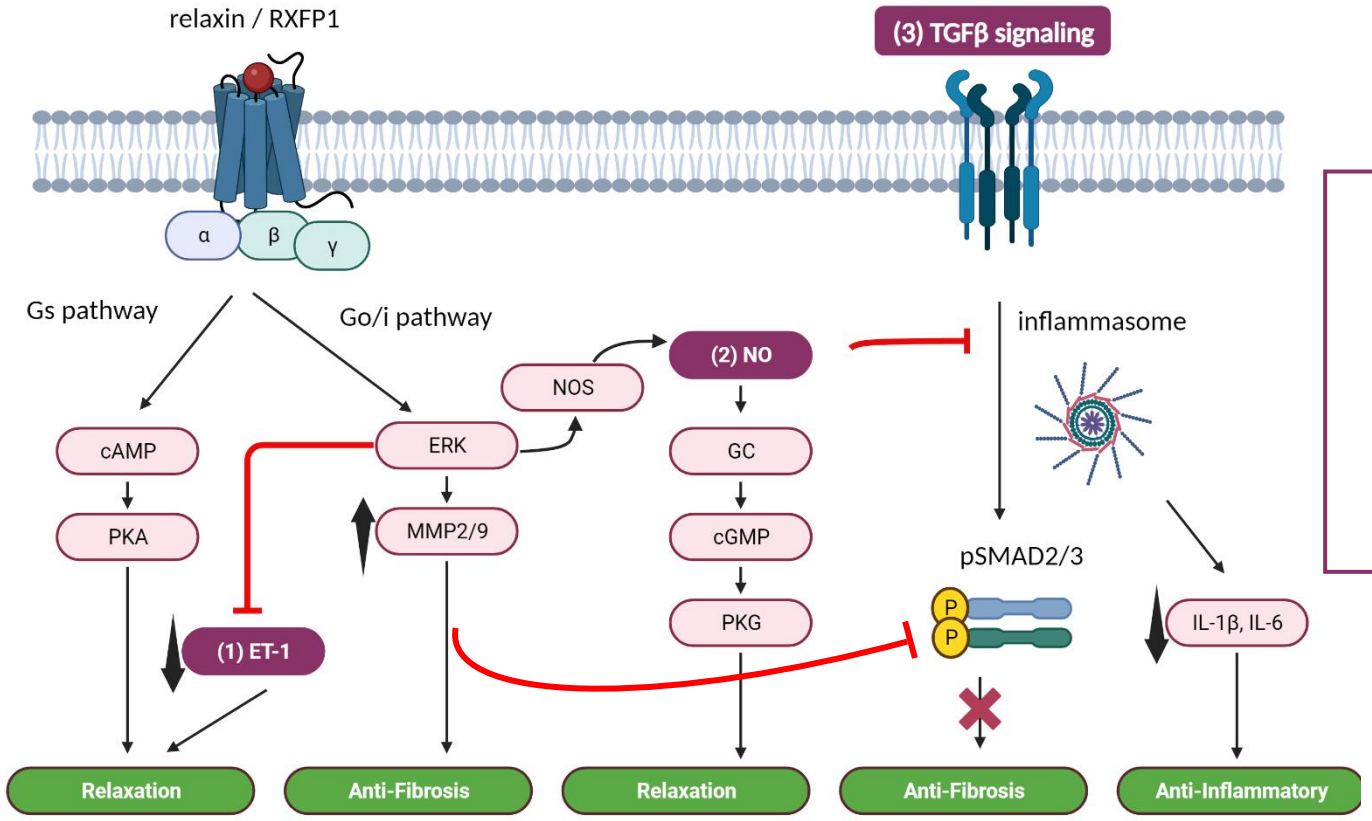
Relaxin Multimodal MOA Addresses Pathways Implicated in Group 2 PH Pathophysiology



Mechanisms Implicated in Group 2 PH

1. Activation of ET-1 pathway(*)
2. Reduced NO pathway activity(*)
3. Activation of TGFβ pathway

(*) Most active in CpcPH subset

Effects of RXFP1 Activation by Relaxin

- ✓ Pulmonary and systemic arterial vasodilation
- ✓ Favorable remodeling: anti-fibrotic effect in heart and pulmonary vasculature
- ✓ Anti-inflammatory

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Relaxation and Anti-Fibrotic Effects of Relaxin Have Potential for Disease Modification in Group 2 PH

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

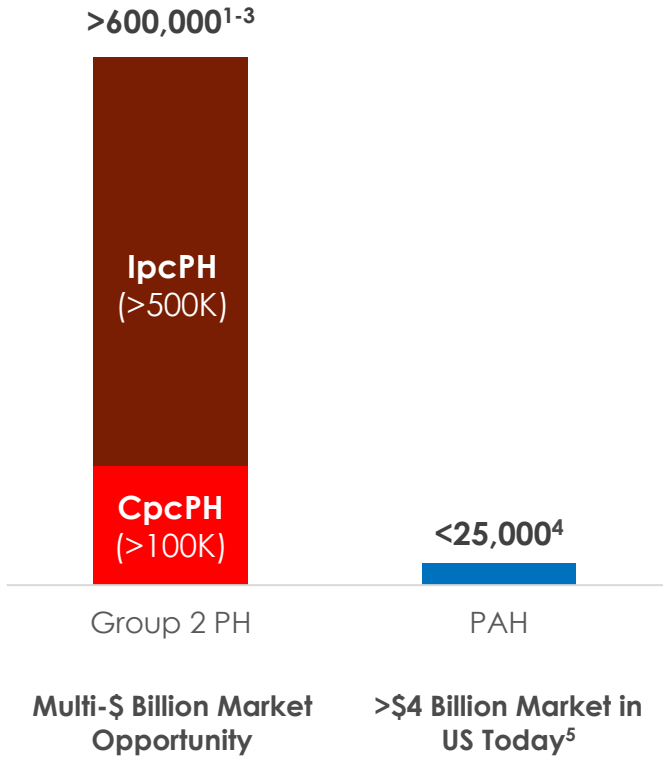
CHARACTERISTICS OF GROUP 2 PH	IpcPH	CpcPH	ANTICIPATED RELAXIN EFFECTS
Pulmonary artery narrowing, thickening, stiffening, fibrotic remodeling		✓	Pulmonary Vasodilation Anti-inflammatory, anti-fibrotic
Right Ventricular Dysfunction	✓	✓	Right ventricular remodeling
Thickening and stiffening of Left Ventricle	✓	✓	Peripheral vasodilation, cardiac relaxation, left ventricular remodeling
Compromised kidney function	✓	✓	Improvement in kidney function

Balanced vasodilation in pulmonary and peripheral vasculature needed for safety and efficacy

Group 2 PH vs. PAH

- Significant opportunity for a first-in-indication therapy
- Highly motivated physicians and patients

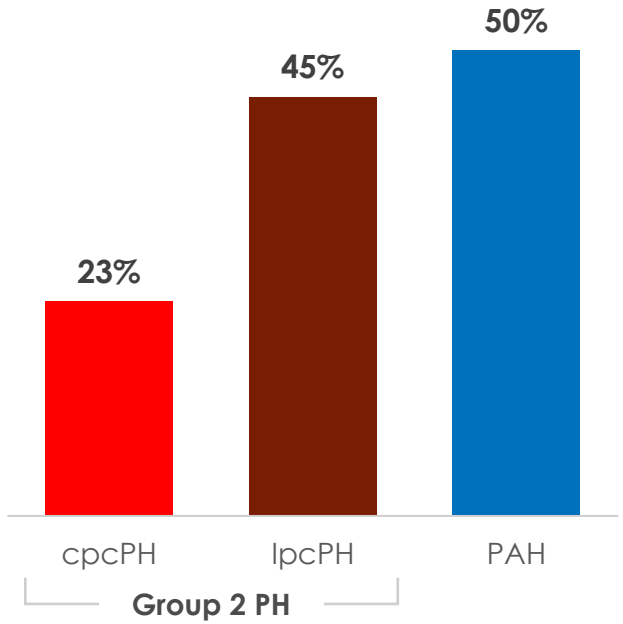
US PREVALENCE >> PAH



Multi-$ Billion Market Opportunity

>$4 Billion Market in US Today[5]

5 YEAR SURVIVAL < PAH[6]



NO THERAPEUTIC OPTIONS

No approved therapies

…

Limited pipeline

PAH Drugs have failed in Group 2 PH with the exception of PDE5i in CpcPH

Group 2 PH

Multiple drugs/ mechanisms approved

ET1R antagonists
PDE5 inhibitors
GC stimulators

ACTRII-Trap

PAH

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
4. www.pahinitiative.com
5. GlobalData
6. https://doi.org/10.1371/journal.pone.0199164.g003

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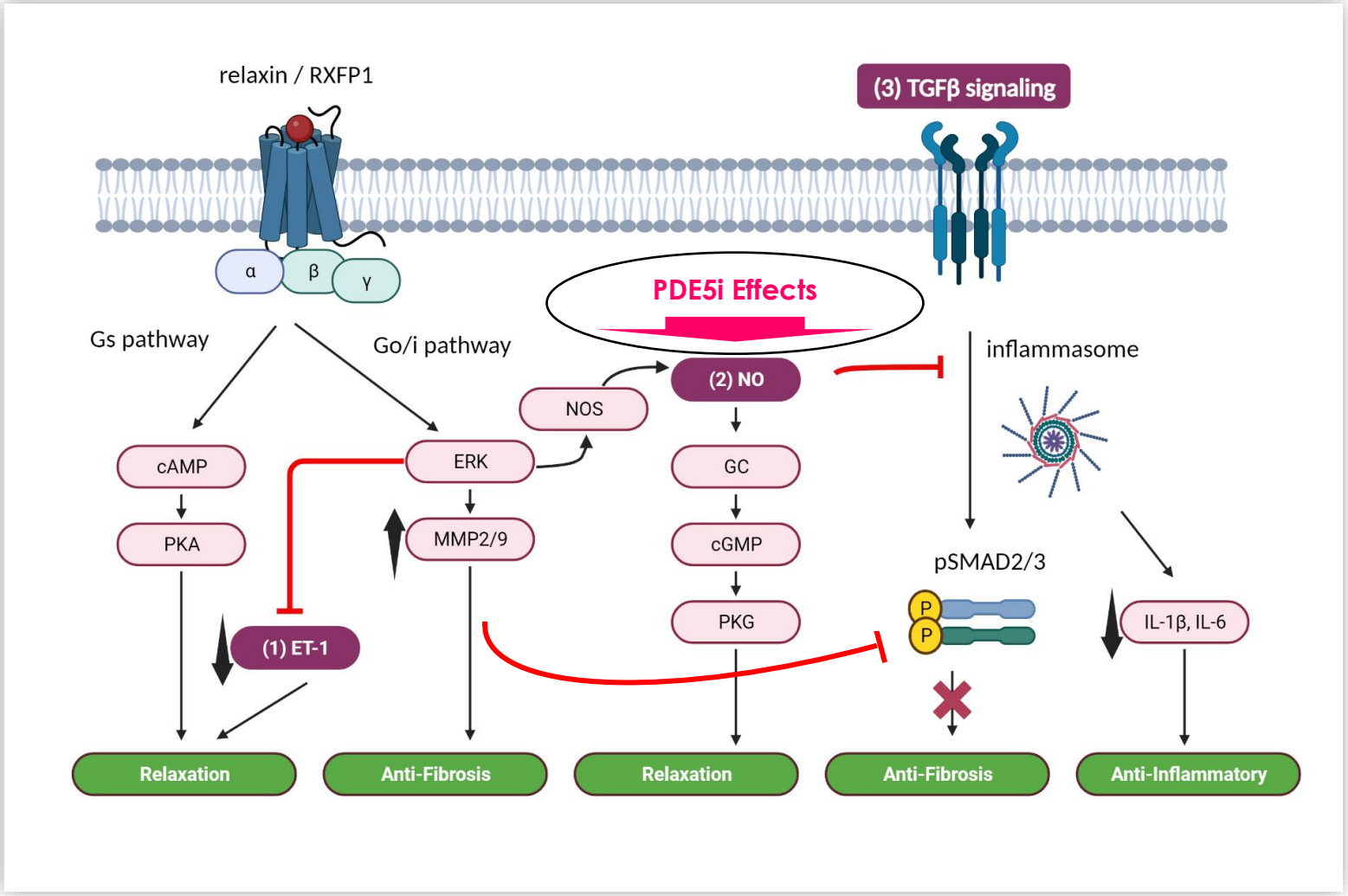
PDE5 Inhibitors Affect Only One of Several Pathways Addressed by Relaxin



PDE5 inhibitors demonstrated efficacy across 3 studies [1-3] including:

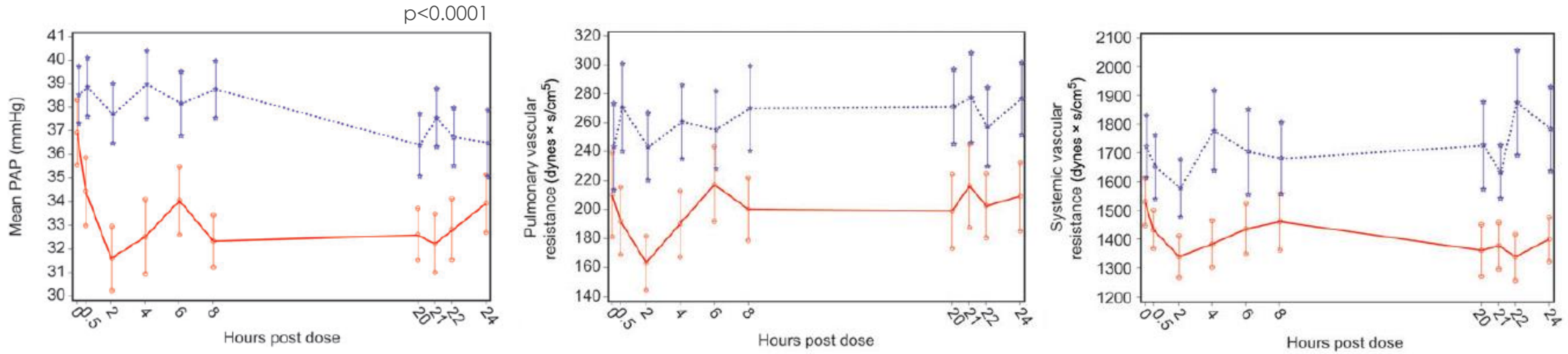
- ✓Reduction in PVR
- ✓Improvement in exercise capacity
- ✓Decrease in heart failure hospitalizations

TX45 anticipated to be effective in both Cpc-PH and Ipc-PH because it targets additional anti-fibrotic and anti-inflammatory mechanisms on top of activation of the NO pathway

1. Guazzi et al. 2011
2. Belyavskiy et al. 2020
3. Kramer et al. 2019

Relaxin Improves Hemodynamics in Heart Failure

Balanced pulmonary and peripheral vasodilation, and increased cardiac output relevant to Group 2 PH



- Above: serelaxin infusion for 20hrs in Acute Heart Failure patients with elevated pulmonary artery pressure (PAP) **rapidly lowered mPAP, pulmonary vascular resistance (PVR), systemic vascular resistance (SVR) and improved renal function***
- Not shown: serelaxin also improved additional hemodynamic parameters including **pulmonary capillary wedge pressure (PCWP), right atrial pressures (RAP) and cardiac index (CI)**
- In a similar study in patients with chronic CHF, **a reduction in PCWP and an increase in cardiac output** was demonstrated**

*Ponikowski P. et al. Eur. Heart J. 2014, **Dschietzig T. et. Al. Ann NY Acad Sci 2009

TECTONIC Therapeutic

TX45 Development Program Overview

Planned readouts in mid-2024, 2H 2025, 2026

	2024	2025	2026
Phase 1A **Safety, tolerability, PK/PD**	**Healthy Volunteers (ongoing)**	**Mid-2024** • Safety • PK • PD (Renal Blood Flow)	
Phase 1B **RHC study to establish hemodynamic proof of concept**		**Group 2 PH with HFpEF** **2025** • mPAP • PVR • CO	
Phase 2 **Randomized, 6-month study**		**Group 2 PH with HFpEF (enriched for CpcPH)**	**2026** • Primary: PVR • Secondary: mPAP, 6MWT

RHC: Right Heart Catheter
mPAP: Mean Pulmonary Arterial Pressure
PVR: Pulmonary Vascular Resistance
CO: Cardiac Output
6MTW: 6-Minute Walk Test

Preliminary PK/PD Analysis After TX45 Administration in Healthy Volunteers

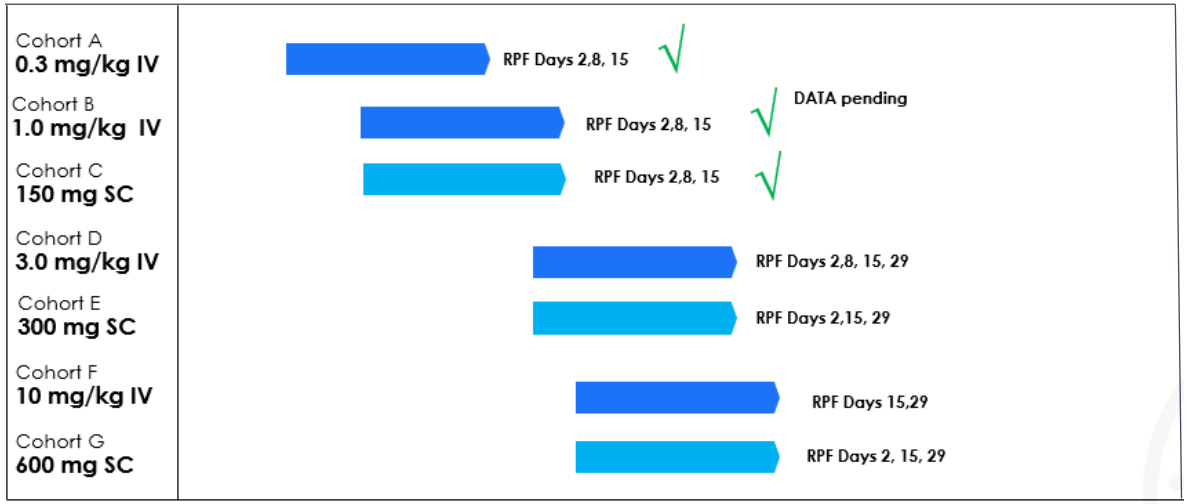
January 2024

Summary of preliminary data from TX45 SAD study[1]

Cohort A (0.3 mg/kg IV) and Cohort C (150 mg SC)

- **Well tolerated with minimal adverse events, no drug-related SAEs**
- **Pharmacokinetics**
  - Low intersubject variability in serum concentrations (≤ 20%)
  - No evidence of immune mediated clearance
- **Pharmacodynamics from 0.3 mg/kg cohort (lowest dose)**
  - ~38% increase in renal plasma flow on Day 2 post dose persisting at least until Day 8 post dose
  - Consistent with serelaxin's effect
  - **Meets "go criteria"**

TX45 SAD Dose Escalation Plan



RPF= Renal Plasma Flow
*Cohorts F and G are optional

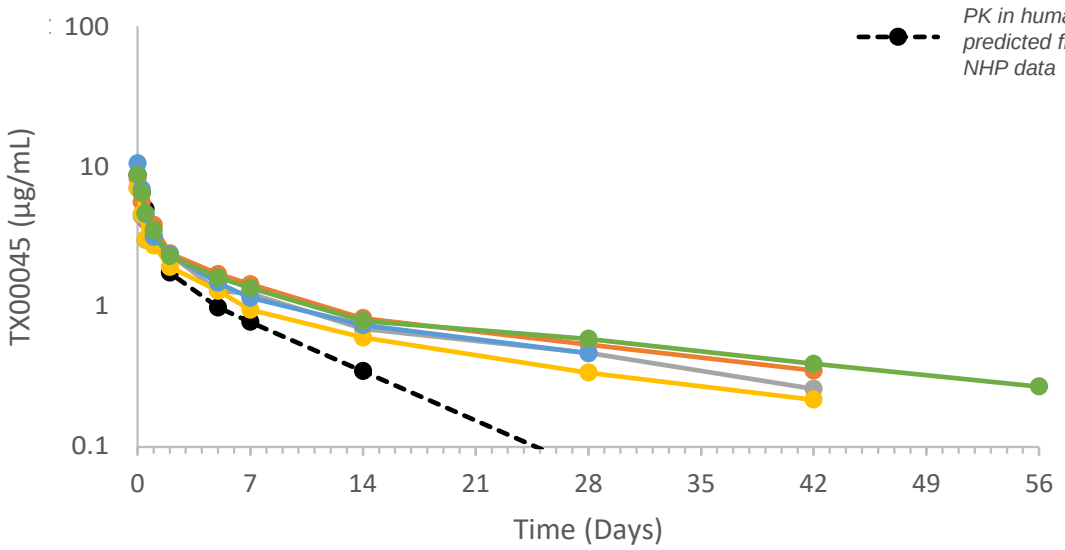
Based on preliminary data, we anticipate Q4W dosing at optimal SC dose

1. As of Jan 18, 2024

Phase 1A Study
Preliminary Single Dose TX45 PK/PD Data (0.3 mg/kg)

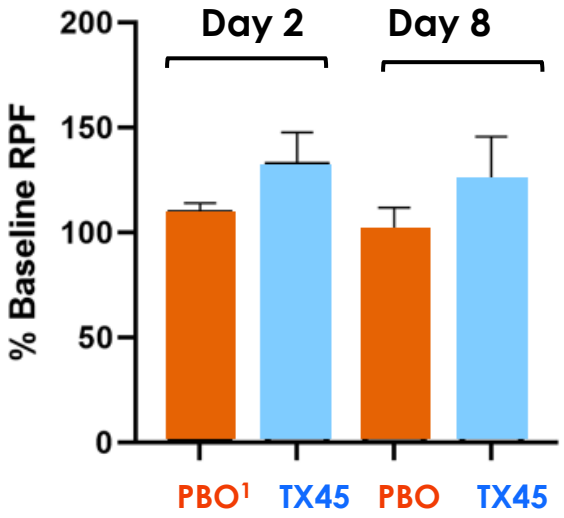
TX45 Serum Concentrations from Phase 1A Subjects

Cohort A 0.3 mg/kg IV



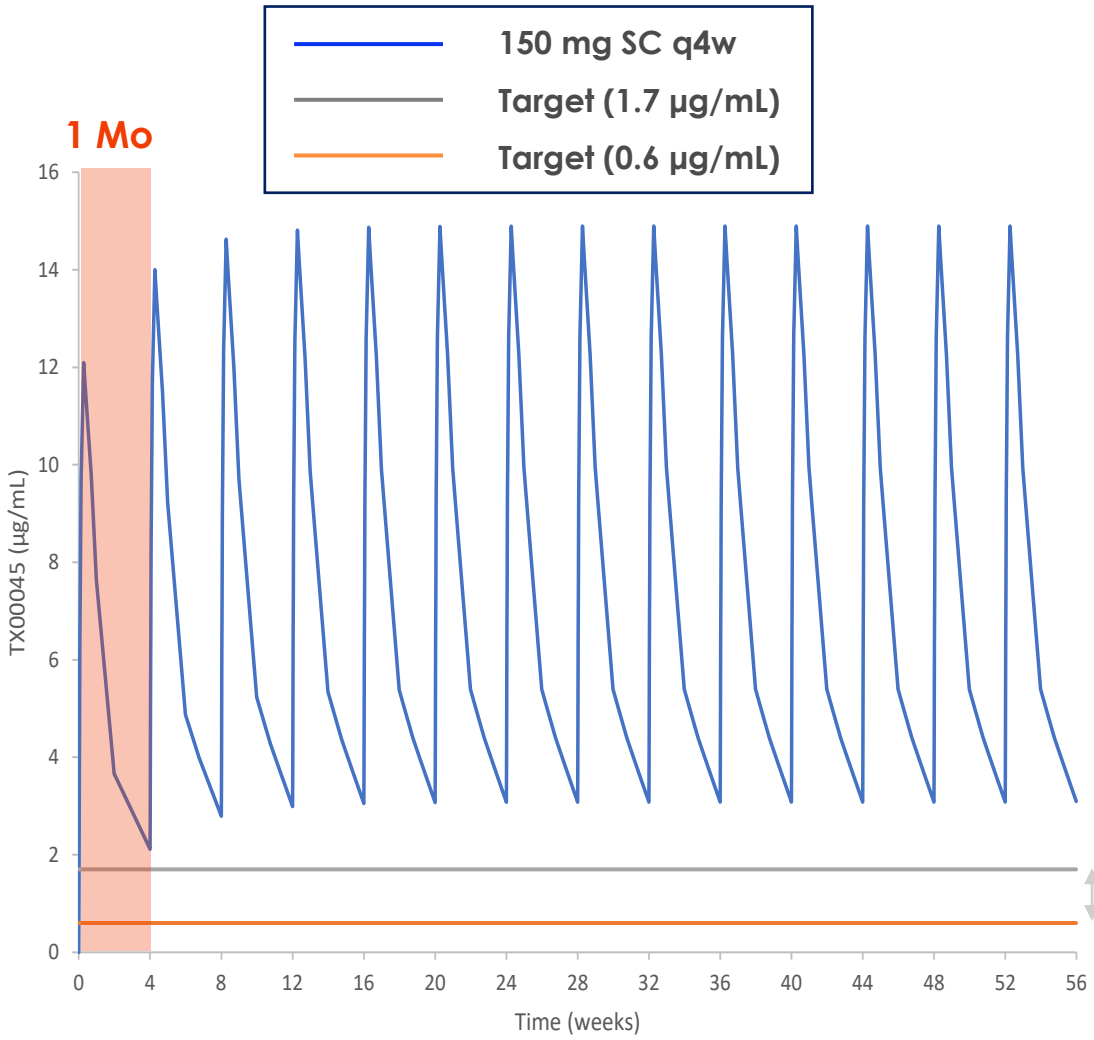
Renal Plasma Flow in Phase 1A Subjects

TX45 Dosed on Day 1 - Cohort A 0.3 mg/kg IV



1. Placebo

PK Modeling based on Preliminary Data Suggests TX45 Can be Given Monthly



- A model was constructed using observed data from both 0.3 mg/kg IV and 150 mg SC cohorts to predict trough concentrations of 150 mg SC Q4W
- Terminal $t_{1/2}$ is based on 0.3 mg/kg IV cohort as data beyond 14 days from 150 mg SC cohort was not available for accurate half life determination

Model assumptions

- Steady state terminal $t_{1/2}$, similar for IV and SC
- **Terminal $t_{1/2}$ of 16.7 days**, observed in 0.3mg/kg IV cohort is maintained in additional cohorts

Target Exposure Range Predicted to Provide Maximal Efficacy based on Preclinical Models

TECTONIC Therapeutic

Significant Pharma Interest in Relaxin Tectonic has Potential Best-in-Class Molecule

Company	Format	Formulation	Expected Dosing Frequency
TECTONIC Therapeutic	Fc-Fusion *Engineered for optimal PK, biodistribution, high [C] formulation*	SubQ *High [C] achievable*	Q4 Weeks
AstraZeneca	Fc-Fusion	SubQ	Q2 Weeks
Lilly	h-Albumin-mAb-Fusion	SubQ *Injection site reactions*	Q Weekly

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Summary

TECTONIC Therapeutic

Uniquely Positioned to Deliver on Value Creating Milestones

Pipeline of Uniquely Differentiated Assets

Multiple Inflection Points 2024, 2025, 2026

Address important clinical problems, underserved patient populations

Accomplished Team World-leader Founders

20 1st Approvals

>$50 Billion in Annual Sales

Leadership with Proven Track Record

Strong Balance Sheet Anticipated Post Transaction

~$165 Million

>3 Year Runway

Well positioned to execute

Transforming the Discovery of Novel GPCR-Targeted Therapies

JANUARY 2024

TECTONIC Therapeutic