345. New bronchodilators and other novel drugs for asthma and COPD

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A dual-acting muscarinic antagonist, β_2-agonist [MABA] molecule (GSK961081) improves lung function in COPD. A randomised trial

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Introduction: GSK961081 is a dual pharmacophore demonstrating both muscarinic antagonist and beta agonist activities in one molecule (MABA). Recent COPD treatment guidelines have recommended that combining bronchodilators with different mechanisms may increase the degree of bronchodilation for equivalent or lesser side effects (GOLD 2010).

Methods: This was a 4 week, multicentre, randomised, double blind, double dummy, placebo and salmeterol controlled parallel group study. Dose ranging across three twice-daily (BD) doses and three once-daily (QD) doses were assessed in moderate and severe COPD subjects. Trough FEV_1 at day 29 was the primary endpoint. Other efficacy endpoints, included serial FEV1 over 24h, FVC, and rescue salbutamol use. Safety endpoints included heart rate, glucose and QTc

Results: The study recruited 436 subjects. GSK961081 showed statistically and clinically significant differences from placebo in all doses and regimens for FEV_1 trough on day 29 (155-277ml $p<0.001$). The optimal daily dose was 400mcg, either as once (400mcg QD) or as twice a day (200mcg BD) dosing with an improvement in Day 29 trough FEV_1 of 215ml (95%CI) (140,290) $p<0.001$ and 249ml (170,320) $p<0.001$ respectively. Other efficacy endpoints including FVC and rescue salbutamol also showed improvement. The molecule showed no effects on glucose, potassium, heart rate, blood pressure and no dose response effect on QTc elongation.

Conclusion: This study showed that GSK961081 is an effective bronchodilator in moderate and severe COPD subjects. GSK961081 was safe and well tolerated.

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Lung function effects and safety of fluticasone furoate (FF)/vilanterol (VI) in patients with COPD: Low-mid dose assessment

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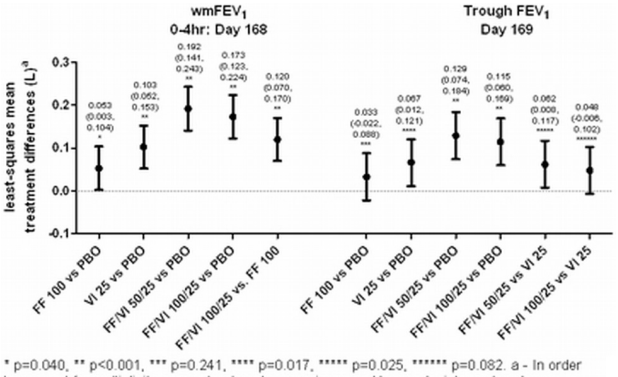
Rationale: FF/VI is in development as a novel once-daily (OD) inhaled corticosteroid/long-acting $beta_2$ agonist combination therapy for COPD.

Objective: To evaluate the efficacy and safety of FF/VI (100/25 and 50/25mcg) vs placebo (PBO), FF (100mcg), and VI (25mcg), given OD via a novel dry powder inhaler for 168 days in moderate-severe COPD patients.
Methods: A multicentre, randomised, PBO-controlled, double-blind, parallel-group study (N=1030 (ITT)). Co-primary endpoints: weighted mean (wm) FEV_1 0–4h (Day 168) to assess the contribution of VI, and trough FEV_1 (Day 169) to assess the contribution of FF and 24h duration of VI. Additional endpoints included CRQ-SAS dyspnoea and safety.
Results: Co-primary endpoints: see Figure. FF/VI 100/25 was numerically superior to components on dyspnoea score (treatment differences from PBO =0.30 vs 0.06 [FF] and 0.14[VI]). On-treatment AEs were more frequent with active treatment (54–60%) than PBO (48%). There were no treatment effects on 24h urinary cortisol, laboratory values, or cardiac monitoring parameters.



* p=0.040, ** p<0.001, *** p=0.241, **** p=0.017, ***** p=0.025, ****** p=0.082. a - In order to account for multiplicity across treatment comparisons and key endpoints, a step-down testing procedure was applied , whereby inference for a test in the pre-defined hierarchy is dependent upon statistical significance having been achieved for the previous tests in the hierarchy. Endpoints were assessed in the order VI 25 vs PBO, FF/VI 100/25 vs PBO, FF/VI 100/25 vs FF 100 for wmFEV_1 and VI 25 vs PBO, FF/VI 100/25 vs PBO, FF/VI 100/25 vs VI 25 for trough FEV_1 then the same comparisons for lower dose. Inference for secondary endpoints required significance at <0.05 for the primary endpoint at that dose.

Conclusion: Addition of VI to FF produced a clinically significant improvement in wmFEV_1 (0-4h). Addition of FF to VI provided numerical improvements only in trough FEV_1. Combination therapy was superior to PBO for both co-primary endpoints. All treatments were well tolerated.
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The safety and tolerability of twice-daily oral doses of AZD5069, a novel CXCR2 antagonist, in patients with moderate-to-severe COPD

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Background: This Phase IIa study evaluated the safety and tolerability of the CXCR2 antagonist AZD5069 in patients with moderate-to-severe COPD.
Methods: This was a 4-week, randomised, double-blind, placebo-controlled, parallel group, multi-centre study. Patients were aged 40–80 years, with a diagnosis of moderate-to-severe COPD for >1 year. Patients received placebo (PBO) bd (n=29), AZD5069 50 mg twice-daily (bd) (n=30) or AZD5069 80 mg bd (n=28) for 4 weeks. Primary safety and tolerability outcome variables included adverse events (AEs), ECG, haematology, clinical chemistry, urinalysis, vital signs, and lung function. The pharmacokinetics (PK) of AZD5069 and the effect of exposure on circulating neutrophils were assessed as secondary objectives.
Results: Patients had a mean age of 64 years (69% male; all white). There were no deaths. Two SAEs (one with 50 mg and one with 80 mg) were assessed by the investigator as not related to AZD5069. The number of patients with AEs was evenly distributed across treatment groups. Discontinuation due to AEs was also similar across treatment groups, but highest in patients receiving AZD5069 50 mg (3, 5 and 2 patients receiving PBO, AZD5069 50 mg and 80 mg respectively). The PK was as predicted from healthy volunteers, but with higher variability. As expected, there was an exposure-related, reversible reduction in circulating neutrophils with AZD5069. No other clinically important changes in primary variables, including infection rates, were observed with AZD5069.
Conclusions: AZD5069 was well tolerated with no safety issues identified in this 4 week Phase IIa COPD patient trial.

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Efficacy and safety of BI 671800, an oral CRTH2 antagonist in controller naïve patients with poorly-controlled asthma

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Background: BI 671800 is an antagonist of the PGD2 receptor, CRTH2. PGD2 stimulates bronchoconstriction and allergic airway inflammation in animal models. Inhibition of CRTH2 may reduce airway inflammatory cells, IL -4, -5, -13 production, serum IgE and airway hyper reactivity.
Objective: To investigate the efficacy and safety of BI 671800 versus placebo and fluticasone proprionate (FP) in controller-naïve patients with poorly-controlled asthma.
Methods: Adults with asthma (FEV_1 60-85% and ACQ >= 1.5) were enrolled in a randomized, double-blind, parallel arm study comparing BI 671800 50, 200 or 400 mg bid with matching placebo bid or FP 110 µg bid for six weeks. The primary study outcome was change in trough FEV_1.
Results: 388 patients were randomised (mean age 37.4 years, FEV_1 72.7%, ACQ 2.29). Changes from baseline in adjusted mean (SE) trough morning FEV_1% predicted versus placebo were 3.08% (1.65), 3.59% (1.60) and 3.98% (1.64) for 50, 200 and 400 mg BI 671800 bid respectively, and 8.61% (1.68) for FP (one-sided $p < 0.025$ for 200 and 400 mg bid and FP), achieving the primary efficacy outcome for the study. Change in ACQ mean (SE) scores versus placebo were 0.07 (0.11), -0.08 (0.11) and -0.06 (0.11) for 50, 200 and 400 mg BI 671800 bid respectively, and -0.33 (0.12) for FP (one sided $p < 0.025$ for FP). No significant imbalance in adverse events, or differences in vital signs or laboratory assessments were observed.
Conclusion: Treatment with BI 671800 was associated with a significant improvement in FEV_1 in controller-naïve patients with poorly-controlled asthma. BI 671800 was well tolerated at total daily doses up to 800 mg for 6 weeks.

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Efficacy and safety of BI 671800, an oral CRTH2 antagonist, as add on therapy in poorly controlled asthma patients prescribed an inhaled corticosteroid

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Background: BI 671800 is an antagonist of the PGD2 receptor, CRTH2. PGD2 stimulates bronchoconstriction and allergic airway inflammation in animal models. Inhibition of CRTH2 may reduce airway inflammatory cells, IL -4, -5, -13 production, serum IgE and airway hyper reactivity.
Objective: To investigate the efficacy and safety of BI 671800 administered once in the morning or evening versus a split twice daily dose compared to placebo in poorly controlled asthma patients as add on therapy to fluticasone propionate (FP) MDI (88 µg, bid).
Methods: Adults with asthma (FEV_1 60-85% and ACQ >= 1.5) were enrolled in a randomized, double-blind, three period, incomplete cross-over study comparing BI 671800 400 mg AM, PM or 200 mg bid with matching placebo over 3 consecutive 4-week treatment periods. The primary study outcome was change in trough FEV_1.
Results: 108 patients were randomised (mean age 41 yrs, FEV_1 73%, ACQ 2.13). Change from baseline in mean (SE) trough morning FEV_1 % predicted versus placebo were 0.08% (0.62), 0.67% (0.62) and 0.28% (0.61) and change in ACQ mean (SE) scores were -0.056 (0.063), -0.026 (0.063) and -0.093 (0.062) versus placebo for 200 bid, 400 PM, and 400 AM BI 671800 respectively (all values one-sided $p > 0.025$). No imbalance in adverse events, or differences in vital signs or laboratory assessments were observed.
Conclusion: Total daily treatment with 400 mg BI 671800 did not demonstrate additional effect on FEV_1 on top of FP. BI 671800 was well tolerated at total daily doses of 400 mg for 4 weeks.

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Effects of the novel toll-like receptor 7 (TLR7) agonist AZD8848 on allergen-induced responses in patients with mild asthma

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Background: AZD8848 is an antedrug TLR7 agonist being evaluated for treatment of asthma and allergic rhinitis. This double-blind, placebo-controlled, randomised, parallel-group trial (NCT00999466) investigated efficacy, safety and tolerability of intranasal (IN) AZD8848 in mild-to-moderate allergic asthma patients (pts) who were subsequently challenged with an inhaled allergen.

Methods: 51 pts (mean age 32 yrs) with a confirmed late asthmatic response (LAR) received 8 once-weekly IN doses of AZD8848 60μg (n=26) or placebo (n=25). Key assessments of efficacy and safety were made at 1 and 4 weeks (wk) after last dose of study drug.

Results: Allergen-induced LAR was 27% lower with AZD8848 than placebo at 1 wk after last dose (p=0.035); no differences were seen at 4 wk. Similarly, AZD8848 reduced allergen-induced airway methacholine responsiveness at 1 wk ($p<0.05$) but not at 4 wk. There was no significant effect on allergen-induced increases in sputum eosinophils and Th2 cytokines. AZD8848 was safe and generally well tolerated; most AZD8848-related adverse events were mild and consisted of headache and influenza-like symptoms. Plasma AZD8848 concentrations (as metabolite) peaked 15 min after last dose, then rapidly declined to undetectable levels.

Conclusions: IN AZD8848 attenuated allergen-induced LAR and allergen-induced increases in airway methacholine responsiveness 1 wk after 8 weekly doses, but these effects were not maintained at 4 wk. AZD8848 was safe and generally well tolerated. The data show that IN administration of a TLR7 agonist can ameliorate allergen-induced responses in the lower airways.

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Effects of anti-M1 prime monoclonal antibody, MEMP1972A following allergen challenge in patients with mild asthma

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Background: Elevated serum IgE is associated with allergic asthma. Membrane IgE includes the M1 prime epitope, present in human IgE-switched memory B cells and plasmablasts. MEMP1972A, a therapeutic antibody specific for M1-prime that depletes M1-prime-expressing cells.

Aim: To test proof-of-activity of MEMP1972A.

Methods: This randomized, double-blind, controlled study (NCT01196039) assessed the activity and safety of MEMP1972A in adults with mild asthma after allergen inhalation challenge (AIC). Subjects (n=29) were randomized (1:1) to intravenous MEMP1972A (5 mg/kg) or placebo every 4 weeks for 12 weeks. The primary outcome was the area under the curve (AUC) of the late asthmatic response (LAR) at Wk 12. Secondary outcomes included early asthmatic response (EAR). Serum total IgE and allergen-specific IgE were measured to confirm mechanistic activity of MEMP1972A. Other exploratory biomarkers were measured eg sputum and blood eosinophils.

Results: MEMP1972A treatment was well tolerated. At Wk 12, MEMP1972A reduced the LAR AUC by 36% (90% CI: -14, 69, p=0.21) and the EAR AUC by 26% (6, 43, p=0.046) vs placebo. AIC at screening and Wk 12 induced a ~2-fold increase in allergen-specific IgE which was abrogated by MEMP1972A and more than ~10-fold increase in sputum eosinophils, which was reduced by MEMP1972A at Wk 12. MEMP1972A reduced total IgE by ~20% at Wk 8, and blood eosinophils by ~45% at Wk 28 vs baseline.

Conclusions: Attenuation of EAR, LAR, serum IgE, sputum and blood eosinophils following AIC is consistent with the mechanism of action of MEMP1972A. Depletion of the M1 prime-expressing B-cell lineage may be effective for the treatment of allergic asthma.