

An Open Label, Phase 2a Exploratory Study of Inhaled Sirolimus (LAM-001) for the Treatment of Pulmonary Hypertension

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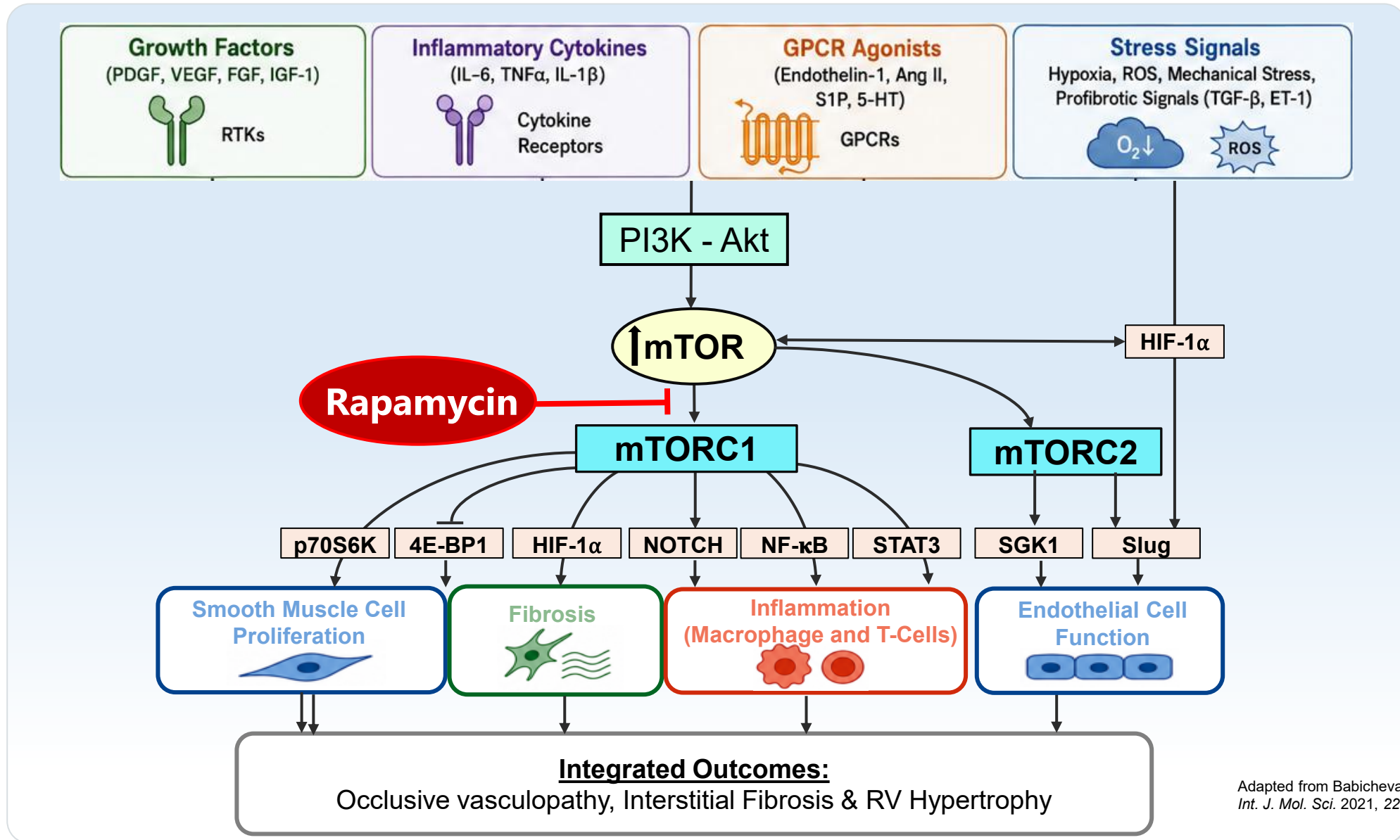
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Disclaimers

- Paul B. Yu has served as a consultant for Orphai Therapeutics, Inc (New Haven, CT), Keros Therapeutics (Waltham, MA), Ingenia Therapeutics (Watertown, MA), and has received research funding from Pfizer, Inc. (New York, NY), Gossamer Bio (San Diego, CA), and Regeneron Pharmaceutical (Tarrytown, NY).
- Aaron B. Waxman served as consultant for Merck & Co., Inc. (Rahway, NJ, USA), and United Therapeutics Corporation (paid to self); received clinical study grant/contract from Orphai Therapeutics, Inc.; and served on data and safety monitoring committee for Insmmed, Inc. (paid to self).
- Fraz Ismat currently serves as a consultant for Orphai Therapeutics, Inc (New Haven, CT), Haya Therapeutics (Lausanne, Switzerland), Thryv Therapeutics (Montréal, Quebec, Canada), Mineralys Therapeutics (Radnor, PA), and Edgewise Therapeutics (Boulder, CO).
- Adriano Tonelli has participated in advisory boards of United Therapeutics, Insmmed, and Merck.
- Franz Rischard receives research support from NIH/NHLBI, Ismed, United Therapeutics, Bayer, Acceleron, Merck, Tenax, and 35Pharma. He serves on the steering committee(s) for United Therapeutics, and two NHLBI DSMB(s).
- Phillip Joseph has no disclosures.
- Patrick D. Sarmiere, Joan Edwards, Joel Hale, Keith Fandrlick, and Brigette Roberts are employees and equity holders of Orphai Therapeutics, Inc.

mTOR is a master integrator of metabolic state and environmental stress that regulates smooth muscle cell proliferation, fibrosis and inflammation



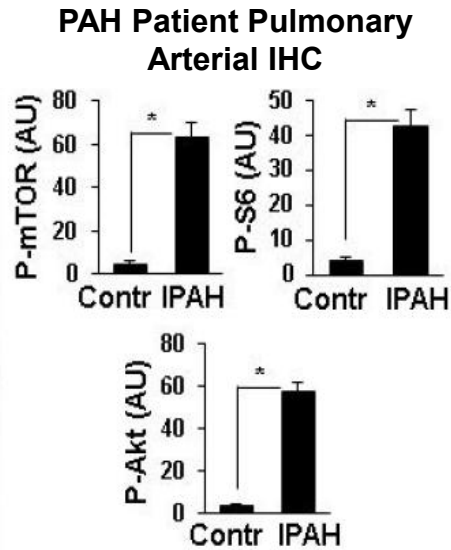
Adapted from Babicheva A et al.,
Int. J. Mol. Sci. 2021, 22(4), 2144

Translational and Pre-Clinical Validation of mTOR as a PH target

Rapamycin inhibits mTOR, which is Activated in PH

Rapamycin Reverses Vascular Remodeling and Improves Hemodynamics

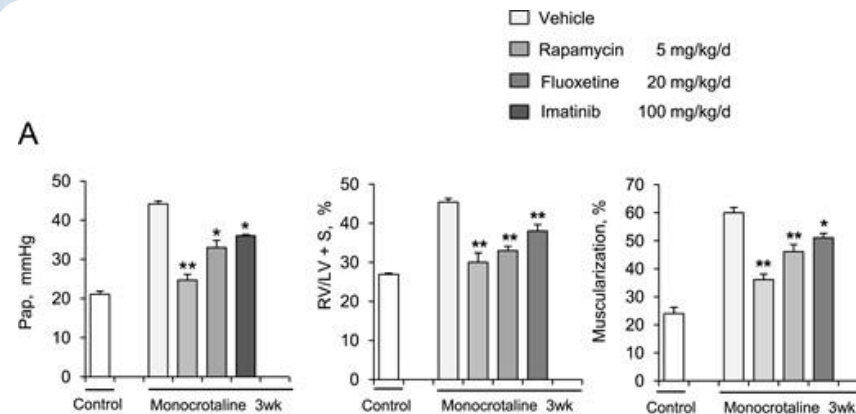
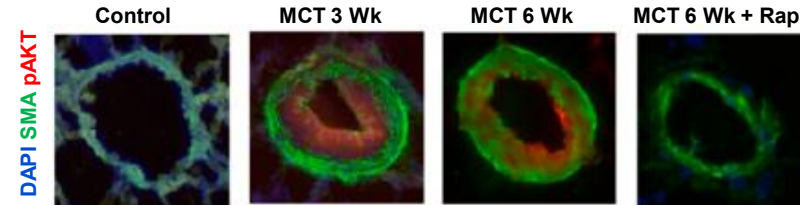
IPAH distal arteries have an activated mTOR signature



Goncharov et al., *Circulation*. 2014 129: 864.

Rapamycin is effective in multiple pre-clinical models of PH

Monocrotaline Rat Model

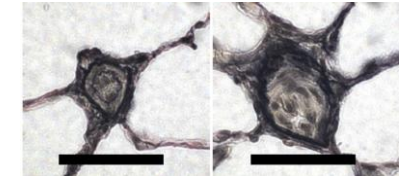


Houssaini et al., *AJRCMB*. 2013

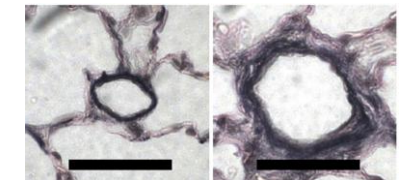
SMA = Smooth Muscle Antigen
DAPI = Nuclear/DNA Stain
pAKT = phosphorylated Akt

Pap = Pulmonary Artery Pressure
RSVP = Right ventricular systolic pressure
RV/LV+S = Right ventricle/left ventricle + septum ratio

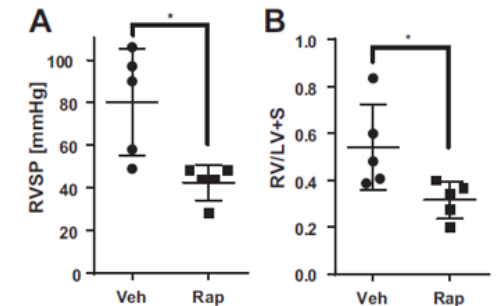
SU-Hx Rat (3+5 week) Model



Vehicle Control



Rapamycin 5 weeks

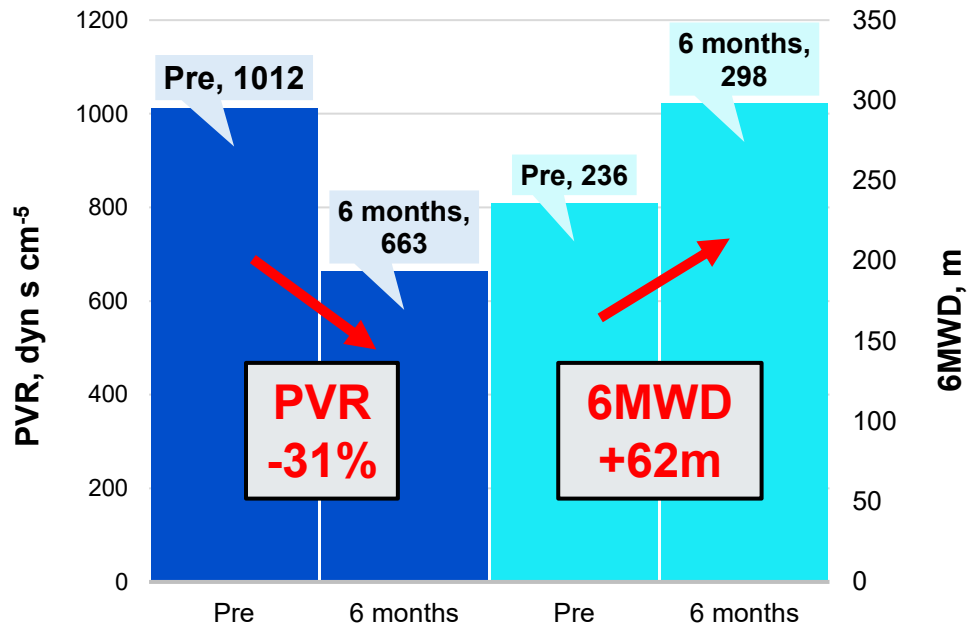


Kato et al.,
Am J Physiol Lung Cell Mol Physiol. 2017

Contr = Control
IPAH = Idiopathic Pulmonary Hypertension

Early clinical evidence that mTOR Inhibition is effective in PAH

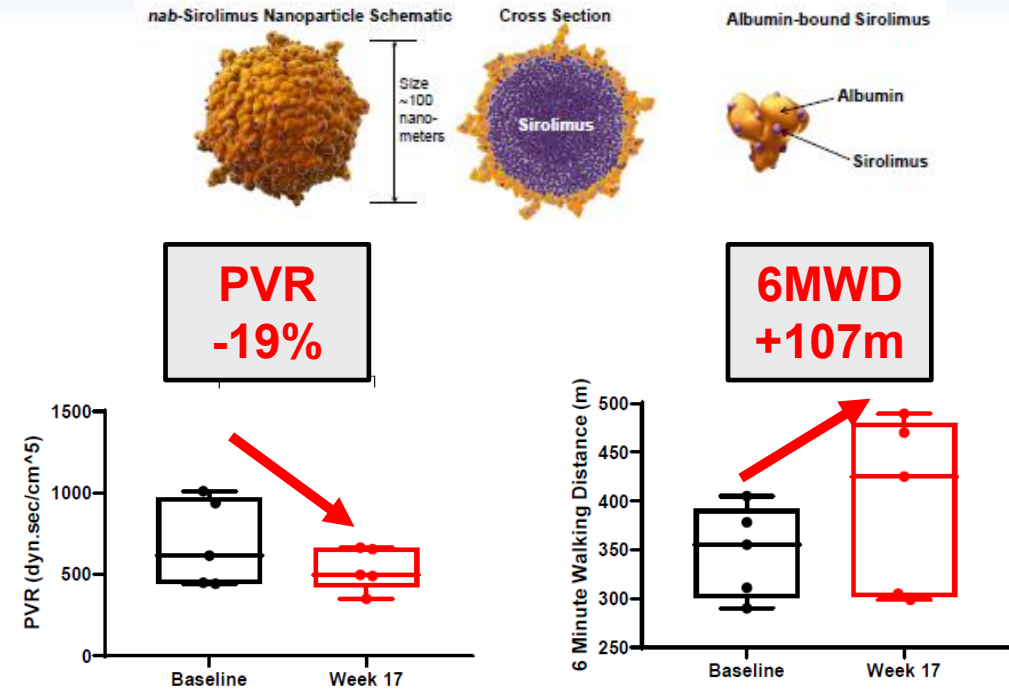
Oral Everolimus



Adapted from Seyfarth HJ et al., Pulm. Circ. 2013; 3: 632

10 patients with progressive PAH (n=8) or CTEPH (n=2) on ≥2 SOC drugs

IV-nab-Sirolimus (ABI-009)

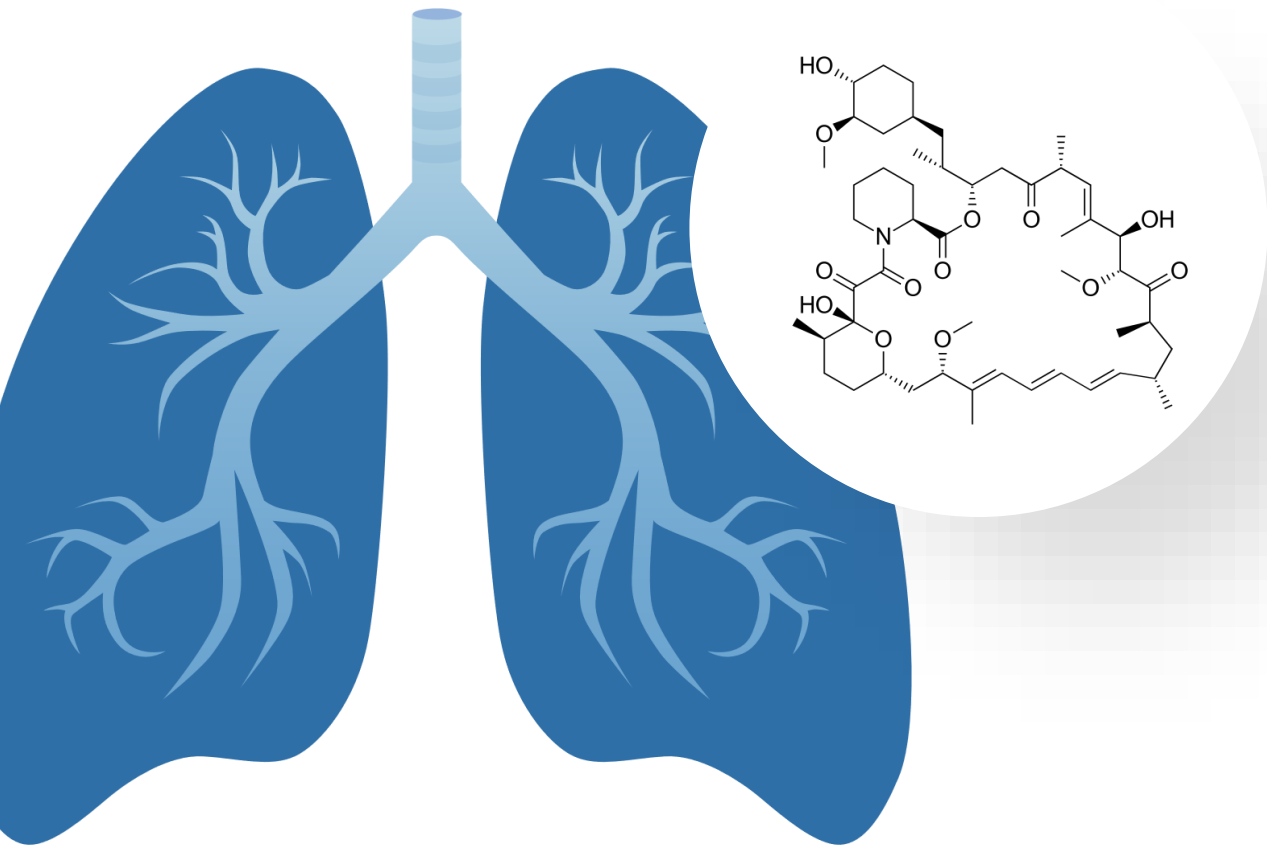


Based on Simon M et al., JACC Supplement Vol 73:9 2019

6 patients with FC III PAH on ≥2 SOC drugs; once weekly IV dosing

6MWD = 6-minute walk distance
PVR = Pulmonary Vascular Resistance

Limitations of Systemic Therapy with Oral Rapamycin



✗ **Systemic Exposure with Significant Safety Profile:** Prohibitive systemic toxicities with oral rapamycin

Oral Rapamune® Key Label Warnings and Precautions: Angioedema, Fluid Accumulation and Impairment of Wound Healing, Hyperlipidemia, Decline in Renal Function, Proteinuria, Latent Viral Infections, Male Infertility, Embryo-Fetal Toxicity

✗ **Limited Lung Exposure with Oral Delivery:** Systemic toxicity with oral delivery limits dosing levels and precludes sufficient lung exposure

✗ **Low and Variable Oral Bioavailability*:** Requiring inconvenient plasma monitoring and frequent dose adjustments

Despite mechanistic support, the case for systemic therapy with oral rapamycin in PVD limited by toxicity and challenging bioavailability

NCT05798923: Phase 2A Trial of LAM-001 (rapamycin DPI) in PAH and PH-ILD



Design

- Open Label; 24 wks; 4 sites; **Invasive Cardiopulmonary Exercise Testing (iCPET)¹**

Inclusion

- >18 yo; **WHO Functional Class III; PAH or PH-ILD**; symptomatic despite background tx

Primary Endpoints

- Peak oxygen uptake (**VO₂ max**) at 24 wks versus baseline, Safety, Tolerability

Secondary Endpoints

- Multiple hemodynamic measures (**mPAP, PVR, CO, CI, PCWP, PAC, VE/VCO₂, Ca-vO₂**)
- **6MWD; WHO functional class**

Exploratory Endpoint

- **NT-proBNP** vs baseline

¹iCPET or invasive CardioPulmonary Exercise Testing, protocol based on Maron BA et al *Circulation* **2013**, 1157-1164

LAM-001 Enrollment Characteristics

Subject	<u>1</u>	<u>3</u>	<u>2</u>	<u>16</u>	<u>4</u>	<u>5</u>	<u>7</u>	<u>8</u>	<u>14</u>	<u>10</u>
Age	80	59	63	48	74	65	67	71	65	47
Gender	Female	Male	Female	Female	Female	Female	Male	Female	Male	Male
PH Group	1					3				5
Diagnosis	PAH					Systemic Sclerosis	Idiopathic Fibrotic NSIP	IPF	Idiopathic Fibrotic NSIP	Pulmonary Sarcoidosis
Background PH Meds*	Ambrisentan	+	+							
	Macitentan			+	+	+	+			
	Riociguat					+				
	Selexipag				+					
	Sildenafil				+			+	+	+
	Tadalafil	+	+	+			+			+
	Treprostinil**	+		+ (po)		+ (sq)	+ (sq)	+	+	+
Background ILD Medications*						Cellcept	Elipta	Methylpredni- solone	Azathioprine Prednisone	Prednisone Methotrexate Folic acid

*Patients were on stable therapy (≥30 days) prior to enrollment.

** Inhaled/DPI unless indicated otherwise

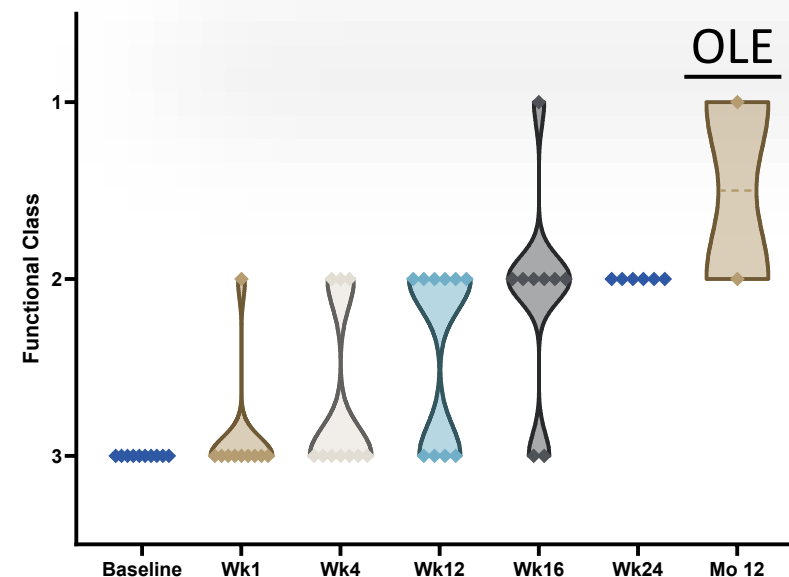
*** No dose interruptions due to AEs, no discontinuations due to drug, and no drug related SAEs

LAM-001: Functional Class Endpoint – All Enrolled

WHO Functional Class Assessment

Subject	Group	Underlying ILD	Baseline	Wk 1	Wk 4	Wk 12	Wk 16	Wk 24	Mo 12
1	1	---	III	III	III	III	III		
3	1	---	III	III	III	III	II	II	II
2	1	---	III	III	II	II	II	II	n/a
4	1	---	III	III	III	III			
16	1	---	III	II	II	II	I		
5	3	Systemic Sclerosis	III	III	III	II	II	II	I
7	3	Idiopathic Fibrotic NSIP	III	III	II	II	II	II	
8	3	IPF	III	III	III	III	III		
14	3	Idiopathic Fibrotic NSIP	III	III	III	II	II	II	
10	5	Pulmonary Sarcoidosis	III	III	III	II	II	II	

All Completers Improved from WHO FC III to II



WHO Functional Class Definition*

- Class: I** Symptom-free when physically active or resting
- Class: II** No symptoms at rest, but normal activities such as climbing stairs, grocery shopping or making the bed cause some discomfort and shortness of breath
- Class: III** Resting may be symptom-free, but normal chores around the house are greatly limited due to shortness of breath or feeling tired
- Class: IV** Symptoms at rest and severe symptoms with an activity

Early Terminations

- Subject 1:** Respiratory failure/GI infection at ~month 5 lead to hospitalization, unrelated to study drug, developed aspiration pneumonia in hospital and died
- Subject 4:** Acute coronary syndrome from proximal LAD coronary lesion identified mid-study unrelated to study drug and withdrew from study for emergent stenting
- Subject 8:** Multiple complications and hospitalizations unrelated to study drug and withdrew.
- Subject 16:** Terminated following vaping induced lung injury, confirmed by BAL and exposure history

LAM-001: Endpoint Summary By Patient - Completers

	Group	PAH Individuals		PH-ILD Individuals				Evaluable Population			PH-ILD Individuals Only		
		1	1	3			5						
	Diagnosis			Systemic Sclerosis	Idiopathic Fibrotic NSIP	Idiopathic Fibrotic NSIP	Pulmonary Sarcoidosis	Mean	Median	n	Mean	Median	n
Subject	3	2	5	7	14*	10							
6MWD	Change in Distance (meters)	+23.1	+195	+85	-12**	+35.2	+161.5	+81.3	+60.1	6	+67.4	+60.1	4
VO ₂ Max	Abs Change from Baseline (% Predicted)	2%	5%	4%	9%	n/d	7%	5.4%	5%	5	6.7%	7%	3
PVR (Exercise)	% Change from Baseline (dynes-sec/cm ⁵)	-26.6%	5.2%	-1.4%	-38.6%	n/d	-65.9%	-25.5%	-26.6%	5	-35.3%	-38.6%	3
PVR (Supine)	% Change from Baseline (dynes-sec/cm ⁵)	-26.7%	-6.5%	10.5%	-46.4%	-58.8%	-41.0%	-28.1%	-33.9%	6	-33.9%	-43.7%	4
NT-proBNP	% Change from Baseline (pg/mL)	-46.9%	-11.6%	-6.6%	-59.8%	bloq***	-48.8%	-29.0%	-29.3%	6	-28.8%	-27.7%	4
FVC	Abs Change from Baseline (% Predicted)	+5%	+17%	+2%	+5%	0%	0%	+4.8%	+3.5%	6	+1.8%	+1.0%	4

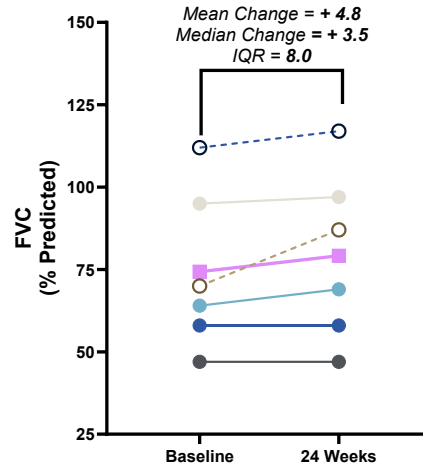
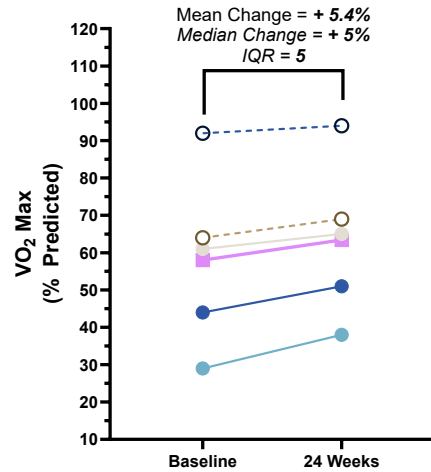
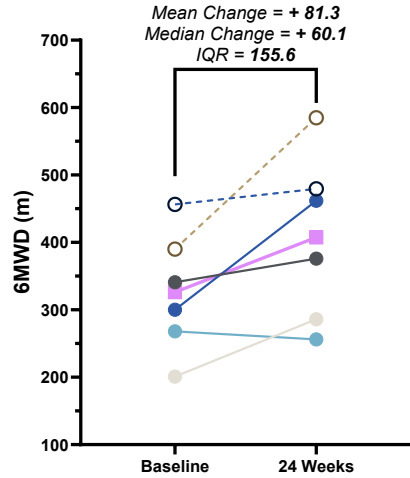
Consistent improvement seen on top of standard of care across multiple endpoints: 6MWD, VO₂Max, PVR, NT-proBNP, and FVC

*Subject 14 experienced contrast agent reaction, thus Peak Exercise iCPET was not conducted at baseline visit

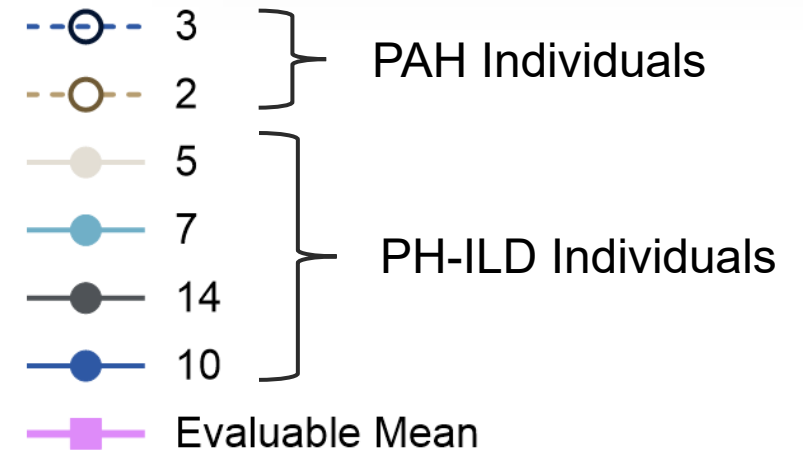
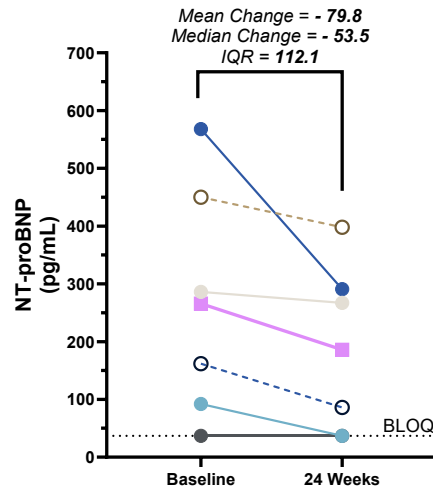
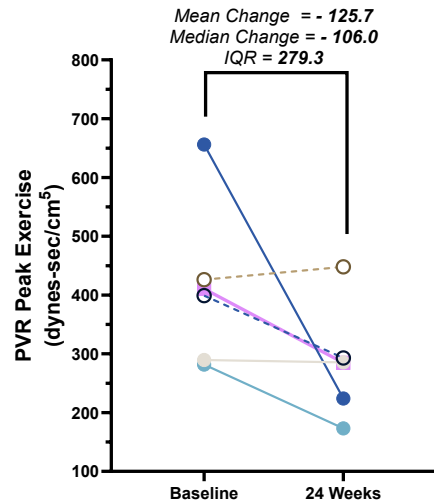
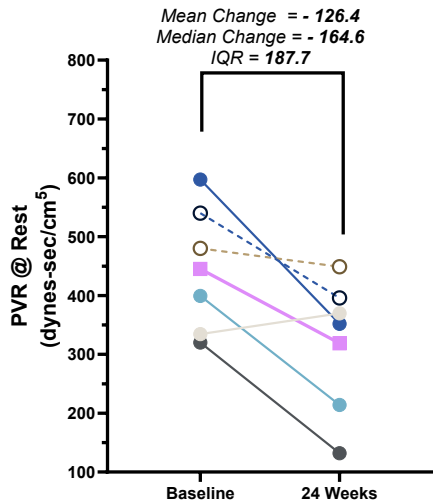
**Subject 7: Week 24 6MWD performed without supplemental oxygen. All other Subject 7 6MWD performed with oxygen.

*** bloq = Below limit of quantitation

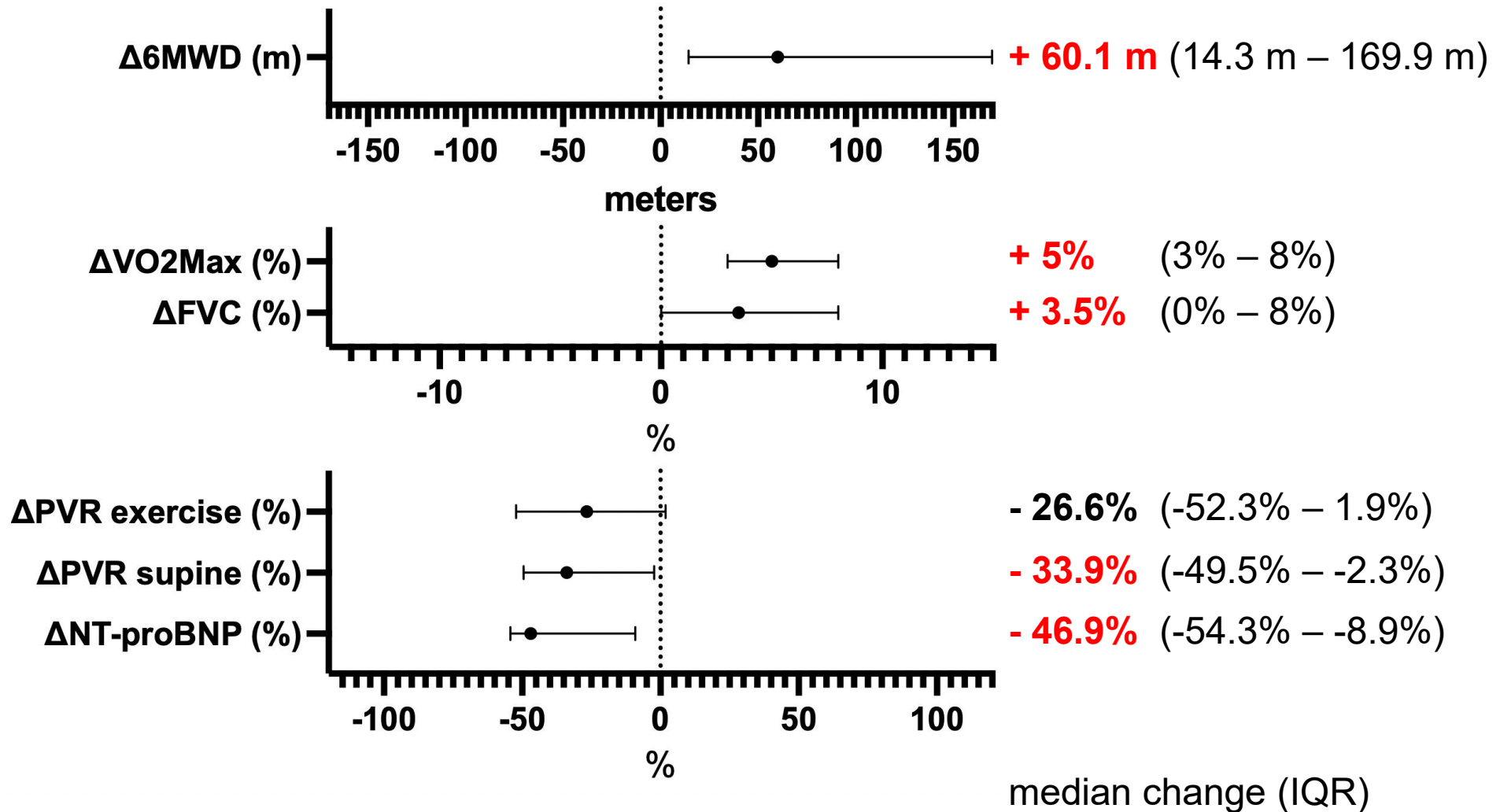
Endpoint Summary By Patient (Completers): Baseline vs 24 Weeks



Consistent improvements or stabilization across exercise capacity, hemodynamics, FVC, and NT-proBNP.



Treatment elicited consistent directionality of effect across multiple endpoints



Safety Summary through 24-Weeks

Drug Related AEs

- Grade 1 Productive Cough (n = 1) - Resolving
- Grade 2 Cough (n = 1) - Not Resolved
- Grade 1 Gingivitis (n = 1) - Resolving

LAM-001 was well tolerated

No dose interruptions due to AEs

No discontinuations due to drug

No drug related SAEs

LAM-001 Phase 2A Study Summary



Favorable tolerability in adults with WHO FC III Pulmonary Hypertension on SOC therapy



Improvements or Stabilization in VO_2 Max, PVR, 6MWD, NT-proBNP, and FVC suggest an underlying physiological benefit beyond test variability



Shift of all evaluable patients from FC III to FC II by week 24, some with early improvement, consistent with hemodynamic and biomarker changes.



Biologically plausible mechanism targeting key pathways in pulmonary vascular and interstitial disease.

These results position LAM-001 as a potential adjunctive therapy in pulmonary hypertension, supported by a favorable tolerability profile and a differentiated mechanistic rationale

Acknowledgements

Investigators

Aaron B. Waxman, MD, PhD

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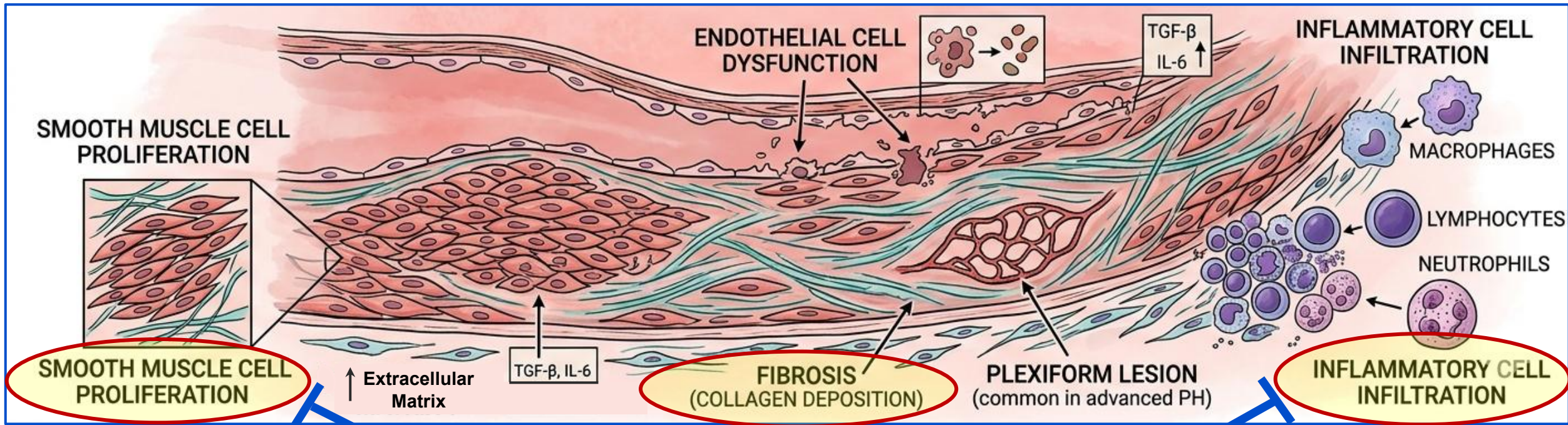
Keith Fandrlick

Brigette Roberts, MD

FICC LLC

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Rapamycin Targets PH Pathobiology



Rapamycin inhibits pulmonary arterial smooth muscle cell proliferation, fibrosis, and vascular inflammation – all of which contribute to PH remodeling