Safety/Efficacy of RT234 Vardenafil Inhalation Powder on Exercise Parameters in Pulmonary Arterial Hypertension: Phase 2 Dose-Escalation Study Design

Carol Satler,[1] Raymond L. Benza,[2] Veronica Franco,[2]
Mandar A. Aras,[3] Leslie Spikes,[4] Daniel Grinnan[5]

[1]Respira Therapeutics, Inc., Boston, MA, USA; [2]The Ohio State University Wexner Medical Center, Columbus, OH, USA; [3]University of California San Francisco, San Francisco, CA, USA; [4]University of Kansas Medical Center, Kansas City, KS, USA; [5]Virginia Commonwealth University School of Medicine, Richmond, VA, USA

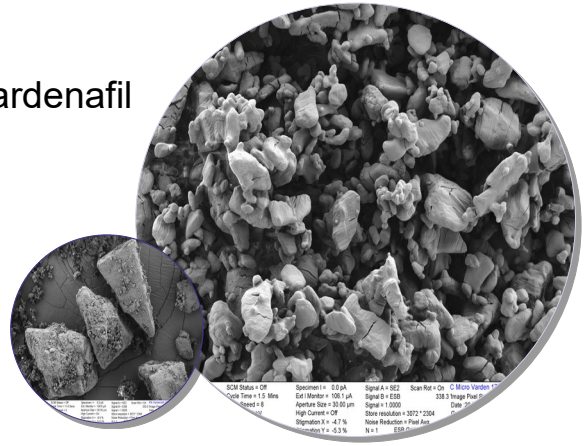
Presenting author disclosure: President, Chief Medical Officer and shareholder of Respira Therapeutics. Respira Therapeutics is supporting this study.

International Meeting on Pulmonary Rare Diseases And Orphan Drugs, March 3-4, 2023, Milan, Italy

Background

- No treatment exists to acutely improve exercise capacity and symptoms on an “as-needed” basis in PAH.
- RT234 is an inhaled drug/device combination of the PDE5 inhibitor vardenafil hydrochloride and the novel AOS DPI.
  - Oral vardenafil is approved for the treatment of erectile dysfunction and its safety profile is well established.
  - A Phase 2A RT234 dose escalating (0.6–2.4 mg) study (N=14) demonstrated a dose-dependent reduction in pulmonary vascular resistance and was safe and well tolerated in PAH[1].
- This Phase 2B study will evaluate efficacy and safety of RT234 AOS DPI on exercise capacity and symptoms assessed by CPET and 6MWT in PAH participants on stable background therapy.

Vardenafil



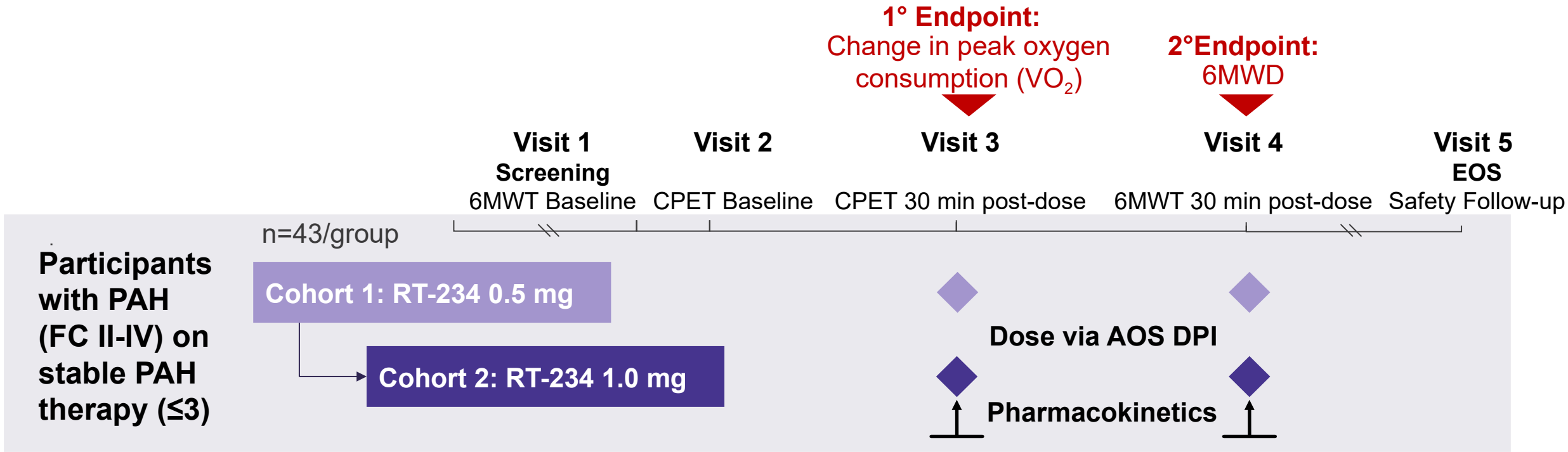
Vardenafil + lactose

1. Keogh A, et al. Presented at: PHA 2022; June 9-12, 2022; Atlanta, GA, USA.

PAH, pulmonary arterial hypertension; PDE5 inhibitor, phosphodiesterase type 5 inhibitor; AOS DPI, Axial Oscillating Sphere dry powder inhaler; CPET, cardiopulmonary exercise testing; 6MWT, 6-minute walk test

VIPAH PRN^{2B} Is a Prospective, Multicenter, Open-Label, Dose-Escalation, Phase 2b Study

Objective: *To evaluate efficacy and safety of RT234 (vardenafil inhalation powder) delivered via AOS DPI on exercise capacity and symptoms assessed by CPET and 6MWT in PAH participants on stable background therapy*



Statistical assumptions

- Sample size derived using 1-sample, 2-sided t test [0.05 significance level and 80% power] to test null hypothesis of no difference between Baseline and post-dose peak VO2; SD 2 ml O_2/kg/min; 5% drop-out rate
- Assumed mean change from Baseline is 1.5 ml O_2/kg/min

VIPAH PRN 2B, Vardenafil Inhaled for Pulmonary Arterial Hypertension PRN 2B trial; CPET, cardiopulmonary exercise testing; VO_2, oxygen consumption; 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; EOS, End of Study

Key Endpoints

Efficacy	• Change from Baseline in peak VO_2 compared to post RT234 treatment. • Change from Baseline in 6MWD compared to post RT234 treatment. • Change from Baseline in ventilatory inefficiency slope (VE/VCO_2) compared to post RT234 treatment. • Change from Baseline in duration of exercise compared to post RT234 treatment.
Safety	• Incidence and severity of AEs, TEAEs and SAEs. • Changes from Baseline to post RT234 treatment in vital signs, physical examinations, and 12-lead ECGs.

RT234, vardenafil inhalation powder; Peak VO_2, maximum oxygen consumption; 6MWD, 6-minute walk distance; VE, minute ventilation; VCO_2, carbon dioxide production; ECGs, electrocardiograms; AEs, adverse events, TEAEs, treatment-emergent adverse events; SAEs, serious adverse events

Key Eligibility Criteria

Inclusion

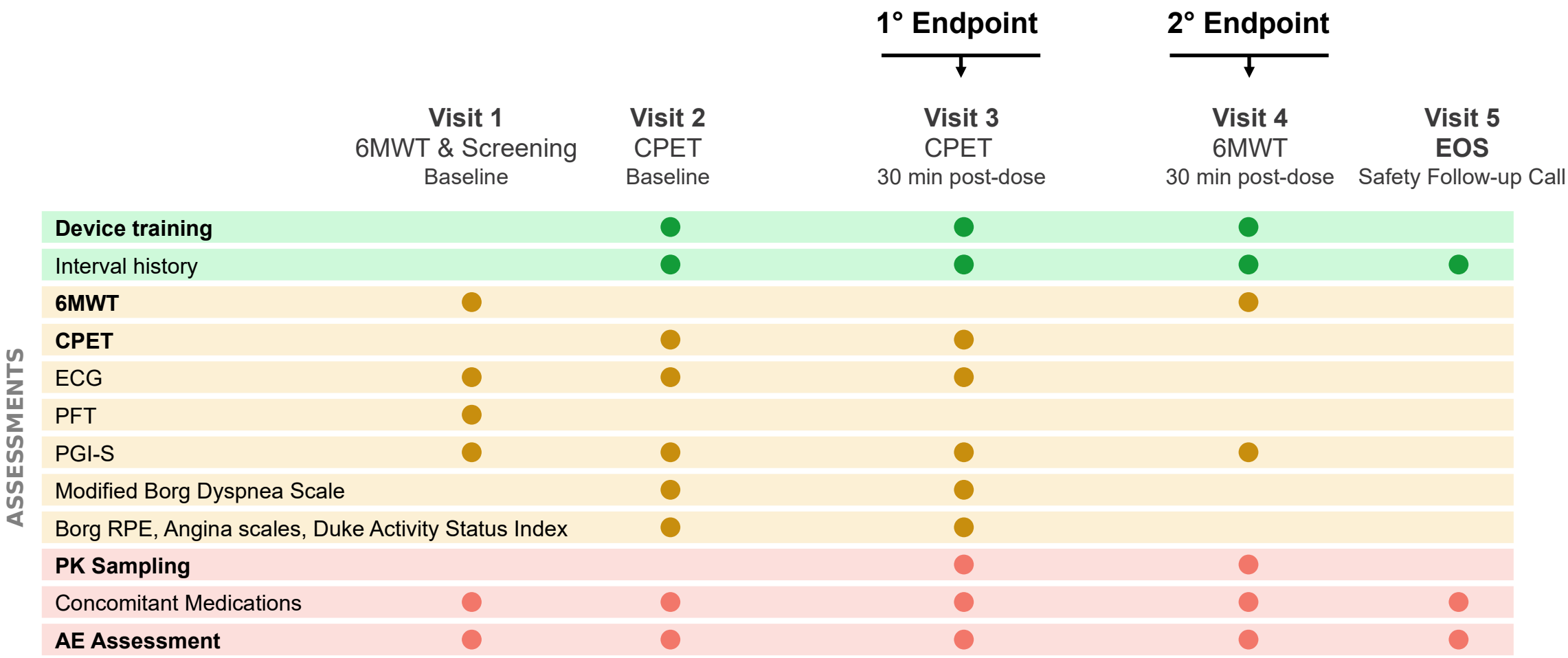
- Aged 18–80 years
- PAH:
  - Idiopathic, primary, or familial
  - Connective tissue disease
  - HIV infection
  - Repaired congenital heart disease
  - Toxin exposure
- WHO FC II-IV
- Up to 3 PAH specific background meds (inhaled/oral)
- 6MWT ≥150 meters
- RHC
  - mPAP ≥ 20 mmHg
  - PVR ≥ 300 dynes/sec/cm^5
  - PCWP or LVEDP of ≤12 mmHg if PVR ≥300 to <500 dynes/sec/cm^5, or PCWP or LVEDP ≤15 mmHg if PVR ≥500 dynes/sec/cm^5
- VE/VCO_2 slope ≥36

Exclusion

- Use of parenteral PAH medications
- Use of riociguat
- Left ventricular disease /dysfunction risk factors (3 or more)

mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end diastolic pressure; 6MWT, 6-minute walking test; RHC, right heart catheterization–confirmed PAH; VE, minute ventilation; VCO_2, carbon dioxide production, VE/VCO_2 slope reflects increase in ventilation in response to CO_2 production (respiratory drive)

Assessment Schedule



6MWT, 6-minute walk test; CPET, cardiopulmonary exercise testing; ECGs, electrocardiograms; PFT, pulmonary function tests; PGI-S, Patient Global Impression of Severity Scale; Borg RPE, Borg Rating of Perceived Exertion; PK sampling, blood sampling for pharmacokinetic analysis; AE, Adverse Event; EOS, End of Study

VIPAH PRN[2B] Baseline Demographics and Disease Characteristics, Enrolled Subjects* (N=9)

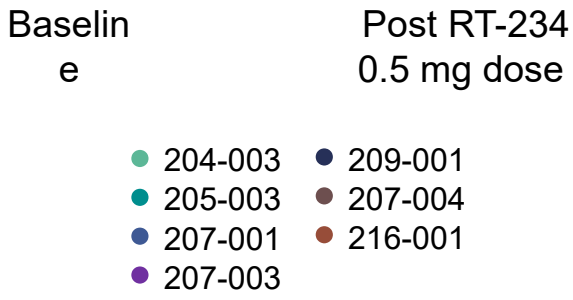
		N=9
Geography		US, Serbia
Median age, years (min, max)		46 (23, 73)
Female, n (%)		9 (100)
Race, n (%)	White	8 (89)
	Black	1 (11)
Median BMI, kg/m^2 (min, max)		26.7 (18.8, 39.2)
Functional PAH Classification, n (%)	Class I	0
	Class II	5 (56)
	Class III	4 (44)
	Class IV	0
Idiopathic, primary, or familial PAH, n (%)		7 (78)
PAH associated with CTD, n (%)		1 (11)
PAH associated with other factors, n (%)		1 (11)
Mean time since diagnosis, months (min, max)		43 (10, 113)
Mean 6MWD, m (min, max)		462.0 (285.5, 595.5)
PAH Disease-Specific Medications**	PDE5i	7 (78)
	ERA	8 (89)
	sGC	0
	Prostacyclin (or analogue)	4 (44)

*N=9 enrolled subjects as of March 1, 2023
**Multiple classes of medications may apply to a single patient.
BMI, body mass index, CTD, connective tissue disease; 6MWD, 6-minute walk distance; PDE5i, Phosphodiesterase type 5 inhibitors; ERA, endothelin receptor antagonists, sGC soluble guanylate cyclase modulators

Change from Baseline in 6MWD Compared to Post RT234 Treatment*

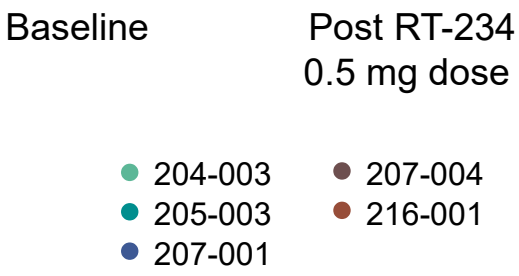
All Participants
(Cohort 1, n=7)

Mean change from Baseline: 23.5 m



Participants with Baseline 6MWT < 500 m
(Cohort 1, n=5)

Mean change from Baseline: 30 m



*US subjects only

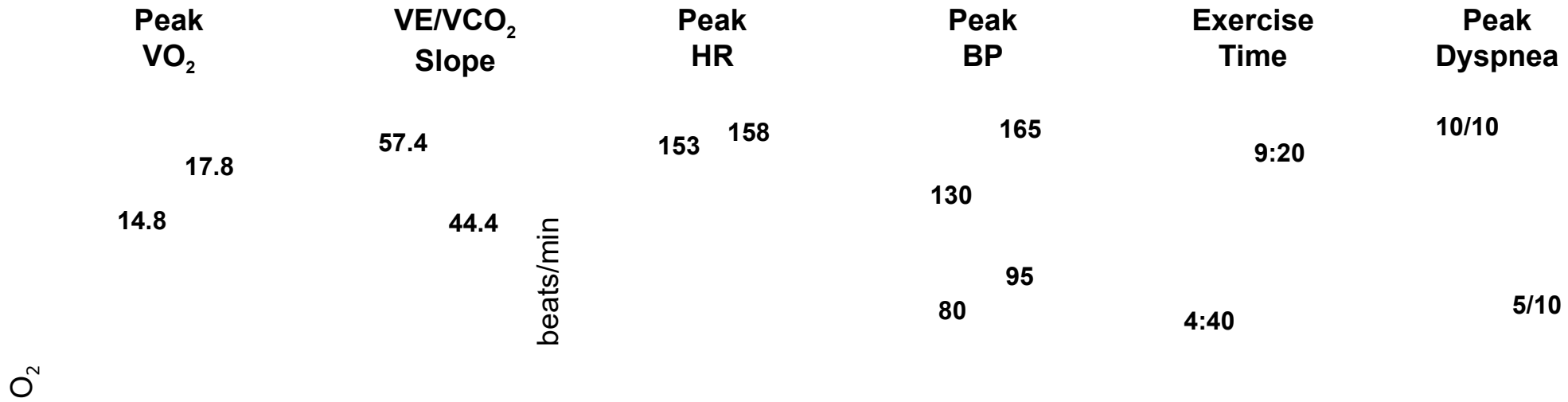
Patient 1: 35 Year Old White Female with Idiopathic PAH (Dx 2019) FCIII treated with Bosentan and Sildenafil

Baseline CPET

- Background PAH meds not held
- Resting Vitals: HR 80, RR 18, BP 130/70; O_2 sat 96%

Post-RT-234 Treatment CPET

- Background PAH meds not held
- Resting Vitals: HR 81, RR 22, BP 124/75; O_2 sat 98%
- No AEs reported



Oct 2020 screening visit: Vitals: HR 68, RR 22, BP 122/77; BMI 29 kg/m$^{2;}$ O_2 sat 97%; 6MWT = 451 m.

Summary

- VIPAH PRN[2B] is the first study investigating RT234 (vardenafil inhalation powder) for an “as-needed” treatment for PAH, in addition to stable, disease-specific background therapy, to acutely improve exercise and/or quality of life.
- The preliminary results suggest inhaled RT234 may offer a clinical benefit, with minimal side effects, for patients with PAH.
- This proof-of-concept study is actively enrolling in US.
- Results will inform the design of the global RT234 Phase 3 clinical program.
- We would like to thank the patients, their families, caretakers, investigators and research staff for all their contributions to this program.