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Title: Safety, pharmacokinetic and pharmacodynamic profile of RV568, a narrow spectrum kinase inhibitor, following repeat inhaled dosing in COPD patients

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Body: RATIONALE To evaluate the safety, pharmacokinetic (PK) and pharmacodynamic (PD) profile of RV568 in GOLD stage II/III Chronic Obstructive Pulmonary Disease (COPD) patients. METHODS 30 COPD patients aged 40–75 years were recruited. Inhaled RV568 50mg, 100mg or placebo were given daily for 14 days. Forced expiratory volume in 1 second (FEV1) was recorded primarily for safety; PK was measured on Days (D) 1, 7 and 14. PD included 54 sputum and 20 serum biomarkers measured by Luminex, biochemical assay or ELISA. RESULTS Twenty eight subjects completed the study, 2 met the withdrawal criterion of decrease in FEV1 >20%. One subject [placebo] had a serious adverse event (hospitalised for COPD exacerbation) otherwise no clinically significant safety signals attributable to RV568 were reported. On D14 compared to baseline, RV568 showed a significant ($p<0.05$) increase in FEV1 compared with placebo. PK data showed plasma exposure was approximately 2 fold greater on D14 than D1, the effective half-life was 19-29 h and steady state was reached by D7. RV568 showed a significant ($p<0.05$) decrease in sputum malondialdehyde (MDA; both doses) on D14 compared with baseline and placebo, and matrix metalloproteinase 1 (50μg) on D14 compared with baseline. Reduction of MDA correlated well with the increase in FEV1 ($p<0.02$, $r<-0.59$). In serum RV568 showed a significant ($p<0.05$) reduction of myeloperoxidase (both doses) and macrophage inflammatory protein 1 beta (100 μg) on D14 compared with baseline; decreases were also seen in the placebo group. CONCLUSIONS The safety, PK and PD profile support progression of inhaled RV568 into further clinical studies in COPD.