# A single dose of RT234, vardenafil inhaled via the Axial Oscillating Sphere Dry Powder Inhaler (AOS™ DPI), acutely improves exercise capacity and reduces dyspnea in PAH patients (WHO Group 1 PH) – Results from the open-label Phase 2b CPET (Cardiopulmonary Exercise Testing) study (NCT04266197)

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***on behalf of Study Participants, Investigators and Study Personnel***

## Background

- Despite multiple chronic therapies, most PAH patients remain highly symptomatic, exhibiting profound exercise intolerance, dyspnea and fatigue,[1] which limit activities of daily living.
- RT234 (vardenafil inhalation powder) is a novel drug-device combination incorporating a dry-powder inhaler (AOS™ DPI)* designed to maximize drug delivery to the distal lung (Fig 1).
- RT234 aims address the unmet need for an on-demand (PRN) treatment that acutely improves exercise tolerance and reduces exertional symptoms, e.g., dyspnea.

**Figure 1: AOS™ DPI**


*AOS™ DPI: Axial Oscillating Sphere Dry Powder Inhaler

## Objective

- The objective of the Phase 2b study (CL202) was to determine the effects of a single-dose RT234 treatment on exercise capacity ('function') and exertional symptoms ('feel') in PAH patients.

## Methods

- CL202 was an open-label study of a single RT234 dose in 0.5 mg, 1.0 mg, and 2.0 mg cohorts, sequentially (Fig.2).
- Participants underwent a baseline incremental cycling cardiopulmonary exercise test (CPET) without treatment, and, after 2-14 days, a repeat CPET initiated 30 min after RT234.
- Participants maintained background therapy throughout.
- The primary endpoint was the change from baseline in oxygen uptake at peak exercise (peak $VO_2$)
- Secondary endpoints included the change in $V_E/VCO_2$ slope (ventilatory efficiency) and the change in dyspnea (modified Borg Dyspnea score, 0-10 scale).

**Figure 2: CL202 Study Design**


## Results

- A total of 42 subjects (Intent-To-Treat Population, ITT) were enrolled (Table 1).

| Table 1: Demographics & Background | 0.5 mg (N=7) | 1 mg (N=21) | 2.0 mg (N=14) | Overall (N=42) |
|---|---|---|---|---|
| Age (years), median (range) | 46 (23 - 73) | 51 (36 - 71) | 54.5 (29 – 76) | 52.5 (23 – 76) |
| Female, n (%) | 7 (100%) | 17 (81.0%) | 11 (78.6%) | 35 (83.3%) |
| ***WHO Functional Class, n (%)*** | | | | |
| II | 3 (42.9%) | 20 (95.2%) | 11 (78.6%) | 34 (81.0%) |
| III | 4 (57.1%) | 1 (4.8%) | 3 (21.4%) | 8 (19.0%) |
| ***Type of PAH Etiologic, n (%)*** | | | | |
| Idiopathic, primary or familial PAH | 6 (85.7%) | 9 (42.9%) | 10 (71.4%) | 25 (59.5%) |
| PAH associated with CTD | 1 (14.3%) | 7 (33.3%) | 3 (21.4%) | 11 (26.2%) |
| PAH associated with Other factors | 0 | 5 (23.8%) | 1 (7.1%) | 6 (14.3%) |
| ***Background PAH Therapies, n (%)*** | | | | |
| PDE5 Inhibitors, n (%) | 6 (85.7%) | 19 (90.5%) | 13 (92.9%) | 38 (90.5%) |
| ERAs, n (%) | 6 (85.7%) | 17 (81.0%) | 9 (64.3%) | 32 (76.2%) |
| Prostacyclin, n (%) | 3 (42.9%) | 11 (52.4%) | 10 (71.4%) | 24 (57.1%) |

- The Per-Protocol-Population (PPP, N=39) comprised the ITT, less three subjects due to missing CPET data, a right-left intra-atrial shunt, or insufficient exercise effort.
- Increase of peak $VO_2$ and decrease in $V_E/VCO_2$ slope were dose-dependent with statistically significant effects observed in the 2.0 mg cohort (Figs. 3 & 4)
- The responder fraction (i.e. those with increased peak $VO_2$) rose with dose (0.5 mg: 40%, 1.0 mg: 55%, 2.0 mg: 64%).
- Most responders increased peak $VO_2$ by at least 0.7 mL/min/kg or 6% (Fig. 5), which is considered clinically meaningful. [2,3,4]
- Over all cohorts, modified Borg Dyspnea score at peak decreased independent of dose (Mean -1.3±2.07, p=0.0005, Fig. 6).

**Figure 3: RT234 increased peak $VO_2$**

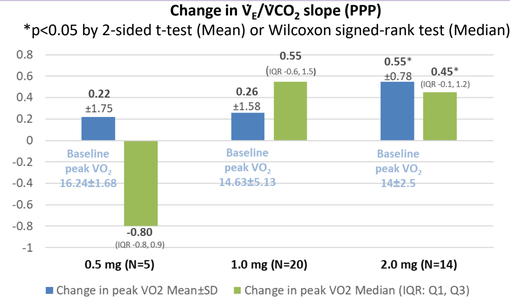



**Figure 4: RT234 decreased $V_E/VCO_2$ slope**

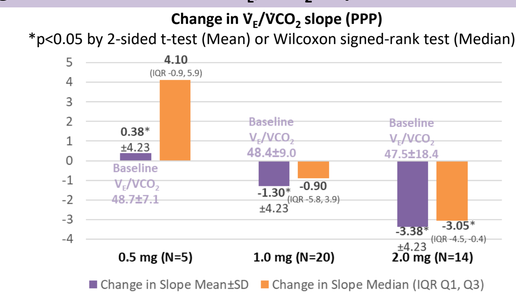



**Figure 5: Peak $VO_2$ Responders (PPP)**

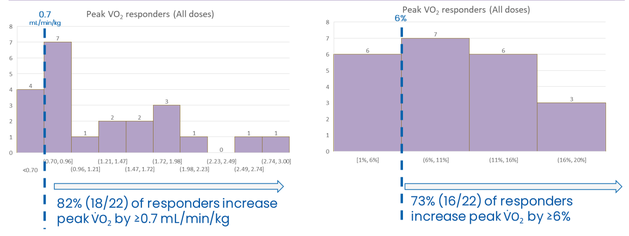
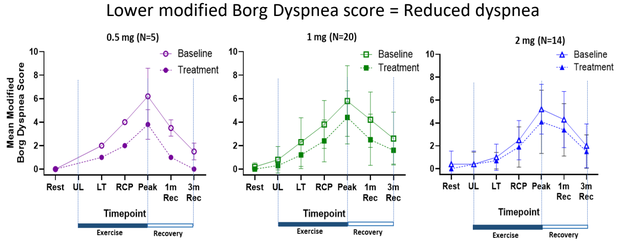
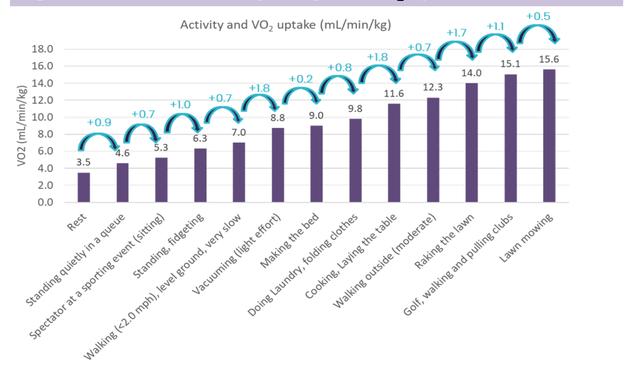



**Figure 6: RT234 reduced dyspnea (PPP)**




- For PAH patients, incremental increases in peak $VO_2$ could translate to meaningful increase in daily activities (Fig. 7). [5]

**Figure 7: Activities of daily living and $VO_2$ uptake**




- RT234 demonstrated favorable safety and tolerability (Table 2).

| Table 2: Treatment-Related Adverse Events | 0.5 mg (N=7) | 1 mg (N=21) | 2 mg (N=14) | Overall (N=42) |
|---|---|---|---|---|
| Any Treatment-Related TEAE | 1 (14.3%) | 4 (19.0%) | 3 (21.4%) | 8 (19.0%) |
| **Nervous system disorders** | **0** | **2 (9.5%)** | **0** | **2 (4.8%)** |
| Headache | 0 | 2 (9.5%) | 0 | 2 (4.8%) |
| Dysgeusia | 0 | 1 (4.8%) | 0 | 1 (2.4%) |
| Presyncope | 0 | 1 (4.8%) | 0 | 1 (2.4%) |
| **Respiratory, thoracic & mediast. disorders** | **0** | **2 (9.5%)** | **3 (21.4%)** | **5 (11.9%)** |
| Cough | 0 | 1 (4.8%) | 3 (21.4%) | 4 (9.5%) |
| Nasal congestion | 0 | 1 (4.8%) | 0 | 1 (2.4%) |
| Rhinorrhea | 0 | 1 (4.8%) | 0 | 1 (2.4%) |
| **Gastrointestinal disorders** | **1 (14.3%)** | **0** | **0** | **1 (2.4%)** |
| Dry mouth | 1 (14.3%) | 0 | 0 | 1 (2.4%) |
| Nausea | 1 (14.3%) | 0 | 0 | 1 (2.4%) |
| **General disorders** | **0** | **1 (4.8%)** | **1 (7.1%)** | **2 (4.8%)** |
| Chest discomfort | 0 | 1 (4.8%) | 1 (7.1%) | 2 (4.8%) |
| Sensation of foreign body | 0 | 1 (4.8%) | | 1 (2.4%) |
| **Vascular disorders** | **0** | **1 (4.8%)** | **0** | **1 (2.4%)** |
| Flushing | 0 | 1 (4.8%) | 0 | 1 (2.4%) |

## Conclusions*

- A single dose of RT234 acutely increased exercise capacity in a dose-dependent manner, reduced exercise-induced dyspnea and demonstrated favorable safety and tolerability. For most responders, the increase in peak $VO_2$ was clinically meaningful.
- RT234 is a novel, on-demand treatment that may be added to chronic PAH therapy to increase function in daily activities and reduce dyspnea i.e., improve "feel and function".
- Further clinical studies for RT234 development are warranted.

***Respira Therapeutics is the sponsor of study CL202. RT234 is an investigational product that has not been approved by the FDA or any other regulatory authority.**

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**References:** 1. FDA: Pulmonary arterial hypertension: the voice of the patient. 2014. 2. Ross et al. 2010, *Circulation*. 2016;134:e653-e699, 3. Moutchia et al. 2013, *Am J Respir Crit Care Med*. 15;207(8):1070-1079: 6MWD and peak $VO_2$ are correlated, and an increase in 6MWD of 30 meters (the minimal clinically important difference in 6MWD for PAH patients) corresponds to an improvement in peak $VO_2$ of ~0.7 mL/min/kg. 4. Swank et al. 2012, *Circ Heart Fail*. 5(5):579-585: Every ~6% increase in peak $VO_2$ is associated with a 5% lower risk of all-cause mortality or all-cause hospitalization in patients with CHF. 5. Ainsworth BE, et al. 2000, *Med Sci Sports Exerc*;32(9):S498-504.