Acute hemodynamic improvement in chronic pulmonary arterial hypertension on dual therapy following RT234 inhalation

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Conflict of Interest Disclosure

- The RT234-CL201 study was funded by Respira Therapeutics, Inc.
- The institutions of Anne Keogh, Nathan Dwyer, Eugene Kotlyar, and David Kaye received payment for the conduct of the trial.
- Jeffry Weers, Mari Maurer, and Edward Parsley were employees or consultants of Respira, and received compensation in the form of salary, benefits, stock options or consulting fees.
- Jeffry Weers is a co-inventor on two patent applications related to RT234

A PRN inhaled treatment designed to acutely improve symptoms and exercise capacity

RT234-PAH (vardenafil inhalation powder)

For as-needed (PRN) treatment of episodic symptoms of PAH, dosed up to 4x/day, to acutely improve:

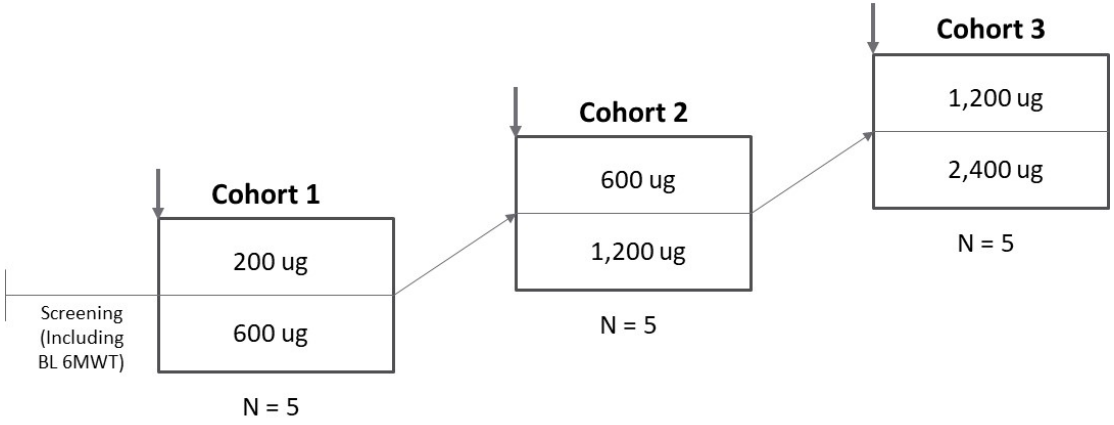
- Symptoms
- Exercise capacity
- Performance of daily activities
- Quality of Life

- ✓ Rapid onset of action (within ~15 min)
- ✓ Acceptable duration of action (~2-3 h)
- ✓ Convenient treatment regimen (i.e., take “as-needed”)
- ✓ Minimal safety/tolerability issues over background therapy
- ✓ Noninvasive, portable, simple-to-administer delivery system designed for PAH patients

RT234-CL201 Baseline Demographics

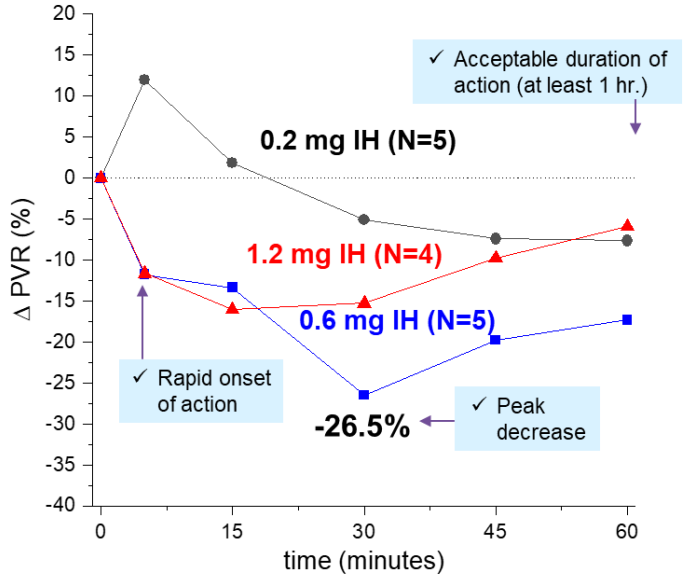
Study Design

- Hemodynamic, dose escalation study in 15 PAH patients, 3 dose cohorts of 5 subjects each
- Two-part study: Part A and Part B
  - Part A: Receive 2 doses while undergoing a Right Heart Catherization procedure (Day 1)
  - Part B: 6MWT post dose at highest tolerated dose achieved in Part A (Day 15)

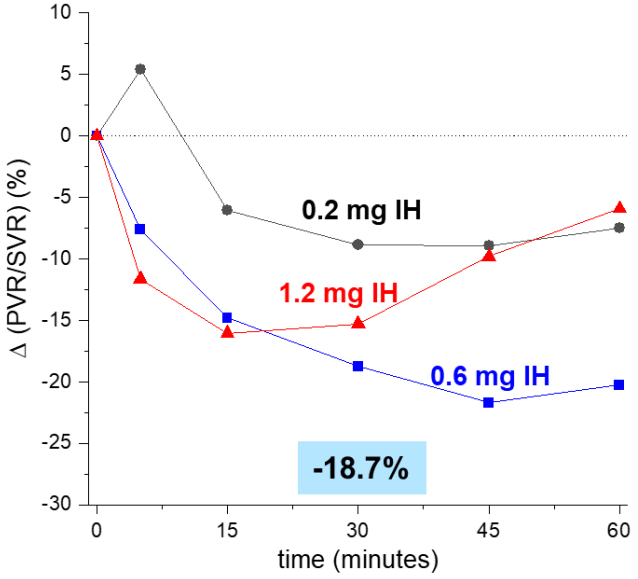


Category	Value	
Age (Years ± SD)	54 ± 14 Range 22 to 80	
Sex (n)	Female (11)	
Race (n)	White (11)	
6MWD (m)	426 ± 129	
FC (n)	II (8); III (5); IV (1)	
mPAP (mmHg)	46 ± 15	
PCWP (mmHg)	12 ± 3	
PVR ($dyn.sec.cm^{-5}$)	584 ± 345	
PDE5i (n)	Sildenafil	5
	Tadalafil	9
ERA (n)	Macitentan	10
	Bosentan	2
	Ambrisentan	2

RT234-CL201 Hemodynamics Study



Decreases in Pulmonary Vascular Resistance (PVR) of > 10% occur within 5 min for the 0.6 and 1.2 mg doses



RT234 has excellent pulmonary selectivity – Pulmonary Vascular Resistance (PVR) Systemic Vascular Resistance (SVR)

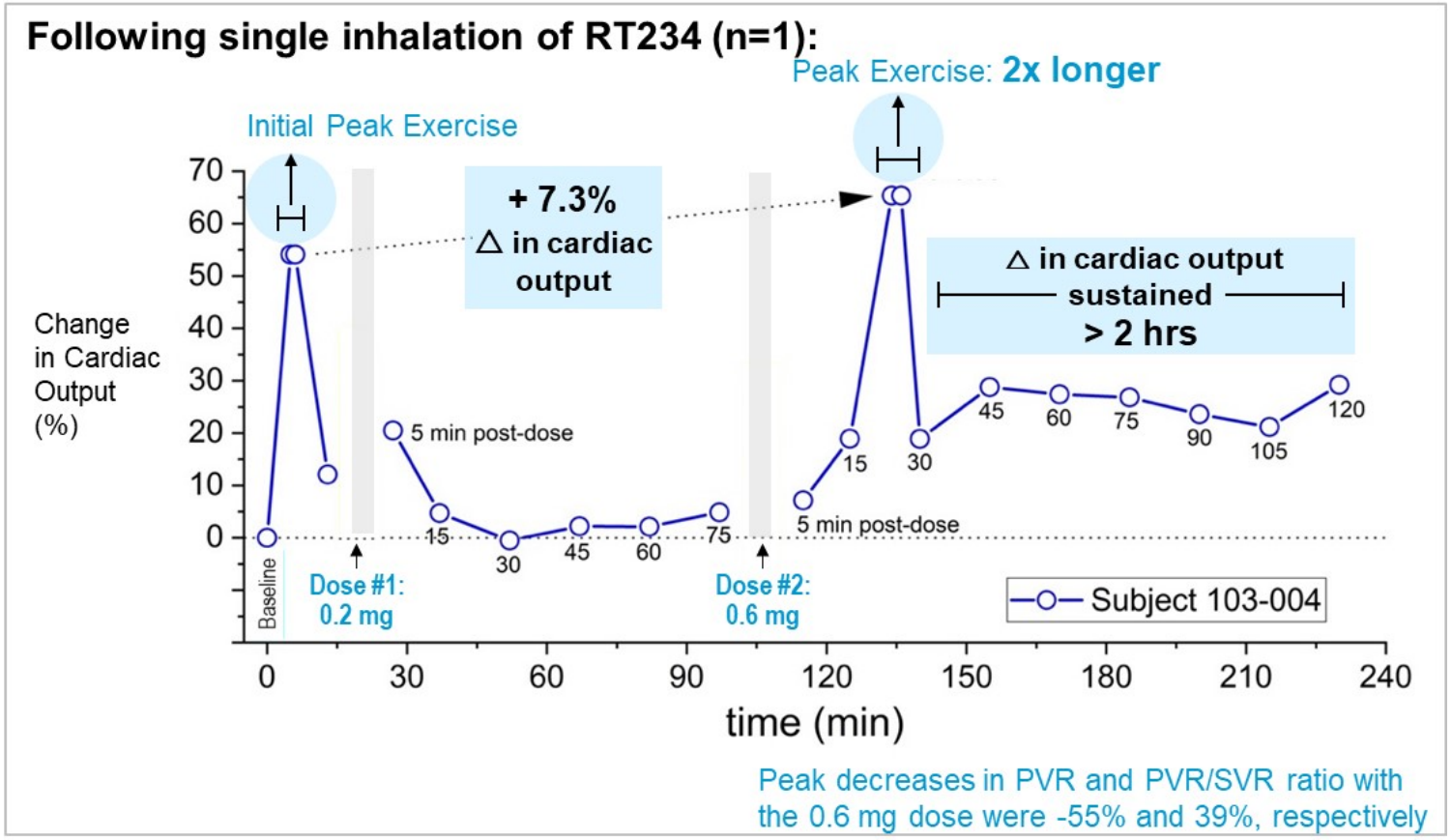
Inhaled vs. Oral: Comparable pulmonary hemodynamics at 1/33rd the dose

	Hemodynamic Metric	% Change from Baseline (95% CI)		
		ORAL VARDENAFIL (20 mg) N=9	RT234* (0.6 mg) N=5	
PULMONARY VASCULAR EFFECT	Pulmonary vascular resistance index (PVR)	-26.3 (-29.2 to -22.8)	**-23.7** (-44.7 to -18.6)	Improvements in pulmonary hemodynamics for 0.6 mg RT234 dose comparable to 20 mg oral tablet
	Mean pulmonary arterial pressure (mPAP)	-12.1 (-15.8 to -7.3)	**-12.3** (-19.6 to -3.3)	
	Cardiac Index (CI)	+18.4 (9.8 to 25.1)	**+11.9** (-5.0 to 31.9)	
SYSTEMIC VASCULAR EFFECT	Systemic vascular resistance index (SVR)	-26.4 (-29.9 to -17.5)	**-9.3** (-22.5 to 15.7)	RT234 exhibits greater pulmonary selectivity (i.e., a lower systemic hemodynamic response) than oral medications
	Mean systemic arterial pressure (mSAP)	-12.1 (-16.9 to -8.1)	**-2.2** (-9.0 to 18.1)	
	PVR/SVR Ratio	-0.1 (-8.2 to 4.2)	**-18.4** (-37.8 to 0.9)	
OXYGENATION	Partial pressure of arterial oxygen (PaO_2)	-2.2 (-17.9 to 13.5)	**+8.1** (-13.3 to 22.6)	RT234 improves oxygenation relative to oral administration

*Measurements at peak effect in PVR (30 min); 95% CI determined using Hodges-Lehman point estimates

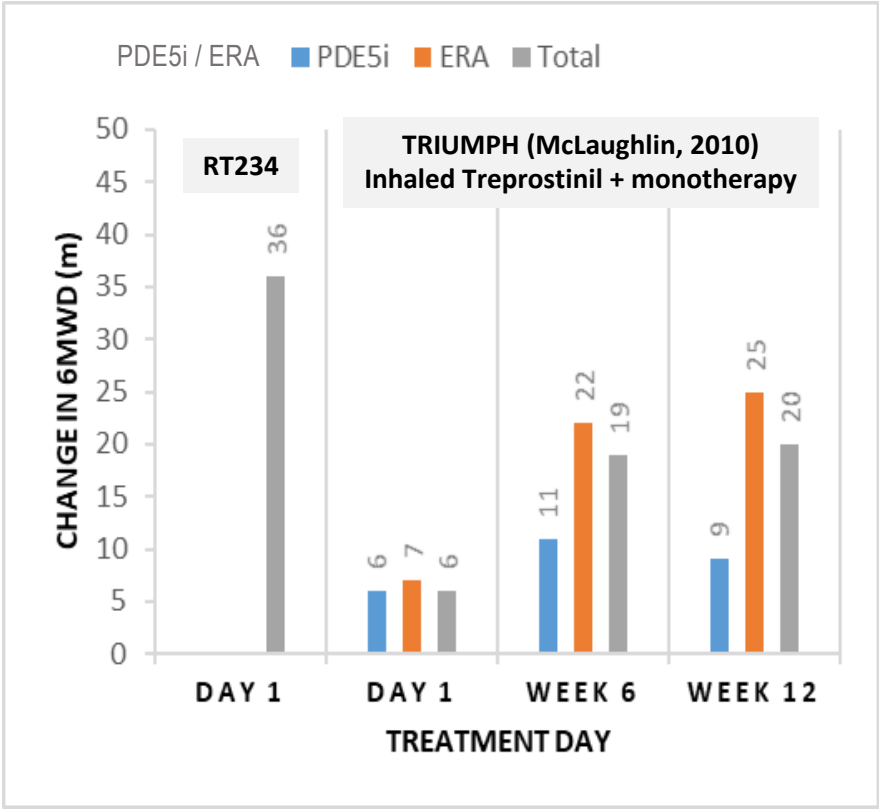
Source (oral vardenafil): Ghofrani *et al.*: J Am Coll Cardiol. 2004; 6: 1488.

RT234 acutely improves cardiac output over 2 h (cycle ergometry)



Acute Improvements in 6MWD (Part B)

- Represents results for PAH patients with a baseline 6MWD < 450 m
- Increases in mean 6MWD is observed for RT234 in the presence of therapeutic levels of PDE5i/ERA dual therapy
- Unlike treprostinil, significant increases in 6MWD are observed after administration of a single dose (36 m vs. 6 m)



Single dose of RT234 is well tolerated on top of maintenance therapies

RT234 Dose (mg) [a]	N	Δ Heart Rate (bpm) [b] Mean (95% CI)	Δ mSAP (mm Hg) [b] Mean (95% CI)	TEAE (drug related)
0.6 mg	**5**	**-8.2 (-16.8 to +0.4)**	**-3.0 (-6.3 to 0.3)**	**None**
1.2 mg	5	3.4 (-0.5 to +7.3)	-2.1 (-10.3 to 6.2)	None
2.4 mg	4	-5.8 (-11.5 to 0.0)	1.0 (-9.1 to 11.1)	1 (mild headache)

[a] RT234 dose is on top of peak background therapy (day 15)
[b] Differences are reported at 60 min following RT234 administration, although subjects were followed for 4 h; 95% CI determined using z statistic

No clinically or statistically significant changes in systemic blood pressure or heart rates noted

Only one TEAE related to study drug was observed at the highest (2.4mg) dose (mild headache)

The low TEAE related to RT234 may be due to the low dose and most subjects are accustomed to oral PDE5i treatment

Conclusions

- **The RT234-CL201 study validated that the RT234 drug product has the critical design features of an as-needed vasodilator**
  - A rapid onset of action within 5 minutes of administration; acute improvements in exercise tolerance of 35 m
  - A duration of action of at least one to two hours post-administration
  - Minimal local and systemic safety and tolerability issues when administered in addition to maintenance therapies
  - Noninvasive delivery system with administration over < 1 minute
- **The results of the study indicate that RT234 has a safety and efficacy profile suitable for continued clinical development as an as-needed vasodilator**

Questions?