controlled trials that investigate the efficacy and safety of QVA149 in patients with moderate-to-severe COPD.

Methods This overview includes data from 4 multicentre, double-blind, randomised controlled trials evaluating the effect of QVA149 110/50 µg versus IND 150 µg, GLY 50 µg, tiotropium (TIO) 18 µg (open-label in the SHINE and SPARK studies; blinded in the BLAZE study), salmeterol/fluticasone (SFC) 50/500 µg, and placebo (PBO) in patients with moderate-to-very severe COPD. Outcomes reported here are lung function, transitional dyspnoea index (TDI), health status (via the St George's Respiratory Questionnaire [SGRQ]), and exacerbations over 6 weeks (BLAZE), 26 weeks (SHINE, ILLUMINATE), and 64 weeks (SPARK).

Results Data from 5138 patients were included in this overview. QVA149 provided statistically significant and clinically meaningful bronchodilation ($p < 0.001$) that was sustained throughout the treatment periods versus all comparators in all studies. QVA149 provided superior benefits versus TIO, SFC, and PBO with respect to TDI score in BLAZE and ILLUMINATE studies. At Week 64, QVA149 significantly improved SGRQ score ($p \leq 0.001$) and significantly lowered the rate of all exacerbations compared with GLY and TIO in the SPARK study (Table). In addition, QVA149 reduced the rate of all exacerbations by 31% and significantly delayed the time to first exacerbation versus SFC in the ILLUMINATE trial.

Conclusion The results from the IGNITE trials demonstrate that superior improvements in lung function with once-daily QVA149 translate into meaningful therapeutic outcomes for patients with COPD as demonstrated by improved lung function, dyspnoea, health status, and reduced exacerbations.

P236 SUPERIOR LUNG FUNCTION WITH ONCE-DAILY QVA149 TRANSLATES INTO IMPROVEMENTS IN PATIENT-REPORTED BREATHLESSNESS COMPARED WITH PLACEBO AND TIOTROPIMUM IN COPD PATIENTS: THE BLAZE STUDY

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Introduction QVA149, a novel once-daily inhaled dual bronchodilator combining a fixed dose of the long-acting β_2 agonist indacaterol and the long-acting muscarinic antagonist glycopyrronium, has demonstrated improvements in dyspnoea versus its mono-components (indacaterol and glycopyrronium), tiotropium, and salmeterol/fluticasone using the interviewer-based Transition Dyspnoea Index (TDI) questionnaire.^{1,2} The BLAZE study evaluated the effect of once-daily QVA149 on patient-reported dyspnoea versus placebo and blinded tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).

Methods This was a 6 week, multicentre, randomised, blinded, double-dummy, placebo-controlled, 3-period, cross-over study. Patients aged ≥ 40 years with moderate-to-severe COPD, post-bronchodilator forced expiratory volume in 1 second (FEV₁) $\geq 30\%$ and $< 80\%$ of the predicted normal, and post-

bronchodilator FEV₁/ forced vital capacity < 0.7 were randomised to receive QVA149 110/50 µg (via the Breezhaler® device) or placebo (via the Breezhaler®/ HandiHaler® device) or blinded tiotropium 18 µg (via the HandiHaler® device). The primary objective of the study was to evaluate the superiority of QVA149 versus placebo in the improvement of patient-reported dyspnoea as assessed by Self-Administered Computerised (SAC) version of the Baseline Dyspnoea Index (BDI)/TDI after 6 weeks of treatment. Other objectives included; standardised FEV₁ area under the curve from 0 to 4 hours post-dose (AUC_{0-4 h}); rescue medication use; safety and tolerability.

Data are LSM ± SE. * $p < 0.001$; ** $p = 0.021$

Abstract P236 Figure 1. TDI total score after 6 Weeks.

Results Of the 247 patients (mean age 62.8 years) randomised, 191 completed the study. The SAC TDI total score was significantly improved with QVA149 compared with placebo and tiotropium after 6 weeks (figure). FEV₁ AUC_{0-4 h} was significantly higher for QVA149 versus placebo and tiotropium at Day 1 and Week 6 (all $p < 0.001$). Rescue medication use was significantly lower with QVA149 versus placebo ($p < 0.001$) and tiotropium ($p = 0.002$). Incidence rate of adverse events was similar across all the treatment groups (QVA 149: 35.0%; tiotropium: 35.5%; placebo: 39.4%).

Conclusion The BLAZE study provides evidence that the improved lung function with QVA149 translates into greater relief of breathlessness and improved patient-reported outcomes.

REFERENCE

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P237 COMPARISON OF COPD EXACERBATIONS WITH ONCE-DAILY QVA149 VERSUS TWICE-DAILY SALMETEROL/ FLUTICASONE COMBINATION: THE ILLUMINATE STUDY

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Introduction Exacerbations are the most frequent cause of hospitalisation and death among patients with COPD. Combinations of long-acting bronchodilators maximise bronchodilation and may reduce the risk of exacerbations. QVA149, a once-daily dual bronchodilator containing the long-acting β_2 agonist (LABA) indacaterol and long-acting muscarinic antagonist (LAMA) glycopyrronium, improves lung function, breathlessness and rescue medication use compared with twice-daily salmeterol/fluticasone combination (SFC), in patients with moderate-to-severe COPD.¹

Methods In this 26-week, multicenter, double-blind study, patients ≥ 40 years with COPD (forced expiratory volume in 1 second [FEV₁] $\geq 40\%$ to $<80\%$ predicted and no history of exacerbations in the previous year) were randomised (1:1) to QVA149 110/50 g or SFC 50/500 g. In this post hoc analysis, we report the rate of mild, moderate or severe COPD exacerbations during 26 weeks of treatment with QVA149 or SFC.

Results Of 522 patients randomised [QVA149 (n = 258), SFC (n = 264); mean age: 63.3 years; mean post-bronchodilator FEV₁: 60.2% predicted], 82.6% completed. Rate ratio of QVA149 versus SFC [RR] of moderate or severe exacerbations was 0.80 (95% confidence interval [CI]: 0.41–1.56) and for all COPD exacerbations (mild, moderate, and severe), RR was 0.69 (95% CI: 0.44–1.07) (neither statistically significant).

Conclusion Risk of exacerbations with once-daily QVA149 was numerically, but not statistically significantly, lower than twice-daily SFC in patients with moderate-to-severe COPD and no previous history of exacerbations. The LABA/LAMA combination QVA149 has the potential to be an alternative to LABA/ICS in preventing COPD exacerbations.

REFERENCE

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Pulmonary infection

P238 ROLE OF NATURALLY-ACQUIRED IGG IN PROTECTION FROM *S. PNEUMONIAE* LUNG INFECTION

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Preventing *Streptococcus pneumoniae* lung infections will have substantial health benefits, yet existing polysaccharide vaccines are not effective against pneumonia. Identifying the mechanisms of naturally-acquired immunity to *S. pneumoniae* lung infections could indicate alternative preventative strategies. Human intravenous immunoglobulin (IVIG) preparations pooled from >1000 donors prevent respiratory infections in patients with hypogammaglobulinaemia. IVIG therefore provides a tool to investigate the naturally-acquired antibody responses to *S. pneumoniae* within a population. We have used mouse models and *in vitro* assays to assess the efficacy of IVIG for preventing *S. pneumoniae* lung infections and to identify the immunodominant target antigens.

In a mouse pneumonia model, IVIG treatment was highly protective against bacteraemia (17% septicaemia v. 100% in controls, $P = 0.015$) and partially protected against lung infection (lung CFU log₁₀ 3.7 for IVIG v. 6.3 for controls, $P = 0.041$) but not against nasopharyngeal colonisation. Depletion of phagocyte subsets demonstrated that IVIG-mediated protection required neutrophils and macrophages for lungs and blood respectively. Flow-cytometry assays demonstrated that IgG within IVIG preparations opsonised *S. pneumoniae* effectively. Importantly, IgG opsonisation was reduced by pre-treatment of bacteria with pronase to remove bacterial surface proteins but not by depletion of anti-capsular antibody. Furthermore, *in vitro* assays demonstrated that IVIG facilitated phagocytosis, growth impairment and bacterial agglutination of capsule-deficient *S. pneumoniae* mutants, in mice IVIG depleted of anti-capsular antibody remained protective against lung infection and septicaemia. These results

demonstrate that surface proteins rather than the capsule are targets for naturally-acquired adaptive immunity to *S. pneumoniae*. The potential *S. pneumoniae* protein antigen targets in IVIG were assessed using a semi-quantitative assay against 18 recombinant pneumococcal proteins. The results demonstrated significant IgG responses to the conserved pneumococcal protein antigens PhtD, PspC, PspA and PsaA. Interestingly, antibody titres to some of these antigens were reduced in sera from elderly compared to younger subjects, potentially identifying people at higher risk of *S. pneumoniae* infection. Our data demonstrate that the accepted paradigm that naturally-acquired immunity to *S. pneumoniae* depends on anti-capsular antigen is inaccurate, and instead antibody to proteins is dominant. These data will allow better evaluation of those at risk of *S. pneumoniae* infection and improved vaccine design.

P239 A ROLE FOR POLYCYSTINS IN AIRWAY MUCOCILIARY CLEARANCE?

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Polycystins 1 and 2 are the gene products of the mutated genes PKD1 and PKD2 in autosomal dominant polycystic kidney disease (ADPKD). They are localised to primary cilia in the kidney and thought to detect fluid flow. Recently patients with ADPKD have been shown to have an increased incidence of radiological findings of bronchiectasis, an abnormal dilatation of the bronchioles involving impaired mucociliary clearance (Driscoll *et al* 2009). We hypothesise that proteins from the polycystin pathway are present in respiratory epithelium and that this pathway is defective in bronchiectasis.

We demonstrate using immunofluorescent antibodies that the extracellular portion of polycystin 1 and the n terminal tail of polycystin 2 consistently localise to cilia of nasal epithelial cells from healthy individuals and that blocking polycystin 1 with antibodies can alter ciliary beat. Contrary to our hypothesis there were no differences in the distribution of these proteins in a group of patients with bronchiectasis (n = 13)

In conclusion we have shown that polycystins 1 and 2 are present in the motile cilia of the airways and may be involved in ciliary beat frequency regulation. We did not find any evidence of disruption of the polycystin proteins in a small population of patients with bronchiectasis.

P240 DOES A RELATIONSHIP EXIST BETWEEN SERUM ALBUMIN AND LACTATE WITH THE LENGTH OF STAY IN PATIENTS ADMITTED WITH COMMUNITY ACQUIRED PNEUMONIA?

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Introduction Previous studies have shown that high lactate and CURB65 scores are associated with increased mortality and morbidity in patients with community acquired pneumonia (CAP). We attempted to investigate a simple way to identify those patients who are likely to have prolonged hospital admission from CAP by using different biomarker.

Method We included first 50 patients who were diagnosed to have CAP by respiratory physicians on admission at Russell's