SAFETY AND TOLERABILITY OF PUR1800, AN ORALLY INHALED NARROW SPECTRUM KINASE INHIBITOR, IN PATIENTS WITH STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD).

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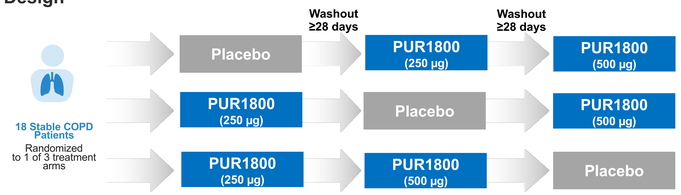
Rationale: Acute exacerbations (AE) in patients with COPD cause significant morbidity. PUR1800 is a novel inhaled iSPERSE™ dry powder formulation of RV1162, a narrow spectrum kinase inhibitor, targeting p38 MAPK, Src and Syk kinases, under development for the treatment of AECOPD. This study evaluated the safety, tolerability and pharmacokinetics of inhaled doses of PUR1800 for 14 days in patients with stable and 1+ years of Grade II/III COPD.
Methods: Eighteen subjects (7 males,11 females, 54 to 76 years) participated in a double-blind 3-way crossover study, with 14-day treatment periods, followed by a 28-day washout. Subjects were randomized to 1 of 3 arms receiving inhaled placebo, 250 µg, or 500 µg PUR1800 in random order. Seventeen subjects received study drug and 13 completed all three dose periods.
Results: PUR1800 at doses of up to 500 µg/day for 14 days was safe and well tolerated. Adverse events and mean FEV_1 and FVC were similar between placebo and both doses of PUR1800. Systemic exposure resulted in geometric mean C_{max} of 320 and 347 pg/mL and $AUC_{0-τ}$ of 1557 and 2471 h*pg/mL for 250 µg and 500 µg, respectively on Day 14, with steady state and 2-fold accumulation by approximately Day 7. Previously, inhalation of 500 µg RV1162 as a lactose blend resulted in approximately 6-fold accumulation with steady state at 28 days.
Conclusion: Inhaled PUR1800 was safe and well tolerated in stable COPD patients. Systemic exposure resulted in minimal accumulation with steady state by 7 days. A proof-of-concept study with PUR1800 is warranted in patients with AECOPD.

Background & Rationale

PUR1800 is a dry powder formulation of a narrow spectrum kinase inhibitor (NSKI), developed using the proprietary Pulmatrix iSPERSE technology for oral inhalation. The active ingredient, RV1162 inhibits p38 MAPK, as well as members of the Src and Syk families of non-receptor tyrosine kinases. RV1162 was previously administered by oral inhalation to healthy subjects and patients with COPD as a lactose blend. That formulation was safe and well tolerated but resulted in substantial accumulation, limiting its potential as a maintenance therapy for COPD. Pulmatrix reformulated RV1162 using our iSPERSE technology and refocused development toward shorter term dosing for acute exacerbations of COPD (AECOPD). This study aimed to evaluate the safety, tolerability and PK profile of inhaled PUR1800 in subjects with stable COPD. Biomarkers of the pharmacodynamic (PD) activity of PUR1800 were also explored.

Study Design



This was a single-center randomized, placebo-controlled, double-blind 3-way crossover study in adult subjects with stable COPD over 3 discrete Treatment Periods (TPs). Safety, tolerability, PK, and PD endpoints were assessed following 14 daily doses of PUR1800 or placebo. Sputum PD endpoints included total and differential cell counts and a novel quasi-quantitative measurement of phospho-p38 MAPK (p-p38MAPK) in sputum cells using a flow cytometry method validated to assess the mean fluorescence intensity of p-p38MAPK within gated cell types.

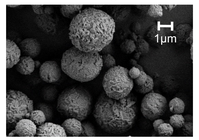
- TP1: On Day 1 all eligible subjects were randomised to 1 of 3 treatment sequences and received either placebo or the lowest nominal dose of PUR1800 (PUR1800, 250 µg) for 14 consecutive days
- TP2: Following a washout period of at least 28 days, subjects received a treatment other than that received during TP1 for 14 consecutive days
- TP3: Following a washout period of at least 28 days, subjects received the treatment that they had not received during TPs 1 or 2 (placebo or PUR1800, 500 µg) for 14 consecutive days.

Subjects were to participate for approximately 22 weeks including the screening phase (up to 28 days). Treatment was administered as a single daily dose during each TP. Subjects were required to attend study site visits during Days 1, 2, 7, and 14 of each TP and an EOS visit at Day 28 post last study drug dose.

PUR1800 Drug Product and Dry Powder Inhaler

PUR1800 Dry Powder Inhaler

PUR1800 iSPERSE Engineered Particles



The iSPERSE formulation containing RV1162 is designated as PUR1800 and contains RV1162 as the active ingredient and sodium sulfate, mannitol and polysorbate 80 as excipients. PUR1800 is intended to be administered via oral inhalation for the treatment of AECOPD. PUR1800 was delivered to the lungs with a capsule-based passive dry powder inhaler (DPI), which utilizes the subject's inhalation energy to deliver and disperse the formulated powder.

Demographics

	PUR1800 Sequence			All Subjects N=18
	Placebo, 250 µg, 500 µg N=5	250 µg, Placebo, 500 µg N=8	250 µg, 500 µg, Placebo N=5	
Age, mean years (SD)	73.4 (1.95)	65.9 (7.38)	67.8 (7.16)	68.5 (6.77)
Sex, n (%)				
Male	1 (20.0)	3 (37.5)	3 (60.0)	7 (38.9)
Female	4 (80.0)	5 (62.5)	2 (40.0)	11 (61.1)
BMI, mean kg/m² (SD)	28.46 (2.11)	26.38 (3.79)	28.00 (4.25)	27.41 (3.49)
History of smoking, n (%)				
Former smoker	2 (40.0)	5 (62.5)	4 (80.0)	11 (61.1)
Current smoker	3 (60.0)	3 (37.5)	1 (20.0)	7 (38.9)
Smoking, mean pack years, (SD)	65.3 (53.63)	40.4 (14.74)	53.4 (21.88)	50.1 (29.36)
Alcohol consumption, mean units per week, (SD)	3.0 (2.65)	2.8 (2.12)	2.0 (2.35)	2.6 (2.23)

Safety and Tolerability

	PUR1800 500µg N=14		PUR1800 250µg N=18		Placebo N=18	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
TEAEs	20	9 (64.3)	15	9 (50.0)	11	8 (53.3)
Serious TEAEs	1	1 (7.1)	0	0	0	0
Serious study treatment related TEAEs	0	0	0	0	0	0
Intensity						
Mild	9	2 (14.3)	11	6 (33.3)	7	4 (26.7)
Moderate	10	6 (42.9)	4	3 (16.7)	4	4 (26.7)
Severe	1	1 (7.1)	0	0	0	0
Relationship to study treatment						
Not related	20	9 (64.3)	15	9 (50.0)	11	8 (53.3)
Related	0	0	0	0	0	0
TEAEs leading to withdrawal from study	0		0		1 (6.7)	
TEAEs leading to discontinuation of treatment	1 (7.1)		0		0	
Treatment-related TEAEs leading to discontinuation of treatment	0		0		0	

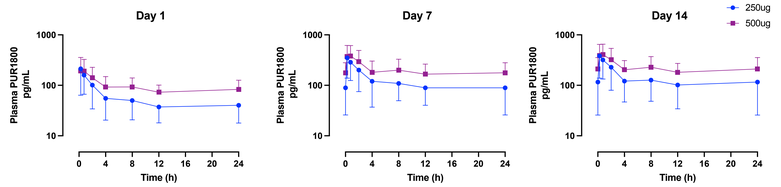
PUR1800 was safe and well tolerated

- 1 SAE unrelated to treatment
- All other TEAEs were mild to moderate in severity
- No TEAEs were drug-related
- Most frequently reported TEAE was headache

6 subjects had exacerbations:

- 2 in 500 µg treatment period
  - 1 on last day dosing
  - 1 on day after last day of dosing
- 1 during 250 µg treatment period (Day 10)
- 3 in placebo treatment period
  - 1 during dosing (Days 2-10)
  - 2 after dosing (during washout)

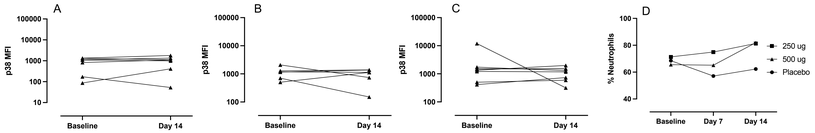
PUR1800 Pharmacokinetics



Day	Dose (ug)	T_{max} (h)	C_{max} (pg/mL)	$AUC_{(0-t)}$ (pg*h/mL)	Accumulation (AUC)
1	250	0.35	183	1133	-
	500	0.79	170	1962	-
7	250	0.29	298	1433	-
	500	0.69	328	2218	-
14	250	0.34	320	1557	2.07
	500	0.60	347	2471	2.05

Blood samples were collected pre-dose and 0.25, 0.75, 2, 4, 8, and12 hours post-dose on Days 1, 7, and 14 and pre-dose on Day 2 (Day 1 + 24 hours). Figures shown are mean plots of plasma exposure on Days 1, 7 and 14, In addition, a tabulated summary data of the primary pharmacokinetic variables is shown. Data show controlled and reproducible kinetics over 14 days of daily dosing.

PUR1800 Sputum Pharmacodynamics



Individual plots of phosphorylated p38 levels in sputum neutrophils from individuals with paired baseline and Day 14 data. Plots show the response to placebo (A), 250 µg (B) and 500 µg (C). In addition, mean neutrophil differential counts for each dose (D) at baseline and on Days 7 and 14 of dose. Data indicate no pharmacodynamic effect of PUR1800.

Pharmacokinetic and Pharmacodynamic Summary

- Systemic absorption following inhalation of PUR1800 was rapid on all days and doses.
- Plasma exposure increased with increasing dose following single and multiple dosing.
- There was a generally dose proportional increase in AUC_{0-t} and accumulation was approximately 2-fold.
- Steady-state was likely achieved by Days 7.
- The $t_{½}$ was approximately 36 to 50 hours following the first dose and T_{max} was generally ≤ 0.75 hours post-dose on all days and doses.
- There was no change in any of the sputum PD parameters during dosing for either PUR1800 dose.

Safety Summary

- PUR1800 was safe and well tolerated
- There were no treatment-related adverse events
- All adverse events were mild to moderate in severity, with the exception of one unrelated SAE

Conclusions

PUR1800 is safe and well tolerated at daily inhaled doses of up to 500 µg for 14 days. Exposure shows consistent and well controlled pharmacokinetics with minimal accumulation. Pharmacodynamic assessments did not show evidence of target engagement in a population of stable COPD patients, however this may not be unexpected in this population. Further study is warranted to assess efficacy in exacerbating COPD patients.