This abstract has been withdrawn at the author's request.

1335. Safety and Pharmacokinetic Profile of PC786, a Novel Inhibitor of Respiratory Syncytial Virus L-protein Polymerase, in a Single and Multiple-Ascending Dose Study in Healthy Volunteer and Mild Asthmatics

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Background. RSV is the most common cause of bronchiolitis in infants and is responsible for severe respiratory infections in the elderly and immunocompromised populations. RSV replicates in the columnar epithelial cells of the proximal and distal airways which are accessible to inhaled therapies. PC786 is a potent non-nucleoside RSV L-protein polymerase inhibitor designed for inhaled delivery. In preclinical studies, PC786 exhibits prolonged lung tissue residence with minimal systemic exposure, thus limiting the potential for adverse systemic effects.

Methods. A phase 1 study was conducted to evaluate the safety and pharmacokinetics of PC786 delivered in a suspension formulation by nebulizer (PARI LC SPRINT® device). Healthy volunteers (HVs) received placebo or PC786 as single ascending doses (0.5–20 mg, Cohort (C) 1), 5 mg BD for 7 days (C2), or 10 mg BD for 7 days (C3). Mild asthmatics received a single dose of PC786 5 mg or placebo (C4). PC786 PK was measured in plasma and in nasal mucosal lining fluid (MLF) collected using a synthetic absorptive matrix.

Results. PC786 was well tolerated, with no significant adverse clinical nor laboratory findings. Following single inhaled doses PC786 appeared rapidly in the plasma; mean plasma C_{max} of 190, 571, 1,760, and 3,270 pg/mL, for the 0.5, 2, 8, and 20 mg doses, respectively, were measured on average at 0.68 to 0.93 hours (T_{max}) post-inhalation. Following administration of 5 mg BD (C2) the extent of accumulation was approximately 2-fold. The geometric mean apparent terminal half-life measured following 10 mg BD (C3) was 97 hours. The ratio of MLF:plasma concentrations ranged from 6,347 (+2 hours) to 1,050 (+24h).

Conclusion. PC786 was well tolerated by HVs and asthmatics. The compound showed a rapid T_{max}, suggesting rapid exposure of the respiratory epithelium. The PC786 concentrations in MLF exceed the IC_{90} for RSV, but circulating plasma concentrations were low. The MLF:plasma measured in this study was consistent with lung:plasma ratios measured in preclinical studies. The long plasma half-life is consistent with slow absorption from the lung being the dominant process controlling systemic kinetic behavior. The long t½ and 2-fold accumulation ratio observed on repeat dosing supports once daily dosing in subsequent studies.

Disclosures. **L. Cass**, Pulmocide Ltd.: Employee and Shareholder, Salary. **A. Davis**, Pulmocide Ltd.: Employee and Shareholder, Salary. **A. Murray**, Pulmocide Ltd.: Employee and Shareholder, Salary. **K. Woodward**, Pulmocide Ltd.: Consultant, Consulting fee. **K. Ito**, Pulmocide Ltd.: Employee and Shareholder, Salary. **P. Strong**, Pulmocide Ltd.: Board Member, Employee and Shareholder, Salary. **G. Rapeport**, Pulmocide Ltd.: Board Member, Employee and Shareholder, Salary.

1336. Assessment of the *In Vivo* Efficacy of WCK 5222 (Cefepime-Zidebactam) Against Carbapenems-Resistant *Acinetobacter baumannii* (CR-ACBN) in the Neutropenic Murine Thigh Infection Model

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Background. Zidebactam (ZID) is a novel β-lactam enhancer with high binding affinity to PBP2 and intrinsic activity against many Gram-negative pathogens, with the exception of ACBN. ZID also inhibits β-lactamases but not OXA carbapenemases associated with ACBN or metallo-β-lactamases. However, WCK 5222 (a combination of cefepime [FEP] and ZID) has shown *in vitro* activity against ACBN, including OXA producers. Moreover, we have previously shown that WCK 5222 human-simulated regimen (HSR) causes extensive (i.e., >2 log) eradication of ACBN from neutropenic mice lung. This study aimed to evaluate the *in vivo* efficacy of the HSR of WCK 5222 compared with FEP HSR or ZID HSR alone against ACBN in the neutropenic murine thigh infection model.

Methods. Six CR-ACBN clinical isolates, including five isolates expressing OXA-23 or OXA-24, were studied. FEP and WCK 5222 MICs were 128 to >512 and 16 to 64 mg/L, respectively. The ZID MIC was >512 mg/L for all isolates. ICR mice were rendered transiently neutropenic via cyclophosphamide prior to thigh inoculation with bacterial suspensions of 10^7 CFU/mL. Treatment mice received either FEP HSR (equivalent to a clinical dose of 2 g IV q8h as a 1 hour infusion), ZID HSR (equivalent to a clinical dose of 1 g IV q8h as 1 hour infusion), or WCK 5222 HSR (FEP HSR + ZID HSR). Control mice were vehicle-dosed. Changes in $\log_{10}$ CFU/mL at 24 hours compared with 0 hours controls were measured to assess efficacy.

Results. The average $\log_{10}$ CFU/thigh at 0 hours across all isolates was 5.85 ± 0.22. Compared with 0 hours control, the mean bacterial growth at 24 hours in the untreated control mice, FEP HSR, and ZID HSR were 2.34 ± 0.93, 1.36 ± 1.40, and 2.04 ± 0.80 $\log_{10}$CFU/thigh, respectively. The WCK 5222 HSR produced a decline in bacterial burden for all isolates [mean reduction of −2.09 ± 1.01 $\log_{10}$CFU/thigh]; 4/6 isolates achieved ≥ 2-log reduction while ≥1-log reduction was attained with the remaining two isolates.

Conclusion. HSR of WCK 5222 showed potent *in vivo* activity against CR-ACBN expressing OXA carbapenemases in the murine thigh model which is attributed to the β-lactam enhancing effect of ZID, driven by the complementary PBP binding of FEP and ZID. These results support the clinical evaluation of WCK 5222 for the management of infections due to CR-ACBN.

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1337. SYN-004 (Ribaxamase) Protects the Gut Microbiome of Patients Treated With Ceftriaxone From Disruption and Reduces the Emergence of Antimicrobial Resistance

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Background. When β-lactam antibiotics are administered intravenously, a significant portion of each dose can be excreted through the bile into the intestine. This excess antibiotic disrupts the balance of the gut microbiome making the recipient more susceptible to certain infections and can lead to the emergence of antimicrobial resistance. SYN-004 (ribaxamase) is an orally administered β-lactamase designed to be given with IV β-lactam antibiotics (penicillins and cephalosporins) to degrade excess antibiotics excreted into the upper GI tract before they can disrupt the gut microbiome and resistome.

Methods. During a Phase 2b, clinical study with ribaxamase which demonstrated a significant reduction in *Clostridium difficile* infection in patients receiving ceftriaxone + ribaxamase, longitudinal fecal samples were collected from the patients. DNA extracted from these samples was 16S rRNA and whole genome sequenced, and the sequences were analyzed for changes in the gut microbiome and resistome. Statistical analyses were performed to determine correlations between changes in the gut microbiome and resistome and clinical study data.

Results. Sequence analyses revealed that ribaxamase protected the integrity of the gut microbiome, including preventing enterococcal mono-domination (defined as >30% of the microbiome being from one genus), and identified over 1,300 AMR genes in the gut resistome. LefSe analysis of the gut resistome identified a family of β-lactamases (CfxA) and vancomycin resistance genes which demonstrated a significant increase in placebo-treated vs. ribaxamase-treated patients from pre-to post-antibiotics. Analysis by