244. Asthma treatment: efficacy and safety

P2081

The evaluation of the efficacy and safety of phospholipids' inhalation in patients with bronchial asthma (BA): A prospective randomized placebo-controlled study

Alexander Lisitsa[1], Igor Klimanov[2], Svetlana Soodaeva[3], Alexander Averyanov[1], Oleg Kuzovlev[1]. *[1]Clinical Trials Dept., Federal Research Clinical Center under Federal Medical&Biological Agency of Russia, Moscow, Russian Federation; [2]Clinical Lab Dept., OJSC "Medical Club Consilium", Moscow, Russian Federation; [3]Human Pathology Dept., First Moscow State Medical University, Moscow, Russian Federation*

Background: The new method of BA treatment based on the reparation of damaged cell membranes by phospholipids was proposed.
The aim of the study was to evaluate the efficacy and safety of phospholipids' inhalation (PhLI) in BA patients during the 24-week course of treatment.
Materials and methods: The prospective, single-blind, randomized, placebo-controlled, parallel-group study was performed. 58 patients (age 67.5±12.3; male 68.3%) with partly controlled and uncontrolled BA were enrolled (FEV1>50%). Group1 contains 30 patients who received a PhLI by compressor nebulizer once a day in addition to traditional therapy; group2 - 28 patients who received a traditional therapy only (control). The lung function test was performed in each clinical visit, as well as PEF measurements were performed twice daily by the patient itself. Usage of short-acting β2-agonists and the asthma symptoms score were also determined.
Results: It was shown the statistically significant increase of FEV1 level in group1 compared with control (79.3±8.7 vs 72.9±9.2%; p=0.01). The PEF increase was also determined in group 1 (557.0±120.6 vs 486.3±98.3 l/min; p=0.03). The strong correlation between these two parameters was observed (r=0.94; p=0.0052). The number of inhalations of bronchodilator reliever medication was significantly lower in group 1 (1.7±0.8 vs 2.9±1.6; p=0.027) as well as asthma symptoms score (4.2±1.1 vs 6.3±1.0; p=0.01).
Conclusion: The results obtained demonstrate that a phospholipids' inhalation in addition to traditional therapy of BA has a significant positive effect both in clinical status and lung function test in patients with BA.

P2082

Onset of bronchodilation with fluticasone/formoterol versus fluticasone/salmeterol

Guy Brusselle[1], René Aalbers[2], Tammy McIver[3], Birgit Grothe[3], Anna Bodzenta-Lukaszyk[4]. *[1]Longziekten - Laboratory for Translational Research of Obstructive Pulmonary Disease, Gent University Hospital, Gent, Belgium; [2]Department of Pulmonary Diseases, Martini Hospital, Groningen, Netherlands; [3]European Medical Science, Mundipharma Research Ltd., Cambridge, United Kingdom; [4]Department of Allergology and Internal Medicine, Medical University of Bialystok, Poland*

Background: Rapid bronchodilation has been identified as a key attribute of ICS/LABA combination therapy for asthma. This post-hoc analysis assessed the onset of bronchodilation with fluticasone propionate/formoterol fumarate (FLUT/FORM) and fluticasone propionate/salmeterol xinafoate (FLUT/SAL).
Methods: 202 adults with asthma (forced expiratory volume in 1 sec [FEV_1] reversibility of ≥15%) were randomized to 12 weeks' treatment with either FLUT/FORM (pMDI; 100/10 or 250/10 µg b.i.d. [treatment doses]; n=101) or FLUT/SAL (pMDI; 100/50 or 250/50 µg b.i.d. [treatment doses]; n=101) in an open-label, parallel-group study. The percentage of patients with onset of bronchodilation within 5 min and 120 min post-dose was assessed on days 0 and 84. Onset of bronchodilation was defined as the first time point post-dose with a ≥12% increase in FEV_1 versus pre-dose.
Results: Baseline mean FEV_1 was 2.1±0.6 L (reversibility 27.6±12.8%) and 2.1±0.5 L (reversibility 24.9±9.9%) in the FLUT/FORM and FLUT/SAL groups, respectively. On day 0, a significantly greater proportion of patients had an onset of bronchodilation with FLUT/FORM than FLUT/SAL within 5 min (38.6% vs 14.0%; odds ratio [OR] 4.0; 95% CI 2.0, 8.0) and within 120 min post-dose (78.0% vs 64.0%; OR 2.0; 95% CI 1.1, 3.9). This was sustained over 12 weeks; on day 84, the percentage of patients with an onset of bronchodilation was greater with FLUT/FORM than FLUT/SAL within 5 min (16.3% vs 2.0%; OR 9.6; 95% CI 2.1, 42.9) and within 120 min post-dose (51.0% vs 35.1%; OR 1.9; 95% CI 1.1, 3.4).
Conclusion: FLUT/FORM consistently provided more rapid bronchodilation than FLUT/SAL in patients with asthma over 12 weeks of therapy.

P2083

Intermittent *versus* daily inhaled corticosteroids (ICS) in children and adults with mild persistent asthma: A Cochrane review

Francine Ducharme[1,2], Bhupendrdasinh Chauhan[1], Caroline Chartrand[1]. *[1]Paediatrics, CHU Sainte-Justine, Montreal, QC, Canada; [2]Reseach Centre, CHU Sainte-Justine, Montreal, QC, Canada*

Introduction: Although guidelines recommend daily ICS in mild persistent asthma, most patients use, and many physicians prescribe, intermittent ICS.
Objectives: To compare the safety and efficacy of intermittent *versus* daily ICS in mild persistent asthma.
Methods: Randomised trials comparing intermittent *vs.* daily ICS in children and adults were eligible. Outcomes included: patients requiring rescue oral steroids (primary efficacy), serious adverse health events (primary safety), hospitalisations, lung function, asthma control, adverse effects, and withdrawals.
Results: Six (4 children; 2 adult) parallel-group trials using beclomethasone or budesonide, were included. There was no significant group difference in patients requiring rescue oral steroids (RR=1.07, 95%CI 0.87, 1.32) and serious adverse events (RR=0.82, 95%CI 0.33, 2.03). Compared to daily ICS, intermittent ICS was associated with lower change in PEF, fewer control days, more β_2-agonists use, and higher exhaled nitric oxide. There was no group difference in acute care visits, hospitalisations, FEV_1, adverse effects, and withdrawals. Compared to intermittent, daily budesonide was associated with lower growth in children (MD=0.41cm, 95%CI 0.13, 0.69).
Conclusions: Intermittent and daily ICS strategies did not significantly differ in the use of rescue oral steroids, nor did they reach equivalence. Daily ICS was superior to intermittent ICS in several indicators of lung function, airway inflammation, control, and reliever use. The findings would support the greater efficacy of daily ICS in children and adults with mild persistent asthma, while using the safest, and lowest effective dose of, ICS in children.

P2084

Oral polyunsaturated fatty acid supplementation as adjuvant therapy for asthmatic children

Malak Shaheen[1], Magdy Mahmoud[1], Dina Elshinaway[2]. *[1]Pediatric Department - Pulmonology Unit, Ain Shams Faculty of Medicine, Cairo, Egypt; [2]Clinical Pathology Department, Ain Shams Faculty of Medicine, Cairo, Egypt*

Background: Omega-3 polyunsaturated fatty acids (PUFA) competitively inhibit the formation of leukotrienes and prostaglandins produced from omega-6 fatty acids and thus provide anti-inflammatory effect. However, the precise impact of

omega-3 fatty acid oral supplements for asthmatic children has not been established. The aim of this study was to assess safety and efficacy of omega-3 PUFA supplementation for asthmatic children.
Method: In a prospective study, 44 known asthmatic children and 15 matched healthy children received oral supplementation with omega-3 PUFA for 5 weeks duration. All children underwent; history taking, clinical examinations, pulmonary function testing and assessment of omega-3 PUFA serum levels, total IgE (TIgE) levels and interleukin 4 (IL4) levels before and after the supplementation.
Result: Basal omega-3 PUFA serum levels were significantly lower in asthmatic children compared to controls (p 0.03) and much lower with severe grades of asthma (r = 0.25, p 0.03). Three folds rise was documented in the mean omega-3 PUFA level of asthmatic children compared to eight folds increase in healthy children after PUFA supplementation (p 0.0004). Clinical asthma scores showed one step down improvement only in 13.5% of asthmatic children (6/44). Mean values of TIgE serum levels in asthmatic children showed a significant reduction after supplementation (p 0.04) while IL4 serum levels showed a rise after supplementation.
Conclusion: Significant difference exists between healthy children and asthmatic children regarding the impact of oral PUFA supplementation. However; it showed some positive effects for asthmatics, its safety is questionable in children.

P2085
Does a formal prednisolone absorption test lead to improved control in difficult-to-treat asthma?
Lisa Midgley[1], John Blakey[2], Adel Mansur[1]. *[1]Severe and Brittle Asthma Unit, Heart of England NHS Foundation Trust, Birmingham, United Kingdom; [2]Respiratory Medicine, University of Nottingham, United Kingdom*

Patients with disabling asthma may have poor concordance with prescribed therapy and admit this only when confronted with firm evidence. Control may then improve through greater concordance with agreed management.
Hypothesis: In individuals prescribed long term prednisolone, an absorption test may provide formal evidence of poor concordance and thus lead to improved clinical outcomes.
Design: Observational cohort
Population: 27 patients (22 female) with asthma and poor control despite specialist review, regular prednisolone, and reported concordance.
Intervention: 0.5mg/kg prednisolone orally. Prednisolone, prednisone, cortisol and cortisone levels every hour for 3 hours.
Assessment: First visit to the asthma service, appointment at which test requested, test day, and 6 months thereafter
Outcomes: ACQ7, FEV1% predicted, FeNO, peripheral blood eosinophil count, and regular prednisolone dose.
Analysis: Paired t tests. Results = mean ± SEM (2sf).
Results: Patients had impaired lung function (FEV1 65% predicted ±6.0) and poor control (4.1±0.56) at time of test request despite prednisolone (30mg daily ±3.9).
12 (44%) patients had suppressed cortisol at test baseline. All tests showed adequate absorption of prednisolone.
FEV1, FeNO, prednisolone dose and ACQ did not change significantly across the four time points. Eosinophil count fell by a mean of 0.30 (CI 0.02-0.58, p=0.037) between request and test. This improvement was sustained from request to follow-up (mean 0.50, CI 0.11-0.90, p=0.016)
Conclusion: In this small study a prednisolone absorption test was associated with a sustained fall in eosinophil count; This was not reflected in improved exhaled, spirometric or clinical markers.

P2086
Patient characteristics that can predict response to omalizumab an (anti-IgE antibody) for achieving better control of asthmatic patients
Nancy Abdelaty. *Chest, Suez Canal University, Ismailia, Egypt*

Background: Omalizumab is a monoclonal anti-immunoglobulin E (IgE) antibody indicated for the treatment of inadequately controlled severe persistent asthma despite optimal controller therapy. It is an expensive medication so there is a need to identify those patients most likely to benefit.
Aim of the study: To investigate characteristics associated with response to omalizumab in difficult asthma.
Patients and methods: The study enrolled 42 patients (15 female, 27 male) with age range (20y-52y) with severe asthma that was inadequately controlled despite step 4treatment as described in (GINA) guidelines. Omalizumab was given as add-on therapy to concomitant asthma treatment and administered subcutaneously every 2 or 4 weeks according to patients' pretreatment bodyweight and baseline IgE levels, for at least 16 weeks, those who showed better asthma control, were analyzed to investigate whether pre-treatment patient baseline clinical characteristics could be reliably identified and to be predictive of a superior response to omalizumab.
Results: 12/42 (28.6%) of enrolled patients showed better asthma control. Using univariate and multivariate regression analysis, many variables showed significant effect on response to omalizumab including; age, duration of asthma, history of allergic Rhinitis, history of allergic dermatitis, bronchial reversibility, no of positive results to common allergen, in immediate skin-prick, sputum eosinophilia and baseline total (IgE).
Conclusion: Omalizumab is an expensive medication so it is recommended to target its use to patients most likely to benefit rather than recommend widespread use. Further studies are needed to confirm these data.

P2087
Physician assessment of asthma control in patients receiving omalizumab in a real-world setting
Melinda Szabo[1], Jan Chlumsky[2], Robert Maykut[3], Panayiotis Georgiou[4], Chien-Wei Chen[5], Guy Peachey[4]. *[1]Pulmonology, Koch Róbert Hospital, Edelény, Hungary; [2]Pulmonary Diseases, Thomayer Hospital, Charles University, Prague, Czech Republic; [3]Critical Care, Novartis Pharma AG, Basel, Switzerland; [4]Critical Care, Novartis Pharmaceuticals UK Limited, Horsham, United Kingdom; [5]Critical Care, Novartis Pharmaceuticals Corporation, East Hanover, United States*

GINA guidelines define controlled, partly controlled and uncontrolled asthma based on a number of individual components (symptoms, activity limitation, rescue medication use, lung function and exacerbations).
The 2-year, global, single-arm, observational eXpeRience registry evaluated the efficacy and safety of omalizumab (OMA) in patients with allergic asthma in a 'real-world' setting. Investigators were instructed to assess asthma control using the GINA 2006 definitions. A post-hoc analysis compiled the individual components of control recorded by physicians and applied these to the GINA definitions.
The intent-to-treat population consisted of 916 patients. Investigators' assessment (IA) of control increased from 1.4% at baseline to 41.1% after 2 years of treatment (Table). Asthma control by strict GINA definitions increased from 0.8% at baseline to 21.0% over the 2 year treatment period (Table).

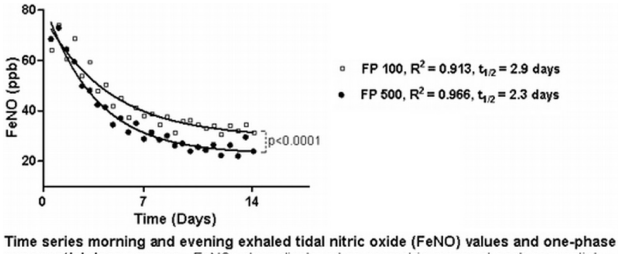
	Baseline, n (%) N=916		1 year, n (%) N=734		2 years, n (%) N=643	
	IA*	GINA	IA	GINA	IA*	GINA
Controlled	13 (1.4)	7 (0.8)	282 (38.4)	138 (18.8)	264 (41.1)	135 (21.0)
Partly controlled	209 (22.8)	120 (13.1)	342 (46.6)	285 (38.8)	296 (46.0)	258 (40.1)
Uncontrolled	690 (75.3)	730 (79.7)	95 (12.9)	211 (28.7)	72 (11.2)	180 (28.0)
Unknown	3 (0.3)	59 (6.4)	15 (2.0)	100 (13.6)	10 (1.6)	70 (10.9)

*Data missing for 1 patient.

These data show differences between physician's assessment of asthma control and control as determined by strict application of GINA 2006 definitions. This study did not explore what determined the differences in assessment, which may be of interest for future study. Regardless of method, asthma control improved over time in patients receiving OMA in this real-world study.

P2088
Effects of inhaled corticosteroids on asthmatic inflammation: The FeNOtype trial
William Anderson, Philip Short, Peter Williamson, Brian Lipworth. *Asthma and Allergy Research Group, University of Dundee, Scotland, United Kingdom*

Background: Personalised treatment for inflammatory asthma phenotypes confers superior benefits. The elevated exhaled nitric oxide (FeNO) inflammatory phenotype requires evaluation of dose-response to inhaled corticosteroids (ICS).
Methods: Randomised, crossover trial in mild-to-moderate asthmatics receiving ICS with elevated FeNO>40ppb after ICS washout. Patients received 2 weeks of: fluticasone propionate 50ug twice-daily (FP100) or 250ug twice-daily (FP500). Primary outcome: response in diurnal domiciliary FeNO levels. Secondary outcomes included: mannitol challenge; serum eosinophilic cationic protein (ECP); blood eosinophil count; and asthma control questionnaire (ACQ).
Results: 21 patients completed. We found significant dose-related reductions of diurnal FeNO compared to baseline: am FeNO: baseline=71ppb; FP100=34ppb, p<0.001; FP500=27ppb, p<0.001; and significant dose separation for am, p<0.05, and pm, p<0.001. Time series FeNO displayed exponential decay:



Time series morning and evening exhaled tidal nitric oxide (FeNO) values and one-phase exponential decay curves. FeNO values displayed as geometric means at each sequential time point for each group. R^2 = coefficient of determination (goodness of fit) of exponential decay curves to each data set. $t_{1/2}$ = half-life of exponential decay. ppb = parts per billion.

ACQ significantly improved exceeding the minimal important difference (>0.5) with values in keeping with controlled asthma (<0.75) after each dose: FP100=0.48, p=0.004; FP500=0.37, p=0.001. All other secondary inflammatory related outcomes showed significant improvements from baseline but no dose separation.

Conclusion: There is significant, dose-response of diurnal FeNO to ICS in patients with a high FeNO phenotype, also associated with well controlled asthma.

P2089

Effects of Arg16Gly polymorphism in ADRB2 gene on responses to salmeterol or montelukast added to inhaled corticosteroids in Japanese asthmatic subjects

Satoshi Konno[1], Hironi Makita[1], Nobuyuki Hizawa[2], Kaoruko Shimizu[1], Fumio Kokubu[3], Takefumi Saito[4], Takeo Endo[5], Hiroki Ninomiya[6], Hiroaki Iijima[7], Norihiro Kaneko[8], Masaharu Nishimura[1]. *[1]First Department of Medicine, Hokkaido University, Sapporo, Japan; [2]Department of Pulmonary Medicine, Tsukuba University, Tsukuba, Japan; [4]Department of Respiratory Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan; [5]Department of Respiratory Medicine, Ibaragihigashi National Hospital, Toukai, Japan; [6]Department of Respiratory Medicine, Mito Medical Center, Higashiibaragi, Japan; [7]Department of Respiratory Medicine, Kobari General Hospital, Noda, Japan; [8]Department of Respiratory Medicine, Tsukuba Medical Center, Tsukuba, Japan; [9]Department of Respiratory Medicine, Kameda Medical Center, Kamogawa, Japan*

Rationale: Long-acting β2-agonists (LABA) and leukotriene receptor antagonists (LTRA) are two recommended agents to add to inhaled corticosteroids (ICS) in asthma patients not adequately controlled by ICS alone. Conflict studies exist on whether the Arg16Gly genotype in b2-adrenergic receptor (ADRB2) gene may influence the bronchodilator effect of β2-agonists, and some indicate that subjects with Arg/Arg show deterioration in pulmonary function with long-term LABA treatment.
Objective: We hypothesized that the Arg16Gly genotype might determine the differential response to either LABA (salmeterol, Sal) or LTRA (montelukast, Mon) when added to ICS in patients with asthma.
Methods: This study was a randomized, cross-over design and 62 mild to moderate asthma patients (26 patients with Arg/Arg, 36 patients with Gly/Gly) were enrolled. The primary endpoint was a difference of the change in the morning PEF at 16 weeks [ΔPEF (Sal) – ΔPEF (Mon)] between the two genotypes.
Results and Conclusion: The mean difference in [ΔPEF (Sal) – ΔPEF (Mon)] was 16±50 (SD) in patients with Arg/Arg, and 16±41(SD) in patients with Gly/Gly ($P>0.05$). This result suggests that the Arg16Gly genotype does not influence the preferential bronchodilator effect of Sal or Mon in mild to moderate persistent asthma patients, at least, in 16 weeks follow-up.

P2090

The efficacy of inhaled fluticasone furoate (FF) and vilanterol (VI) administered in combination in asthma is comparable when administered in the morning or evening

Rodger Kempsford[1], Amanda Oliver[2], Lee Tombs[3], Jo Bal[4]. *[1]Respiratory Medicines Development Centre, GlaxoSmithKline, Stevenage, United Kingdom; [2]Respiratory & Immuno-Inflammation MDC, GlaxoSmithKline, Uxbridge, United Kingdom; [3]Synergy Statistics & Programming, GlaxoSmithKline, Uxbridge, United Kingdom; [4]Clinical Pharmacology Science and Study, GlaxoSmithKline, Uxbridge, United Kingdom*

Introduction: The novel corticosteroid FF and long-acting $beta_2$ agonist VI combination (FF/VI) is being developed as a once-daily inhaled treatment for asthma and COPD.
Objectives: To investigate the effect of time of day of dosing (AM or PM) on the efficacy of FF/VI (100/25mcg).
Methods: Single centre, randomised, double-blind, placebo-controlled, three-way crossover study. Subjects with persistent asthma [N=26; 24–64 years] received FF/VI (AM or PM) or matching placebo (P) once daily for 14(±2) days. FEV_1 (0–24h weighted mean and pre-treatment [AM and PM]) was determined after the Day 14 PM dose together with pre-treatment [AM and PM] PEF on Days 1–12.
Results: FF/VI administered AM or PM produced clinically significant increases in weighted mean FEV_1: the differences [95% CI] from P were 377mL [293, 462] and 422mL [337, 507], respectively; the difference between AM and PM dosing was –44mL [–125, 36]. Pre-treatment AM FEV_1 differences [95% CI] from P were 403mL [272, 533] and 496mL [369, 624] after AM and PM dosing, respectively; the treatment difference was –94mL [–221, 34]. Pre-treatment PM FEV_1 differences [95% CI] from P were 275mL [169, 380] and 309mL [205, 413] after AM and PM dosing, respectively; the treatment difference was –34mL [–138, 70]. FF/VI (AM or PM) produced rapid increases in PEF with the full effect apparent after the first dose and maintained throughout the 14 day treatment period.
Conclusion: The efficacy of FF/VI (100/25mcg) was comparable when dosed in the morning or evening in subjects with persistent asthma.
Funded by GSK (HZA114624; NCT01287065).

P2091

Efficacy of fluticasone furoate (FF) as a monotherapy and in combination with vilanterol (VI) over 12 weeks in patients with persistent asthma

Eugene R. Bleecker[1], Jan Lötvall[2], Paul M. O'Bryne[3], Ashley Woodcock[4], William W. Busse[5], Richard Forth[6], Hilary Medley[7], Carol Nunn[7], Loretta Jacques[7], Eric D. Bateman[8]. *[1]Center for Genomics and Personalized Medicine, Wake Forest School of Medicine, Winston-Salem, United States; [2]Krefting Research Centre, University of Gothenburg, Sweden; [3]Michael G DeGroote School of Medicine, McMaster University, Hamilton, United States; [4]School of Translational Medicine, University of Manchester, United Kingdom; [5]Department of Medicine, University of Wisconsin, Madison, United States; [6]Quantitative Sciences Division, GlaxoSmithKline, Research Triangle Park, United States; [7]Respiratory Medicines Development Centre, GlaxoSmithKline, Uxbridge, United Kingdom; [8]Department of Medicine, University of Cape Town, South Africa*

Introduction: The inhaled corticosteroid FF in combination with the long-acting $beta_2$ agonist VI is under development for the treatment of asthma and COPD.
Objectives: To compare the efficacy and safety of FF/VI and FF in patients (aged ≥12 years) with persistent asthma.
Methods: In a randomised, double-blind, parallel-group study, patients (N=609; ITT) received FF/VI 100/25mcg, FF 100mcg or placebo once daily in the evening via a new dry powder inhaler. Co-primary endpoints: change from baseline in trough FEV_1 and weighted mean (wm) 0–24h FEV_1. Rescue-free 24h periods and safety were also assessed.
Results: Placebo increased trough FEV_1 (196mL) and $wmFEV_1$ (212mL) vs baseline. FF/VI and FF, respectively, significantly improved compared with placebo trough FEV_1 (172mL [$p<0.001$] and 136mL [$p=0.002$]) and $wmFEV_1$ (302mL [$p<0.001$] and 186mL [$p=0.003$]). Treatment differences between FF/VI and FF approached significance for $wmFEV_1$ (116mL, $p=0.060$), but not trough FEV_1 (36mL, $p=0.405$). Percent of rescue-free 24h periods with FF/VI was 10.6% greater than FF and 19.3% greater than placebo. Statistically significant ($p=0.032$) urinary cortisol suppression was seen with FF/VI (ratio=0.82) relative to placebo, but not FF. Adverse event and safety profiles were similar across treatment groups.
Conclusions: Significant improvement in lung function was observed with FF/VI and FF in patients with persistent asthma. Addition of VI to FF did not significantly improve FEV_1, but a numerical increase was seen. The high placebo response in evening trough FEV_1 may have influenced the assessment of efficacy in this study.
Funded by GSK (HZA106827; NCT01165138).

P2092

Safety and tolerability of the novel inhaled corticosteroid (ICS) fluticasone furoate (FF) in combination with the long-acting $beta_2$ agonist (LABA) vilanterol (VI) administered once daily (OD) in patients with asthma

William W. Busse[1], Paul M. O'Byrne[2], Eugene R. Bleecker[3], Jan Lötvall[4], Ashley Woodcock[5], Leslie Andersen[6], Jody West[7], Loretta Jacques[8], Ludovic Apoux[9], Eric D. Bateman[10]. *[1]Department of Medicine, University of Wisconsin, Madison, United States; [2]Michael G DeGroote School of Medicine, McMaster University, Hamilton, Canada; [3]Center for Genomics and Personalized Medicine, Wake Forest School of Medicine, Winston-Salem, United States; [4]Krefting Research Centre, University of Gothenburg, Sweden; [5]School of Translational Medicine, University of Manchester, United States; [6]Respiratory Medicines Development Center, GlaxoSmithKline, Research Triangle Park, United States; [7]Quantitative Sciences Division, GlaxoSmithKline, Uxbridge, United Kingdom; [8]Respiratory Medicine Development Centre, GlaxoSmithKline, Uxbridge, United Kingdom; [9]Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, Uxbridge, United Kingdom; [10]Department of Medicine, University of Cape Town, South Africa*

Introduction: The ICS FF in combination with the LABA VI is in development for asthma and COPD.
Objectives: To assess the safety and tolerability of FF/VI over 52 weeks in patients with asthma.
Methods: Patients (N=503) were randomised (2:2:1) to FF/VI 100/25mcg or FF/VI 200/25mcg OD in the evening, or fluticasone propionate (FP) 500mcg twice daily. Safety evaluations included adverse events (AEs), non-fasting glucose and potassium, urinary cortisol (UC), heart rate (HR), pulse rate and ophthalmic assessments.
Results: Statistically significant UC suppression was seen with FP compared with both FF/VI groups at Weeks 12 and 28 ($p\leq0.006$), but not at Week 52. Potassium and glucose values were similar across groups. Increases in pulse rate (10min post dose; Week 52) were reported with FF/VI vs FP (FF/VI 100/25mcg: 3.4bpm, $p=0.002$; FF/VI 200/25mcg: 3.4bpm, $p=0.003$). No significant effects with FF/VI vs FP were observed on QTc(F) outputs or HR with Holter monitoring. AEs were reported by 66–69% of patients on FF/VI and by 73% on FP. Oral/oropharnygeal candidiasis AEs: FF/VI (6–7%), FP (3%). Twelve SAEs were reported; one (worsening hepatitis on FP) was considered drug related. Low number of 'special interest' AEs (including ocular effects and pneumonia).
Conclusion: FF/VI (100/25mcg or 200/25mcg) administered once daily over 52 weeks was well tolerated by patients aged ≥12 years with asthma. The overall safety profile observed for FF/VI did not reveal any findings of significant clinical concern and was similar to FP.
Funded by GSK (HZA106839; NCT01018186).

P2093

Safety of once-daily QMF149 in patients with persistent asthma

Richard Beasley[1], Bob Lanier[2], István Várkonyi[3], Blanka Novakova[4], Allen Moton[5], Han-Joo Kim[6], Bettina Hederer[7]. *[1]Medical Research Institute of New Zealand, Private Bag, Wellington, New Zealand; [2]Department of Pediatrics, University of North Texas, Fort Worth, United States; [3]Kenézy Kórház Kft., Kenézy Kórház Rendelointézet Egészségügyi Szolgáltató Nonprofit Kft., Debrecen, Hungary; [4]Obdorna Ordinace Alergologie a Klinicke Imunologie, Alergologická a Imunologická ambulance, Kryblická, Trutnov, Czech Republic; [5]Primary Care, Novartis Pharmaceuticals Corporation, East Hanover, United States; [6]Integrated Information Science, Novartis Pharmaceuticals Corporation, East Hanover, United States; [7]Primary Care, Novartis Pharma AG, Basel, Switzerland*

QMF is an investigational once-daily (QD), fixed-dose combination of indacaterol (IND) and mometasone furoate (MF). This study assessed the long-term safety of QMF in patients (pts) with persistent asthma.
In this randomized, double-blind, multi-centre, Phase II study, pts (12–70 y) received QMF (IND maleate 500μg/MF 400μg) or MF (400μg), both administered QD via the Twisthaler®* for 6–21 months. Systemic exposure data show that this QMF dose is comparable to 150μg IND/160μg MF in the Concept1 (Breezhaler®) inhalation device, the delivery device that will be used in future studies. The primary endpoint was time to first serious exacerbation (resulting in hospitalisation, intubation or death). A key secondary endpoint was the cumulative incidence of serious exacerbations. AEs and SAEs were recorded.
8 of 1519 randomised pts (QMF, 756; MF, 763) were hospitalised for a serious exacerbation (QMF, 2; MF, 6); none required intubation or resulted in death. QMF reduced the risk of a serious exacerbation vs MF by 69% (hazard ratio=0.31; 90% CI 0.08, 1.19; p=0.076). The difference in cumulative incidence was -0.52 percentage points (90% CI -1.14, 0.09) in favor of QMF, meeting the pre-specified, non-inferiority margin of 1 percentage point. Similar proportions of pts experienced AEs and SAEs in both groups (QMF, 74.0% and 4.0%; MF, 73.4% and 5.8%). Most frequent AEs with QMF and MF were cough and asthma, respectively. There was one death (MF group), which was not treatment or asthma related. Mean plasma MF concentrations were similar in both groups.
QMF QD was not associated with additional safety concerns vs MF monotherapy in pts with persistent asthma.
* Twisthaler® is a registered trademark of Schering-Plough LTD.

P2094

Is there an unmet need of small airways disease in community treated asthma?

Brian Lipworth[1], Emma Zajda[2], William Anderson[1]. *[1]Asthma and Allergy Research Group, University of Dundee, Scotland, United Kingdom; [2]Health Sciences, University of Abertay Dundee, Dundee, Scotland, United Kingdom*

Background: Asthma treatment guidelines are mainly based on symptoms & spirometry. There is concern regarding persistent underlying small airways disease in asthmatics despite standard care. Impulse oscillometry (IOS) measures small airway function.
Methods: We analysed community referral data from asthmatics (n=378) on standard community stepwise therapy, who had spirometry, IOS & exhaled nitric oxide (FeNO) performed.
Results: Patients receiving extra-fine (EF) particle inhaled corticosteroids (ICS) at Step 2 demonstrated improved resistance at 5Hz (R5%) by 14.2% but no difference in spirometry.

Table 1. Step 2

	EF ICS (n=67)	Non EF ICS (n=125)	P-value
Age, yrs	42 (38–45)	38 (36–41)	ns
Sex M:F	26:41	45:80	
ICS dose, ug/day	279 (249–309)	406 (364–447)	<0.0001
FEV1, %	88.9 (84.8–92.9)	90.3 (87.5–93.1)	ns
FEF25–75, %	63.7 (57.5–69.8)	67.1 (62.7–71.5)	ns
R5, %	124 (114–136)	138 (130–147)	<0.05
FeNO, ppb	31.4 (24.9–39.5)	25.3 (21.9–29.2)	ns

Mean (95% CI).

For Step 3&4 patients, R5% remained elevated (137%) despite the use of long acting beta agonists (LABA) with no difference without LABA: <5% of step 3/4 patients were using EF ICS with no EF ICS/LABA use.

Table 2. Step 3/4

	LABA (n=145)	No LABA (n=41)	P-value
Age, yrs	43 (41–45)	44 (40–49)	ns
Sex M:F	52:93	20:21	
ICS dose, ug/day	1076 (976–1175)	1568 (1388–1749)	<0.0001
FEV1, %	83.8 (80.3–87.2)	87.4 (81.0–93.7)	ns
FEF25–75, %	56.2 (52.0–60.4)	58.0 (49.7–66.2)	ns
R5, %	137 (128–147)	129 (113–148)	ns
FeNO, ppb	21.7 (19.1–24.7)	24.0 (19.1–30.2)	ns

Mean (95% CI).

Conclusion: There is an unmet need in terms of treating small airways disease in asthma. EF ICS showed improved R5% (step 2). Studies with EF ICS +/– LABA at step 3/4 are required to discern any change in small airways function through greater peripheral deposition.

P2095

Utilization of FIXED combination (FC) in the treatment of asthma patients in real life condition in the Czech Republic (UFO)

Viktor Kasak, Eva Kasakova, Jana Vinklerova. *Respiratory Dpt., Lerymed Spol. s. r. o., Prague 4, Czech Republic Respiratory Dpt, Lerymed Spol. s. r. o., Prague 4, Czech Republic Medical, AstraZeneca, Prague, Czech Republic*

Moderate and severe asthma is treated by FC of BUD/FOR, SAL/FP and BDP/FOR in the Czech Republic (CR). We do not have any data about real life utilization of FC in asthma treatment in the CR.
Primary obj.: Utilization of FC in the treatment of asthma pts. per year 2010. Secondary obj.: To describe asthma treatment in the CR in pts. who were prescribed a FC therapy.
Our study looking into the pts. records kept by specialist - allergists (132) and pulmologists (144). Every participating investigator recruited 10 pts. for the study. Asthmatic outpatients older than 6 years (n = 2786) who come to a regular visit were treated with one of three FC for at least 18 months. There were 1,8% pts. with intermittent asthma, 18,8% pts. with mild persistent, 67,6% pts. with moderate persistent, 12,2% pts. with severe persistent including 3,4% pts. with asthma difficult to treat.
60.8% pts. were treated with BUD/FOR (55.9% pts. in convectional regime, 44.1% pts. in the SMART regime), 37.3% pts. were treated with SAL/FP, 1.9% pts. were treated with BDP/FOR). Median of number of pack prescribed per year to pts. with asthma for BUD/FOR in convectional regime was 7 and in SMART regime was 7, for SAL/FP 12, for BDP/FOR 6. Total compliance of using FC was 53%, compliance of using FC in convectional regimes was 48.5%, compliance of using BUD/FOR in the SMART regime was 68%.
The utilization of BUD/FOR in SMART regime in the treatment of asthma pts. per year was the same as the utilization of BUD/FOR in convectional regime. Therapy of BUD/FOR in SMART regime increased compliance in comparison with convectional regimes of the other FC.

P2096

Asthma exacerbation with fluticasone propionate/formoterol fumarate combination therapy versus its individual components

Sanjeeva Dissanayake[1], Mark Lomax[1], Kirsten Kaiser[2], Tammy McIver[1]. *[1]European Medical Science, Mundipharma Research Ltd., Cambridge, United Kingdom; [2]Medicinal and Regulatory Development, SkyePharma AG, Muttenz, Switzerland*

Background: Asthma control remains suboptimal in many patients as indicated by exacerbations and deteriorating symptoms. This pooled analysis of up to 5 randomized double-blind studies assessed the effects of fluticasone propionate (FLUT) and formoterol fumarate (FORM) in a single aerosol inhaler (FLUT/FORM) on asthma exacerbations.
Methods: Adults and adolescents with asthma (all severities) were randomized to FLUT/FORM (100/10, 250/10 or 500/20 μg bid), or equivalent nominal doses of FLUT (100, 250 or 500 μg bid; 5 studies) or FORM (10 μg bid; 3 studies) for 8 or 12 weeks. The proportion of patients with an exacerbation was assessed. Mild-to-moderate exacerbation was defined as peak expiratory flow rate >30% below baseline, awakening at night due to asthma or rescue medication use >3–4 times/day (each on ≥2 consecutive days); severe exacerbation was need for additional therapy, or emergency visit/hospitalization due to asthma.
Results: Significantly fewer patients reported exacerbations with FLUT/FORM than FLUT (27% [172/641] vs 33% [211/643]; odds ratio [OR] 0.75; 95% CI 0.59, 0.96) or FORM (18% [62/341] vs 31% [108/345]; OR 0.49; 95% CI 0.34, 0.70). The annualised exacerbation rate was significantly lower with FLUT/FORM than FLUT (ratio 0.69; 95% CI 0.61, 0.79; p<0.001) or FORM (0.55; 95% CI 0.44, 0.68; p<0.001). The risk of severe exacerbation was similar for FLUT/FORM and FLUT (2% [12/641] vs 3% [18/643]; OR 0.66; 95% CI 0.32, 1.39), but lower with FLUT/FORM than FORM (2% [8/341] vs 10% [33/345]; OR 0.23; 0.10, 0.50).
Conclusion: FLUT/FORM significantly reduces the risk of reported asthma exacerbations (any severity) compared with its individual components.

P2097

The effect of salmeterol/fluticasone on markers of airway inflammation in patients with uncontrolled asthma

Dmitry Tikhanov, Galina Sergeeva, Alexander Emelyanov. *Department of Respiratory Medicine, North-West State Medical University named after I.Mechnikov, Saint-Petersburg, Russian Federation*

Aim: To assess changes of markers of airway and systemic inflammation in patients with uncontrolled asthma treated with salmeterol/fluticasone.
Materials and methods: Thirteen nonsmoking patients (62% males) aged 35-61 yrs (mean 47.4 yrs) with uncontrolled asthma (ACQ-5 >1.5) despite of previous monotherapy with ICS (medium dose 910.7±49.77 mcg BDP) for >30 days were included in this study. Patients were treated with salmeterol/fluticasone (Seretide Discus) 50/250 mcg twice daily during 12 weeks. Spirometry, methacholin chal-

lenge test (dry spirometer 2120 Vitalograph, UK), exhaled nitic oxide (FeNO) (Logan 4100 analyser), differential cell count in induced sputum and serum C reactive protein (CRP) were measured at baseline and in 12 weeks.
Results: There was a significant reduction of exhaled FeNO (14.9 vs 10.8 ppb, p=0.003) and increase of PC20 to methacholine(0.072 vs 0.203 mg, p=0.005) that was associated with impove asthma contol during the treatment with salmetrol/fluticasone. However, eosinophil counts in induced sputum (13.2 vs 8.9%, p>0.05) and serum CRP level (5.5 vs 4.5 mg/l, p>0.05) did not decrease compared to baseline level.
We conclude that FeNO and airway hyperesponsiveness to methacholine change faster and may reflect asthma control in steroid-treated patient with asthma. Eosinophil count in induced sputum and serum CRP level may use for to assess the duration of treatment with ICS/LABA.

P2098
Efficacy and safety of ciclesonide in the treatment of patients with persistent allergic or non-allergic asthma
Otto Chris Burghuber[1], Gerhard Köberl[2], Susanna Lenk-Feik[3], Monika Schantl[4], Peter Sander[5], Alexandra Hammer[6]. *[1]Internal Department, Otto Wagner Hospital, Vienna, Austria; [2]Pneumology Practice, Feldkirch, Austria; [3]Pneumology Practice, Baden, Austria; [4]Pneumology Practice, Graz, Austria; [5]Medical Department, Nycomed Deutschland GmbH, Konstanz, Germany; [6]Medical Department, Nycomed Pharma GmbH, Vienna, Austria*

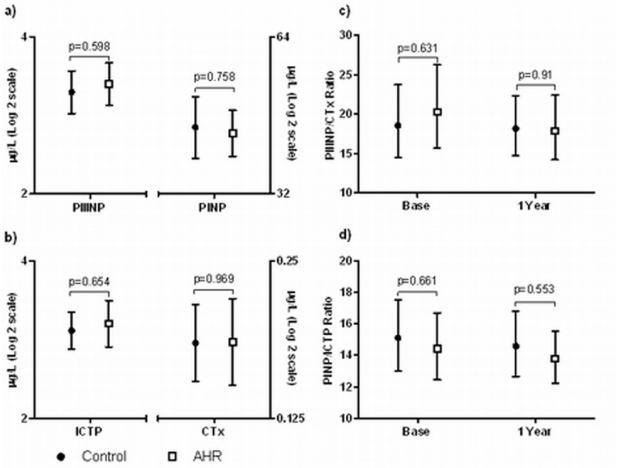
Aim: To evaluate the efficacy and safety profile of ciclesonide (CIC) in the treatment of persistent allergic or non-allergic asthma in a real-life setting in Austria.
Methods: 307 patients suffering from persistent asthma of any severity grade (42% treatment-naive) were enrolled in this non-interventional study (NIS). After prescription of CIC (most frequently 160µg/d) patients were observed for 3 months. At study start 85% were prescribed concomitant medication, primarily short-acting β2-agonists. Efficacy was evaluated by FEV1, Asthma Control Questionnaire (ACQ), Asthma Quality of Life- (AQLQ(S)), asthma symptoms, physical activity limitations and use of rescue medication.
Results: Mean FEV_1 % predicted increased from 75.1±15.4% to 83.7±14.9%. At the end of the observation period, the percentage of patients with daily symptoms had declined from 33.2% to 3.9%, nighttime symptoms from 21.8% to 5.2%, physical activity limitations from 73.9% to 24.4%, and rescue medication usage from 70.0% to 29.3%. The mean total ACQ score was 2.32±1.14 at baseline and 1.08±0.88 at study end. The number of patients with well-controlled asthma (ACQ-score <1) increased considerably from 11.0% to 52.2%. Accordingly, clinically important mean improvements were observed in the total self-assessed AQLQ(S) score. A low incidence of adverse drug reactions (ADR) was observed (4 ADRs in 3/307 patients).
Conclusion: This NIS in patients with persistent asthma confirmed the efficacy and safety of CIC in routine clinical care showing improvements in symptom control, lung function, and quality of life. CIC was well tolerated in this heterogeneous patient population.

P2099
Safety of formoterol in asthma clinical trials
Malcolm Sears[1], Finn Radner[2]. *[1]Medicine, McMaster University, Hamilton, ON, Canada; [2]AstraZeneca R&D, AstraZeneca R&D, Molndal, Sweden*

Background: We have previously reported safety data through 2006 from all AstraZeneca-sponsored, randomised, controlled, parallel-group trials with 3-12 months duration with formoterol. Data from 2007-2011 trials have now been added.
Methods: Risks associated with formoterol relative to non-LABA-treatments (ICS, SABA, placebo), salmeterol treatments, and conventional best practice, were assessed using rate and rate ratios for multiple safety endpoints.
Results: The 2007-2011 data added 15 trials and 22,509 patients including 17,447 treated with formoterol (all with concomitant ICS), increasing the combined dataset to 79 trials and 94,683 patients, of whom 67,380 received formoterol (94% using ICS). There were no asthma-related deaths in the new trials. In total, there were 8 asthma-related deaths among the formoterol-treated patients (exposure 33,700 years), vs. 2 among the non-LABA treated patients (N=18,740; exposure 9500 years) (RR 1.13; 95% CI: 0.23–10.9).
No increased risk was observed for formoterol vs. non-LABA treatments for all-cause mortality (RR 0.94; 95% CI: 0.52–1.80), cardiac mortality (RR 0.47; 95% CI: 0.19–1.22), or cardiac-related SAEs (RR 0.94; 95% CI: 0.52–1.80). Asthma-related SAEs were significantly reduced for formoterol vs. non-LABA treatment (RR 0.63; 95% CI: 0.53–0.75).
The new trials added a substantial number of black patients to the dataset, but no increased risk for asthma-related SAEs was observed for this subgroup in the combined dataset.
Conclusion: Use of formoterol in asthma patients, most using ICS, is not associated with any increased risk of asthma- or cardiac-related deaths or SAEs.

P2100
Prospective follow-up of novel bone turnover markers in asthmatics exposed to low or high doses of inhaled ciclesonide over 1 year
William Anderson, Lesley McFarlane, Brian Lipworth. *Asthma and Allergy Research Group, University of Dundee, Scotland, United Kingdom*

Background: There is concern that asthmatics receiving long-term inhaled corticosteroids could develop systemic adverse effects on bone metabolism. We investigated if exposure to inhaled ciclesonide at high vs low doses over 1 year caused any adverse effects on sensitive biomarkers of bone turnover in asthmatics.
Methods: Post hoc analysis of stored bone marker samples in a subgroup from a prospective, randomised parallel group trial (Lipworth et al. Chest DOI:10.1378/chest.11-1748) where ciclesonide was titrated to control asthma against either mannitol airway hyper-responsiveness (AHR strategy) or control (based on symptoms, reliever use and lung function) over 1 year. 100 mild-moderate asthmatics, 18-65years, with AHR to mannitol challenge had bone marker samples available for analysis. Outcome measures: bone formation (PINP, PIIINP), resorption (ICTP, CTx) and adrenal suppression (overnight urinary cortisol/creatinine: OUCC) at 0 and 12 months.
Results: Mean ciclesonide doses after 12 months were: AHR=507µg/day (n=50); control=202 µg/day (n=50), p<0.0001. There were no significant differences between AHR and control groups at baseline or after 12 months in PINP, PIIINP, ICTP or CTx; ratios of bone turnover as PINP/ICTP; PIIINP/CTx; or OUCC.



Bone turnover markers at 12 months (a,b) and bone turnover ratios at 0 and 12 months (c,d) between groups. Data presented as geometric means with 95% confidence interval error bars. Bone formation markers (a) PINP & PIIINP = serum amino-terminal pro-peptides of type I and III collagen respectively. Bone resorption markers (b): ICTP = serum pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen; CTx = type I collagen cross-linked C-telopeptide. Bone turnover ratios: PIIINP/CTx (c) and PINP/ICTP (d). AHR = airway hyper-responsiveness.

Conclusion: Higher doses of inhaled ciclesonide do not adversely affect sensitive markers of bone turnover in asthmatics over 12 months.