Acute Hemodynamic Improvement in Chronic Pulmonary Arterial Hypertension on Dual Therapy Following RT234 Inhalation

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BACKGROUND

- RT234 (vardenafil inhalation powder) is in development for as-needed (PRN) treatment of episodic symptoms of pulmonary arterial hypertension (PAH)
- RT234 is dosed up to 4 times per day to acutely improve:
  - Symptoms
  - Exercise capacity
  - Performance of daily activities
  - Quality of life
- RT234 is designed to provide:
  - Rapid onset of action (within ~15 min)
  - Acceptable duration of action (~2–3 hrs)
  - Convenient treatment regimen (i.e., take "as needed")
  - Minimal safety/tolerability issues over background therapy
  - Noninvasive, portable, simple-to-administer delivery system designed for patients with PAH

Figure 1: The RS01 device used to deliver powdered vardenafil

REFERENCES

1. Ghofrani HA, et al. *J Am Coll Cardiol.* 2004;44:1488-1496.
2. McLaughlin VV, et al. *J Am Coll Cardiol.* 2010;55:1915-1922.

DISCLOSURES

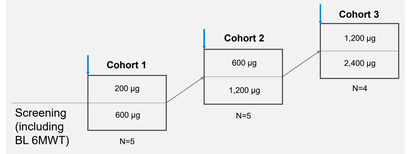
- A. Keogh, N. Dwyer, E. Kotlyar, and D. Kaye: Work at institutions that received funding to conduct the RT234 CL201 trial
- This study is funded by Respira Therapeutics, Inc. Medical writing assistance was provided by Elise Laming, PhD, of ProScribe – Envision Pharma Group, and was funded by Respira Therapeutics, Inc.

METHODS

Study design, CL201 (NCT05343637)

- Study CL201 is a hemodynamic dose-escalation study in 15 patients with PAH (3 dose cohorts containing 5 patients each)
- 2-part study:
  - Part A: Patients received 2 doses while undergoing right heart catheterization (Day 1)
  - Part B: 6-minute walking test post dose at highest tolerated dose achieved in Part A (Day 15)

Figure 2: Study design, CL201



6MWT, 6-minute walk test; BL, baseline.

Table 1: Baseline demographics

Characteristic	Patients (N=14)	
Age (years) [range]	54±14 [22–80]	
Female (n)	11	
White (n)	12	
6MWD (m)	426±129	
FC (n)	II (8); III (5); IV (1)	
mPAP (mmHg)	45±16	
PCWP (mmHg)	12±3	
PVR (dyn·sec·cm^{-5})	558±350	
PDE5i (n)	**Sildenafil**	6
	Tadalafil	8
ERA (n)	**Macitentan**	10
	Bosentan	2
	Ambrisentan	2

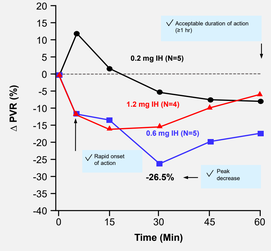
Data are means±SD unless specified otherwise.
6MWD, 6-minute walk distance; ERA, endothelin receptor antagonist; FC, WHO Group 1 PAH functional class; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PDE5i, phosphodiesterase type-5 inhibitor; PVR, pulmonary vascular resistance; SD, standard deviation; WHO, World Health Organization.

RESULTS

Hemodynamic outcomes

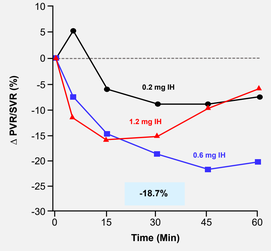
- Decreases in pulmonary vascular resistance (PVR) of >10% occurred within 5 min for the 0.6- and 1.2-mg doses
- RT234 has excellent pulmonary selectivity

Figure 3: Pulmonary vascular resistance



IH, inhalation; PVR, pulmonary vascular resistance.

Figure 4: Pulmonary selectivity



IH, inhalation; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Inhaled vs oral vardenafil

- Comparable pulmonary hemodynamics were observed with inhaled vs oral vardenafil at 1/33rd of the dose

Table 2: Inhaled vs oral vardenafil

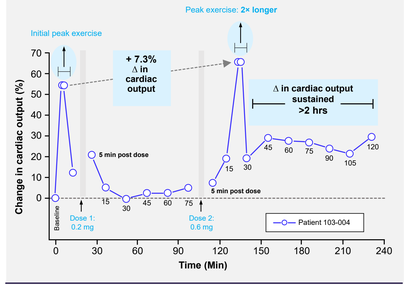
	Hemodynamic metric	% (95% CI) change from baseline: Oral vardenafil (20 mg)[1] (N=9)	% (95% CI) change from baseline: RT234 (0.6 mg)[a] (N=5)	
Pulmonary vascular effect	**PVR**	-26.3 (-29.2 to -22.8)	-23.7 (-44.7 to -18.6)	Improvements in pulmonary hemodynamics for the RT234 0.6 mg dose comparable with 20-mg oral tablet
	mPAP	-12.1 (-15.8 to -7.3)	-12.3 (-19.6 to -3.3)	
	CI	+18.4 (9.8 to 25.1)	+11.9 (-5.0 to 31.9)	
Systemic vascular effect	**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 medication
	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	**PaO_2**	-2.2 (-17.9 to 13.5)	+8.1 (-13.3 to 22.6)	RT234 improves oxygenation relative to oral administration

[a] Measurements at peak effect in PVR (30 min); 95% CI determined using Hodges-Lehman point estimates.
CI, confidence interval; mPAP, mean pulmonary arterial pressure; mSAP, mean systemic arterial pressure; PaO_2, partial pressure of oxygen; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Cardiac output over 2 hrs (cycle ergometry)

- Single inhalation of RT234 (N=1) acutely improved cardiac output over 2 hrs
- Peak decreases in PVR and PVR/systemic vascular resistance ratio with the 0.6-mg dose were -55% and 39%, respectively

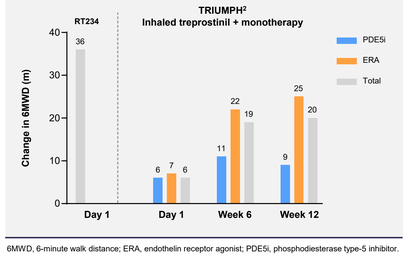
Figure 5: Cardiac output over 2 hrs (cycle ergometry) after inhalation of RT234 by 1 patient



Acute improvements in 6MWD

- Represents results for patients with PAH with a baseline 6-minute walk distance (6MWD) <450 m
- Increases in mean 6MWD were observed for RT234 in the presence of phosphodiesterase type-5 inhibitor (PDE5i)/endothelin receptor agonist dual therapy
- Unlike treprostinil, significant increases in 6MWD were observed after a single dose of RT234 (36 m vs 6 m)

Figure 6: Acute improvements in 6MWD



6MWD, 6-minute walk distance; ERA, endothelin receptor agonist; PDE5i, phosphodiesterase type-5 inhibitor.

Safety outcomes

- A single dose of RT234 was well tolerated on top of maintenance therapies
- No clinically or statistically significant changes in systemic blood pressure or heart rate were noted
- Only 1 treatment-emergent adverse event (TEAE) related to study drug (mild headache) was observed at the highest dose (2.4 mg)
- The low rate of TEAEs related to RT234 may be due to the low dose and most patients being accustomed to oral PDE5i treatment

Table 3: Safety outcomes

RT234 dose[a]	N	Δ Heart rate (bpm),[b] mean (95% CI)	Δ mSAP (mmHg),[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 patients were followed for 4 hrs; 95% CI determined using z-statistic.
bpm, beats per min; CI, confidence interval; mSAP, mean systemic arterial pressure; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Study CL201 validated that RT234 has the critical design features of a PRN vasodilator
  - Rapid onset of action within 5 min of administration
  - Acute improvements in exercise tolerance of 35 m
  - Duration of action of ≥1–2 hrs post administration
  - Minimal local and systemic safety and tolerability issues when administered in addition to maintenance therapies
  - Noninvasive delivery system with administration over <1 min
- The study results indicate that RT234 has a safety and efficacy profile suitable for continued clinical development as a PRN vasodilator

This is an encore of data originally presented at the CHEST Annual Meeting 2020 (October 18–21, 2020)

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