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

3081
A dual-acting muscarinic antagonist, β₂-agonist [MABA] molecule (GSK961081) improves lung function in COPD. A randomised trial
Pascal L.M.L. Wielders¹, Andrea Ludwig-Sengpiel², Nicholas W. Locantore³, Suus F. Baggen⁴, Robert H. Chan⁵, John H. Riley⁵.
¹Dept. of Pulmonary Diseases, Catharina Hospital, Eindhoven, Netherlands; ²KLB Healthresearch, KLB Healthresearch, Luebeck, Germany; ³Quantitative Sciences, GlaxoSmithKline, Durham, RTP, NC, United States; ⁴Clinical Operations, GlaxoSmithKline, Zeist, Netherlands; ⁵Clinical COPD New Chemical Entities, GlaxoSmithKline, Uxbridge, Middlesex, United Kingdom

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 FEV₁ two weeks after the last dose 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 FEV₁ 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 FEV₁ 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 patients. GSK961081 was safe and well tolerated. Clinical Trials Register number NCT01319019. Study code MAB115032 and was funded by GlaxoSmithKline.

3082
Lung function effects and safety of fluticasone furoate (FF)/vilanterol (VI) in patients with COPD: Low-mid dose assessment
Edward M. Kerwin¹, Catherine Scott-Wilson², Lisa Sanford³, Stephen I. Rennard², Alvar Agusti⁵, Neil Barnes⁶, Courtney Crim³. ¹Clinical Science Centre, Clinical Research Institute of Southern Oregon, Medford, United Kingdom; ²Respiratory Medicines Development Centre, GlaxoSmithKline, Research Triangle Park, United States; ³Quantitative Sciences Division, GlaxoSmithKline, Uxbridge, United Kingdom; ⁴Department of Internal Medicine, University of Nebraska Medical Center, Omaha, United States; ⁵Thorax Institute, Hospital Clinic, University of Barcelona, Spain; ⁶Respiratory Medicine, Barts and the London NHS Trust, London, United Kingdom

Rationale: FF/VI is in development as a novel once-daily (OD) inhaled corticosteroid/long-acting beta₂ 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-to-severe COPD patients.

Methods: A multicentre, randomised, PBO-controlled, double-blind, parallel-group study (N=1030 (ITT)). Co-primary endpoints: weighted mean (wmt) FEV1 (0-4h) vs placebo (PBO) and 0-24h (Day 168) to assess the contribution of VI, and trough FEV1 (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.

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

David Miller1, Craig LaForce2, Albert Finn3, Eric Bateman4, Kristin Drda5, Andrew Fowler8, Abhya Gupta3.

Background: BI 671800 is an antagonist of the PGD2 receptor, CRTH2. PGD2 stimulates bronchoconstriction and allergic airway inflammation in animal models.

Methods: Adults with asthma (FEV1 >80% and AECG >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 for six weeks. The primary study outcome was change in trough FEV1.

Results: 358 patients were randomised (mean age 37±4 years, FEV1 72.7%, AECG 2.29). Changes from baseline in adjusted mean (SE) trough morning FEV1% 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 AECG 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 FEV1, in controller-naive patients with poorly-controlled asthma. BI 671800 was well tolerated at total daily doses up to 800 mg for 6 weeks.
Effects of the novel toll-like receptor 7 (TLR7) agonist AZD8848 on allergen-induced responses in patients with mild asthma

Brian Leake1, Dave Singh2, Sam Lindgren3, Gun Almqvist4, Barbara Young4, Brian O’Connor1, 1RCT, Respiratory Clinical Trials Ltd, London, United Kingdom; 2Medicines Evaluation Unit Ltd, University of Manchester, United Kingdom; 3Research and Development, AstraZeneca, Molndal, Sweden; 4Research and Development, AstraZeneca, Charnwood, Loughborough, United Kingdom

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 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=0.035) 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.

Acknowledgments: Leif Eriksson, Lund University, Sweden.

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

Gail Gauvreau1, Louis-Philippe Boulet2, Donald Cockcroft3, Beth Davis1, Mark Fitzgerald4, Richard Leigh5, Barbro Dahlen6, Irvin Mayers7, Heleen Scheerens8, Romeo Maciuca8, John Matthews11, Jeffrey Harris11, Gail Gauvreau1, 1Department of Medicine, McMaster University, Ontario, Canada; 2Department of Pneumology, Institut Universitaire de Cardiologie et de Pneumologie de l’Université Laval, Hôpital Laval, Quebec, Canada; 3Department of Medicine, University of Saskatchewan, Saskatoon, Canada; 4Department of Medicine, University of British Columbia, Vancouver BC, Canada; 5Department of Medicine, University of Calgary, AB, Canada; 6Department of Medicine, Karolinska Institute, Stockholm, Sweden; 7Department of Medicine, University of Alberta, AB, Canada; 8PD Biomarkers, Genentech, Inc, South San Francisco, United States; 9Biostatistics, Genentech, Inc, South San Francisco, United States; 10Product Development - Immunology, Genentech, Inc, South San Francisco, United States; 11Research and Early Development, Genentech, Inc, South San Francisco, United States

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.