Safety And Pharmacokinetics Of Vardenafil Inhalation Powder (RT234) Following Oral Inhalation In Healthy Adult Volunteers

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Introduction

- Vardenafil hydrochloride is a phosphodiesterase type-5 inhibitor. Vardenafil is administered as an oral tablet in the treatment of erectile dysfunction (Levitra®, Bayer).
- RT234 (vardenafil inhalation powder) is being developed for use as an as-needed (PRN) treatment for episodic symptoms of pulmonary arterial hypertension (PAH), to acutely improve exercise capacity, physical function, and disease-associated symptom impacts.
- RT234 is specifically designed for use as a PRN therapeutic with a rapid onset of action, extended duration of action, minimal adverse events when used in addition to background PAH disease-specific therapy, and a convenient delivery system with a low daily treatment burden.
- RT234-CL101 was a Phase 1 single ascending dose (SAD, N=6/dose cohort) study, followed by a multiple ascending dose (MAD, N=8) study utilizing the maximum tolerated dose from the SAD. In the MAD, subjects received the 2.4 mg dose every 4 hr for up to 4 doses (QID) (i.e., 9.6 mg/day) for 7 consecutive days. Of the 32 healthy volunteers, 53.1% were female, 75% were white, and the mean age was 26 yr.

Nonclinical

- Seven nonclinical safety studies in rats and dogs, including 5-d dose range finding, 28-d and 13-w GLP toxicology, and safety pharmacology studies were performed
- NOAEL values were the highest administered dose in each study
- High safety margins relative to the RT234 Phase 2b doses
- Histopathology observations were species-specific generic effects related to powder inhalation, and not related to RT234
  - Nonadverse mild irritation in the upper respiratory tract and trachea in rat and dog
  - Nonadverse reverse sneezing in the dog

RT234: Large safety margins in nonclinical studies, even for four times daily dosing

Dose	Species	NOAEL (mg/kg)	Phase 2 Dose (mg/kg) [c]	QD Safety Margin (Human/Animal)	QID Safety Margin (Human/Animal)
Delivered Dose [a]	Rat	54.5	0.0083	6543	1636
Pulmonary Deposited Dose [b]	Rat	5.5	0.0083	660	165
Delivered Dose [a]	Dog	22.6	0.0083	2713	678
Pulmonary Deposited Dose [b]	Dog	5.7	0.0083	687	172

[a] Delivered dose = dose at breathing zone of the animal
[b] Pulmonary Deposited Dose = 10% of delivered dose in the rat and 25% of the delivered dose in the dog
[c] Phase 2 dose of 0.5 mg in a 60 kg human subject = 0.00833 mg/kg

Materials

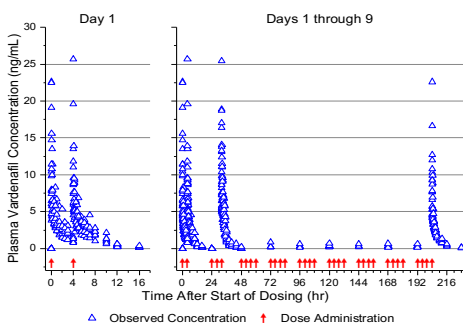
- RT234 is comprised of an adhesive mixture of 2.0% w/w micronized vardenafil and coarse lactose carrier particles (CDMO: Hovione FarmaCiencia, Portugal).
- The dry powder was filled into Hypromellose capsules with an MG2 FlexaLab and packaged in HDPE bottles.
- For Phase 1, the dry powder was administered with the RS01 dry powder inhaler (Plastiape S.p.A., Osnago, Italy).

RT234 and Portable dry powder inhaler (DPI)

Vardenafil inhalation powder | RS01 DPI

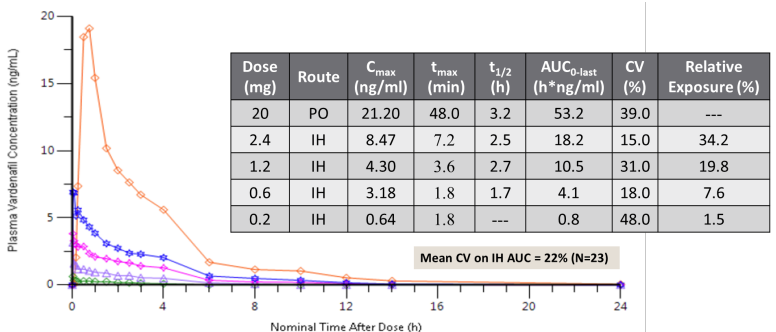
Phase 1: Multiple Ascending Dose (MAD)

Minor accumulation with QID dosing



Phase 1: Single Ascending Dose (SAD)

Rapid, dose proportional systemic uptake with low systemic exposure vs. Levitra



Dose (mg)	Route	C_{max} (ng/ml)	t_{max} (min)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (h*ng/ml)	CV (%)	Relative Exposure (%)
20	PO	21.20	48.0	3.2	53.2	39.0	---
2.4	IH	8.47	7.2	2.5	18.2	15.0	34.2
1.2	IH	4.30	3.6	2.7	10.5	31.0	19.8
0.6	IH	3.18	1.8	1.7	4.1	18.0	7.6
0.2	IH	0.64	1.8	---	0.8	48.0	1.5

IH dosing: 2.4 mg (blue), 1.2 mg (pink), 0.6 mg (violet), 0.2 mg (green); PO dosing: 20mg (orange)

- The t_{max} for RT234 was observed at the first timepoint after dose administration (ca., 2 min)
- Vardenafil exposure (C_{max}, $AUC_{0\text{-inf}}$) was dose proportional from 0.2 mg to 2.4 mg
- Vardenafil systemic exposure for all RT234 doses was significantly less than the 20 mg oral tablet
- Minor accumulation of no clinical significance was observed following dosing of RT234 every four hours QID in the MAD portion of the study

Safety: RT234 was generally well tolerated with TEAEs mild to moderate in intensity

Treatment related Adverse Events (>6.4%)	RT234 (N=31)	Levitra® (N=5)
Headache	10 (32.3)	4 (80.0)
Dizziness	4 (12.9)	3 (60.0)
Nervous Syst. Imbal.	1 (3.2)	1 (20.0)
Flushing	1 (3.2)	1 (20.0)
Chills	1 (3.2)	1 (20.0)
Cough	3 (9.7)	0 (0.0)
Nausea	3 (9.7)	0 (0.0)

- No dose limiting toxicity was observed and the maximum tolerated dose was not reached for doses up to 9.6 mg/day
- No evidence of local airway irritation (dyspnea, wheezing, bronchospasm, or spirometry changes)
- Brief, asymptomatic decreases in systemic blood pressure was noted approximately ~40-100 min post-dosing with RT234 (not clinically significant)
- The 2.4 mg dose is ~2.5 to 5-fold greater than the 0.5 and 1.0 mg doses planned for Phase 2b

Enrollment in a Ph 2a hemodynamic study in PAH patients (ACTRN12619001178134) is complete, and a Ph 2b exercise capacity study as assessed by Cardio-Pulmonary Exercise Testing (CPET) study is underway.

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