460. Late-Breaking Abstracts Session:
New treatments and targets for airway disease

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Late-breaking abstract: Inhaled pan-selectin antagonist bimosiamose in COPD: A double-blind, randomized, placebo-controlled phase II study
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818s
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Late-breaking abstract: Pre-clinical characterization of RP3128, a novel and potent CRAC channel inhibitor for the treatment of respiratory disorders

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Introduction: RP3128 plays a pivotal role in airway remodelling processes that include recruitment and activation of inflammatory cells, cytokine release, mast cell activation and vascular permeability. Given the established criticality of PI3Kδ in airway inflammation, inhibitors specifically targeting this isoform would accelerate progression of asthma and COPD.

Methods: Specificity of RP3128 towards PI3Kδ, suppression of pAKT in THP-1 cells, elastase exocytosis and migration in neutrophils, and IgE-induced mast cell degranulation were determined. Pre-clinical efficacy of RP3128 was confirmed in animal models of airway disorders, namely, LPS-induced pulmonary neutrophilia in rat as well as in acute and chronic cosinophilia models in Guinea Pig.

Results: RP3128 demonstrated significant potency against PI3Kδ (18.5 μM) with several fold selectivity over other isoforms with subsequent inhibition of pAKT. In vitro, the compound inhibited neutrophil function and mast cell degranulation at nanomolar concentrations. RP3128 displayed excellent efficacy in inhibiting LPS-induced neutrophilia in SD rat (65% at 20 mg/kg b.wt). Besides, the compound decreased eosinophil infiltration into the lungs upon induction by PAF (>80% @ 10 μg/kg) or OVA (>60% @ 1 mg/kg) in Guinea pigs. Consistent with in vivo findings, the compound caused a significant inhibition of mast cell degranulation manifested by a reduction in histamine release.

Conclusions: Results demonstrate the therapeutic potential of RP3128 in asthma and related airway disorders acting via the PI3Kδ pathway. Further in vivo studies are in progress to evaluate the efficacy of the compound in airway hyper-responsiveness prior to the initiation of clinical trials.

4949
Late-breaking abstract: The effects of roxithromycin as an anti-inflammatory agent on clinical outcomes in patients with bronchiectasis: A double blinded randomized controlled study

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Bronchiectasis is an inflammatory airway disease with vicious cycle of infection and inflammation. Macrolides have been reported for improve clinical outcomes, we study the effects of macrolide on clinical outcomes such as symptom scores and quality of life in patient with bronchiectasis.

Material and methods: Randomized double blinded placebo controlled trials of roxithromycin 300 mg or placebo once daily for 8 weeks in patient with bronchiectasis. Clinical examination, pulmonary function test, St. George’s Respiratory Questionnaire (SGRQ) and sputum culture for aerobic bacteria were done each visits.

Results: 20 bronchiectatic patients, mean age of 56 years, were participated in this study. Nine patients has randomized to roxithromycin 300 mg and 11 patients received placebo once daily. Roxithromycin was shown to improve symptoms scores (mean difference of symptom scores = 0.00, p=0.50). Quality of life which assessed by SGRQ was significant improved in the intervention group (p=0.04), but not in placebo (p=0.73). Pulmonary function tests (FEV1, FVC and KCO) were not improved in both groups. No patient in intervention group reported any adverse effect.

Conclusion: Once daily roxithromycin showed benefit on clinical outcomes as well as quality of life. Larger studies of the effects of macrolide in bronchiectasis treatment with longer follow-up times should be done.

4947
Late-breaking abstract: Once-daily NVA237 improves exercise endurance from first dose in patients with COPD: The GLOW3 trial

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Introduction: Exercise limitation, dynamic hyperinflation and exertional dyspnea.

Results: Results demonstrated significant benefits over placebo in terms of symptom scores (mean difference of symptom scores = -2.11, p=0.04) compare with placebo received placebo once daily. Roxithromycin was shown to improve symptoms scores (mean difference of symptom scores = 0.00, p=0.50). Quality of life which assessed by SGRQ was significant improved in the intervention group (p=0.04), but not in placebo (p=0.73). Pulmonary function tests (FEV1, FVC and KCO) were not improved in both groups. No patient in intervention group reported any adverse effect.

Conclusion: Once daily roxithromycin showed benefit on clinical outcomes as well as quality of life. Larger studies of the effects of macrolide in bronchiectasis treatment with longer follow-up times should be done.
are key features of COPD. We investigated the effects of NVA237, a once-daily (OD) inhaled long-acting muscarinic antagonist, on exercise endurance in pts with COPD.

**Methods:** 108 pts with moderate-to-severe COPD were randomized to a cross-over design of NVA237 50 μg or placebo OD for 3 weeks, with a 14-day washout. The primary outcome was endurance time during submaximal exercise tolerance test on Day 21 of treatment. Endurance time after first dose, dynamic hyperinflation (inspiratory capacity [IC] at isotime during exercise), and morning trough FEV₁ were also measured.

**Results:** On Day 21, endurance time significantly increased by 21% with NVA237 compared with placebo; this effect was significant from Day 1, with an increase of 10% (Table). Dynamic IC at exercise isotime and trough FEV₁ showed significant and clinically relevant improvements from Day 1 that were sustained throughout the study (Table). The safety profile of NVA237 was similar to that of placebo.

<table>
<thead>
<tr>
<th>NVA237-placebo (LS means, 95% CI)</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Endurance time (sec)</strong></td>
<td></td>
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<tr>
<td>Day 1</td>
<td>43.1</td>
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<tr>
<td>Day 21</td>
<td>88.9</td>
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<tr>
<td><strong>IC at isotime (L)</strong></td>
<td></td>
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<tr>
<td>Day 1</td>
<td>0.23</td>
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<tr>
<td>Day 21</td>
<td>0.20</td>
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<tr>
<td><strong>Trough FEV₁ (L)</strong></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>0.11</td>
</tr>
<tr>
<td>Day 21</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**Conclusion:** NVA237 OD produced immediate and significant improvement in exercise endurance from Day 1, accompanied by sustained and significant improvements in IC at isotime and meaningful improvements in trough FEV₁. Improvement in endurance time increased over the study period, suggesting that mechanisms beyond improved lung function play a role in enhanced exercise tolerance.

**4498 Late-breaking abstract: Preclinical evaluation of an inhibitor of cytosolic phospholipase A₂α for the treatment of asthma**

Christopher Hewson¹, Sheena Patiel¹, Luigino Calzetta², Hinnah Campwala¹, Suzanne Havard³, Emma Luscombe¹, Philip Clarke¹, Peter Peackhill¹, Maria Mateza¹, Mario Cazzola³, Clive Page³, William Abraham³, Cara Williams³, James Clark⁴, Nicholas Clarke⁵, Michael Yeadon¹. 

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**Abstract:**

Asthma is an inflammatory lung disease with considerable requirement for new and effective therapies. Cytosolic phospholipase A₂α (cPLA₂α) is the rate-limiting enzyme responsible for production of eicosanoids implicated in asthma. We investigated a novel cPLA₂α inhibitor, PF-5212372, to establish the preclinical rationale for asthma. PF-5212372 potently and effectively inhibited prostaglandin D₂ (PGD₂) and cytoxin leukotriene release from human lung mast cells (IC₅₀ 0.20±0.11 and 0.45±0.05 μM, respectively). In a mixed human lung cell population, PF-5212372 effectively inhibited leukotriene B₄, thromboxane A₂ and PGD₂ (IC₅₀ 2.6±0.6 and 4.0±0.0 μM, respectively), but was less effective against PGE₂ release (IC₅₀ >30±10 μM, p<0.05). In an in vitro cell retention assay, PF-5212372 retained potency up to 24 h post wash-off. Inhaled PF-5212372 effectively inhibited late-phase bronchoconstriction (78% inhibition, p<0.001) and airway hyperresponsiveness (94% inhibition, p<0.001) in a sheep model of allergic asthma and demonstrated good sheep:human translation in sheep lung mast cells (PGD₂ IC₅₀ 0.7±0.8 μM). PF-5212372 was shown to inhibit AMP-induced constriction of ex vivo human bronchial sections (81% inhibition, p<0.01). PF-5212372 was safe and well tolerated in Ph studies. These data show that inhibition of cPLA₂α using PF-5212372 is effective in a wide range of pre-clinical asthma models and demonstrates cell retention that may yield clinical duration of action. PF-5212372 may represent a new therapeutic option for the treatment of asthma.

**4499 Late-breaking abstract: Inhaled calcium salts reduce tobacco smoke induced airflow impairment and improve lung pathology**

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**Abstract:**

Acute exacerbations (AE) of COPD are associated with bacterial and viral infection, however no available therapy broadly targets infection to prevent AEs. We have developed a novel host-targeted therapy based on the inhalation of dry powder (DP) calcium (Ca) salts that is broadly anti-infective and applicable to AE control. The goal of this study was to evaluate the impact of inhaled Ca salts on inflammation in an acute model of tobacco smoke (TS) exposure.

**Methods:** C57BL6 mice were exposed to TS for 4 or 11d. Treatments with salt-based DP (40μmol/kg) were delivered by inhalation exposure. A p38 MAP kinase inhibitor (100μg/kg) was used as a positive control. Mice were euthanized 24h after the last TS exposure, BAL cells were quantified and histopathology performed.

**Results:** In a 4d-exposure model, treatment with Ca-based DP (PUR118) once daily 1h or 6h before TS reduced inflammatory cells [for 1h, macrophages (52%) and neutrophils (62%)] compared to control DP (p<0.01). Treatment with magnesium (Mg) based DP 1h before TS reduced macrophages 21% (p<0.05); however, neither Mg nor sodium treatment reduced neutrophils. In an 11d exposure model, PUR118 reduced inflammation in prophylactic or therapeutic dosing regimes and markedly reduced the severity and incidence of peri-vascular and peri-bronchiolar inflammation, bronchiolitis, alveolitis, and pneumonitis by histopathological analysis.

**Conclusions:** Ca-based DP reduced TS induced inflammation and improved lung pathology with equivalent efficacy to the p38 MAP kinase inhibitor. By targeting the infectious cause of AEs and baseline airway inflammation, inhaled Ca DP provides a novel multi-pronged approach for AE control.