

Drug Class Review on Controller Medications for Asthma

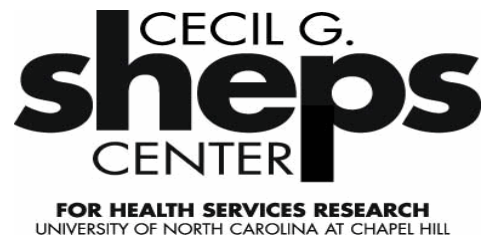
Update #1: Preliminary Scan Report #1

January 2010

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. RTI-UNC Evidence-based Practice Center does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Report

November 2008 (searches through April 2008)

Scope and Key Questions

The Research Triangle Institute International-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP) along with the RTI-UNC EPC, after considering comments received from the public which derived from a draft version posted to the DERP Web site. The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?
2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma?
3. Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?

Inclusion criteria**Populations**

- Populations include pediatric or adult outpatients with persistent asthma

Interventions

- Inhaled corticosteroids (ICSs): beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone, mometasone
- Long-Acting Beta-2 Agonists (LABAs): formoterol, arformoterol, salmeterol
- Leukotriene modifiers: montelukast, zafirlukast, zileuton
- Anti-IgE medications: omalizumab
- Combination products: fluticasone/salmeterol, budesonide/formoterol

Efficacy/Effectiveness outcomes

- Asthma control
 - Asthma exacerbations
 - Days/nights frequency of symptoms
 - Frequency of rescue medication use
 - Courses of oral steroids
- Quality of life
- Ability to participate in work, school, sports, or physical activity
- Adherence
- Emergency department / urgent medical care visits
- Hospitalization
- Mortality

Harms outcomes

- Overall adverse event reports
- Withdrawals due to adverse effects
- Serious adverse event reports
- Specific adverse events including:
 - Growth
 - Bone mineral density
 - Osteoporosis/fractures
 - Ocular toxicity
 - Suppression of HPA axis
 - Anaphylaxis
 - Death

METHODS

Literature Search

To identify relevant citations, we searched PubMed from January 2008 through December 29, 2009 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/index_e.html) Web sites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X.02) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 154 citations. Of those, there are 29 new potentially relevant RCTs (Appendix A).

New Drugs

Ciclesonide was FDA approved in 2008. Our search found an additional 7 trials evaluating ciclesonide (not included in the 29 above).

New Safety Alerts

FDA

Leukotriene Inhibitors: Montelukast (marketed as Singulair), Zafirlukast (marketed as Accolate), and Zileuton (marketed as Zyflo and Zyflo CR)

[UPDATED 08/28/2009] The June 12, 2009 Healthcare Professional Sheet has been updated. FDA provided healthcare professionals with updated information on the original March 2008 early communication and January 2009 follow-up communication about the ongoing safety review for the leukotriene inhibitors, montelukast, zafirlukast and zileuton. Neuropsychiatric events have been reported in some patients taking montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo and Zyflo CR). FDA has requested that manufacturers include a precaution in the drug prescribing information (drug labeling). The reported neuropsychiatric events include postmarket cases of agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior (including suicide), and tremor. FDA recommends that:

- Patients and healthcare professionals should be aware of the potential for neuropsychiatric events with these medications.
- Patients should talk with their healthcare providers if these events occur.
- Healthcare professionals should consider discontinuing these medications if patients develop neuropsychiatric symptoms.

FDA cont.**Omalizumab (marketed as Xolair) - Early Communication about an Ongoing Safety Review**

[07/16/2009] FDA is evaluating interim safety findings from an ongoing study of Xolair (omalizumab) titled *Evaluating the Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS)* that suggests a disproportionate increase in ischemic heart disease, arrhythmias, cardiomyopathy and cardiac failure, pulmonary hypertension, cerebrovascular disorders, and embolic, thrombotic and thrombophlebitic events in patients treated with Xolair compared to the control group of patients not given the drug. Xolair is approved for use by adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who test positive for reactivity to a perennial airborne allergen, and whose symptoms are inadequately controlled with inhaled corticosteroids.

FDA is not recommending any changes to the prescribing information for Xolair and is not advising patients to stop taking Xolair at this time. Until the evaluation of the EXCELS study is completed, healthcare providers and patients should be aware of the risks and benefits described in the prescribing information, as well as the new information from the ongoing EXCELS study that may suggest a risk of cardiovascular and cerebrovascular adverse events.

Health Canada

Information Update

2009-129

August 13, 2009

For immediate release

OTTAWA - Health Canada is informing health care professionals and Canadians that it is conducting a safety review of the potential association between the asthma drug Xolair (the brand name for the drug omalizumab) and an increased risk of cardiovascular problems.

The review comes in light of the interim findings of an ongoing study in the U.S. to assess the long-term safety profile of Xolair. The interim data suggests a disproportionate increase in cardiovascular problems among patients treated with Xolair relative to patients not treated with the drug. The problems reported include: heart attacks, abnormal heart rhythms, heart failure, fainting, mini-strokes, and blood clots.

In Canada, Xolair is indicated for the treatment of asthma in people 12 years old and older who have moderate to severe persistent asthma, who react to airborne allergens, and whose symptoms are not adequately controlled with inhaled corticosteroids.

The study, entitled Evaluating the Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS), is an observational study of approximately 5,000 patients who use Xolair and a control group of approximately 2,500 patients who do not. Study participants are 12 years of age and older with moderate to severe persistent asthma and who have an allergy to an airborne substance, such as pollen or spores. The final results of the 5-year study are expected in 2012.

At this time, Health Canada recommends that patients should not stop taking Xolair without first speaking to their doctor. Patients should contact their health care professional if they have any concerns about the medicines they are taking.

Health Canada has not concluded that there is a relationship between Xolair and cardiovascular problems. The Department is assessing the interim findings of this ongoing study as well as working with the market authorization holder, Novartis Pharmaceuticals Canada, to obtain further information. Should new safety information emerge from the review, Health Canada will inform Canadians and health care professionals and take appropriate action as necessary.

Appendix A. Abstracts of potentially relevant new studies of controller medications for asthma

Bailey, W., M. Castro, et al. (2008). "Asthma exacerbations in African Americans treated for 1 year with combination fluticasone propionate and salmeterol or fluticasone propionate alone." *Curr Med Res Opin* 24(6): 1669-1682.

OBJECTIVE: This long-term prospective study was conducted in African Americans with persistent asthma to examine the safety and effectiveness of the combination of the inhaled corticosteroid, fluticasone propionate (FP), and the long-acting beta-agonist, salmeterol, compared with FP alone. **RESEARCH AND DESIGN METHODS:** This was a randomized, double-blind, parallel group, multi-center trial in adolescent and adult subjects ≥ 12 years of age symptomatic on a low dose of an inhaled corticosteroid (ICS). The study consisted of a 2-week screening period on low dose ICS; a 4-week open-label FP 250 mcg twice daily (BID) run-in; a 52-week double-blind period (FP/salmeterol [FSC] 100/50 mcg [n=239] or FP 100 mcg [n=236] BID), and a 4-week FP 250 mcg BID run-out period. Annualized exacerbation rate was the primary outcome for comparing the two treatments. Other measures of asthma control included peak expiratory flow, asthma symptoms, and albuterol use. Safety was assessed through adverse events. **RESULTS:** Exacerbation rates were not significantly different in those treated with FSC 100/50 mcg (0.449 per year) compared with FP 100 mcg (0.529 per year, $p=0.169$). When the per-protocol analysis was applied, the rates were 0.465 and 0.769 per year for FSC 100/50 mcg and FP 100 mcg, respectively. Treatment with FSC 100/50 mcg provided statistically greater improvements in lung function measures and nighttime awakenings ($p \leq 0.050$) and demonstrated numerically lower daily symptoms ($p=0.216$) and albuterol use ($p=0.122$). Two subjects treated with FSC 100/50 mcg were hospitalized for an asthma exacerbation compared to three treated with FP 100 mcg. The overall incidence of adverse effects during double-blind treatment was similar between the FSC 100/50 mcg and FP 100 mcg treatment groups (61% and 68%, respectively). Frequent study visits were required of subjects during this long-term study, and it remains unknown whether this intervention may affect generalizability. **CONCLUSION:** In this large, prospective study among African Americans with asthma, the addition of salmeterol to FP resulted in a similar low rate of exacerbations and improved other markers of asthma control. Both FSC 100/50 mcg and FP 100 mcg were well-tolerated, and the overall safety-profiles were similar over 1 year of treatment.

Bateman, E. D., J. Bousquet, et al. (2008). "Stability of asthma control with regular treatment: an analysis of the Gaining Optimal Asthma control (GOAL) study." *Allergy* 63(7): 932-938.

BACKGROUND: Uncontrolled asthma is characterized by variability. Current asthma guidelines recommend focussing on the achievement and maintenance of control but few studies have examined in detail, using composite measures of control, the stability and potential duration of control once achieved. In this post-hoc analysis of the results of the Gaining Optimal Asthma control (GOAL) study, we examine the association between the level of asthma control achieved during the step-up phase of the study and the stability of control experienced during the maintenance phase. **METHODS:** GOAL was a 1-year, randomized, stratified, double-blind study of 3421 patients with uncontrolled asthma, which compared salmeterol/fluticasone propionate combination with fluticasone propionate in achieving two composite, guideline-based measures

of control: totally controlled and well-controlled asthma. We analysed the proportion and duration of time spent in control, the effect of treatment on asthma stability, and the impact of asthma control stability on unscheduled use of healthcare resources. RESULTS: In patients achieving well-controlled or totally controlled asthma, at least well-controlled asthma was maintained for a median of almost 3 and 6 months, and for more than 85% and 95% of weeks of follow-up, respectively. A high level of stability was confirmed in a Markov analysis investigating transitional probability of change in control status. Variability in control was associated with increased probability of an unscheduled healthcare resource use (odds ratio: 1.06, $P < 0.001$). CONCLUSIONS: Most patients achieving guideline-defined control can maintain at least a similar level of control with regular, stable dosing, with little likelihood of losing control.

Boonsawat, W., L. Goryachkina, et al. (2008). "Combined salmeterol/fluticasone propionate versus fluticasone propionate alone in mild asthma : a placebo-controlled comparison." *Clin Drug Investig* 28(2): 101-111.

BACKGROUND AND OBJECTIVE: Combined therapy with inhaled corticosteroids (ICSs) and long-acting beta(2)-adrenoceptor agonists (LABAs) is the recommended approach for the treatment of patients with asthma that is uncontrolled on ICSs alone. Additional studies are needed to assess the safety and efficacy of combination treatment with ICSs and LABAs in patients with mild asthma. The aim of this study was to compare the efficacy and tolerability of once-daily salmeterol/fluticasone propionate combination (SFC) with once-daily fluticasone propionate (FP) over a 12-week treatment period in patients with mild persistent asthma.

METHODS: This was a randomized, double-blind, placebo-controlled, parallel-group, multicentre study carried out in primary care or at a hospital outpatient department and included patients 12-79 years of age with mild persistent asthma ($n = 458$). After a 2-week run-in period, patients were randomized to receive SFC 50 microg/100 microg ($n = 149$), FP 100 microg ($n = 154$) or placebo ($n = 155$) once daily in the morning for 12 weeks. The primary efficacy endpoint was patient-recorded pre-dose mean morning peak expiratory flow (PEF). Other assessments included asthma symptom scores, use of rescue medication and investigator-recorded exacerbations. Lung function was measured and assessed during clinic visits.

RESULTS: For the primary efficacy endpoint of mean change in morning PEF, SFC achieved significantly greater increases from baseline than both placebo (difference in adjusted means 23 L/min; 95% CI 15.0, 30.3; $p < 0.001$) and FP (difference in adjusted means 14 L/min; 95% CI 6.3, 21.7; $p < 0.001$). Compared with those who received FP, patients in the SFC group demonstrated significantly greater improvements in mean evening PEF (95% CI 11.7, 28.1; $p < 0.001$), forced expiratory volume in 1 second (95% CI 0.093, 0.257; $p < 0.001$), forced expiratory flow between 25% and 75% of forced vital capacity (95% CI 0.242, 0.617; $p < 0.001$), the percentage of symptom-free days (95% CI 0.34, 0.87; $p = 0.011$), and the percentage of rescue medication-free days (95% CI 0.34, 0.90; $p = 0.018$). During weeks 5-12, 52% of patients in the SFC group achieved 'well controlled' asthma, compared with 42% and 26% of patients in the FP and placebo groups, respectively. Only one patient (receiving placebo) had a severe asthma exacerbation during the study; the frequency of adverse events was similar across the three treatment groups.

CONCLUSION: Once-daily SFC 50 microg/100 microg provided significantly greater improvements in lung function and in asthma symptoms than once-daily FP 100 microg alone in patients with mild persistent asthma. However, twice-daily treatment with either SFC or ICSs

plus short acting beta(2)-adrenoceptor agonists could be required to achieve guideline-defined asthma control in some patients.

Busse, W. W., S. R. Shah, et al. (2008). "Comparison of adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients." *J Allergy Clin Immunol* 121(6): 1407-1414, 1414 e1401-1406.

BACKGROUND: The adjustable-dose budesonide/formoterol dry powder inhaler (DPI) has demonstrated similar or greater asthma control with less inhaled corticosteroid compared with the fixed-dose budesonide/formoterol DPI. **OBJECTIVE:** We sought to evaluate the efficacy, tolerability, and resource use of maintenance therapy with the adjustable-dose budesonide/formoterol pressurized metered-dose inhaler versus the fixed-dose budesonide/formoterol pressurized metered-dose inhaler and the fixed-dose fluticasone propionate/salmeterol DPI. **METHODS:** This was a randomized, open-label, multicenter study of patients (N = 1225) 12 years and older with moderate-to-severe persistent asthma. After 10 to 14 days of current therapy, patients were randomized 2:1 to fixed-dose budesonide/formoterol (160/4.5 microg x 2 inhalations [320/9 microg] twice daily) or fixed-dose fluticasone propionate/salmeterol (250/50 microg x 1 inhalation twice daily) for 1 month (treatment period 1), after which, the fixed-dose fluticasone propionate/salmeterol group continued therapy and the fixed-dose budesonide/formoterol group was randomized 1:1 to fixed-dose budesonide/formoterol or adjustable-dose budesonide/formoterol (adjustable from 2 inhalations [320/9 microg] twice daily to 2 inhalations [320/9 microg] once daily or 4 inhalations [640/18 microg] twice daily) for 6 months (treatment period 2). **RESULTS:** There were no significant between-group differences in asthma exacerbations (primary variable), asthma symptoms, or lung function during the 7-month treatment period. Less study drug (inhalations per day, $P < .001$) was used with adjustable-dose versus fixed-dose budesonide/formoterol. All treatments were well tolerated. **CONCLUSIONS:** Adjustable-dose and fixed-dose budesonide/formoterol showed no differences in asthma control or tolerability versus fixed-dose fluticasone propionate/salmeterol.

Chervinsky, P., J. Baker, et al. (2008). "Patient-reported outcomes in adults with moderate to severe asthma after use of budesonide and formoterol administered via 1 pressurized metered-dose inhaler." *Ann Allergy Asthma Immunol* 101(5): 463-473.

BACKGROUND: Patient-reported outcomes (PROs) are important for evaluating asthma therapy. **OBJECTIVE:** To evaluate PROs in adults with moderate to severe persistent asthma receiving budesonide and formoterol administered via 1 pressurized metered-dose inhaler (pMDI). **METHODS:** This 12-week, double-blind, double-dummy, placebo-controlled, multicenter study randomized 596 patients 12 years or older to budesonide/formoterol pMDI 160/4.5 microg x 2 inhalations (320/9 microg); budesonide pMDI 160 microg x 2 inhalations (320 microg) + formoterol dry powder inhaler (DPI) 4.5 microg x 2 inhalations (9 microg); budesonide pMDI 160 microg x 2 inhalations (320 microg); formoterol DPI 4.5 microg x 2 inhalations (9 microg); or placebo, each twice daily, after 2 weeks of budesonide pMDI 80 microg x 2 inhalations (160 microg) twice daily. PROs were assessed in 553 patients 18 years or older using the standardized Asthma Quality of Life Questionnaire (AQLQ[S]), Medical

Outcomes Survey (MOS) Sleep Scale, Patient Satisfaction With Asthma Medication (PSAM) questionnaire, diary data, and global assessments. RESULTS: Patients receiving budesonide/formoterol reported significantly greater improvements from baseline on the AQLQ(S) and asthma control variables (based on symptoms and rescue medication use; all $P < .001$) vs placebo. Clinically important improvements (increase of $>$ or $=$ 0.5 points) from baseline to end of treatment in AQLQ(S) overall scores were achieved by 43.6% of patients receiving budesonide/formoterol vs 22.6% of patients receiving placebo ($P = .001$). The MOS Sleep Scale scores generally showed no differences among treatment groups. Patients receiving budesonide/formoterol had significantly greater PSAM questionnaire scores and better outcomes on physician-patient global assessments at end of treatment vs placebo (all $P <$ or $= .001$). CONCLUSION: Significantly greater improvements in health-related quality of life and asthma control and greater treatment satisfaction were observed with budesonide/formoterol pMDI vs placebo.

Chuchalin, A., L. Jacques, et al. (2008). "Salmeterol/fluticasone propionate via Diskus once daily versus fluticasone propionate twice daily in patients with mild asthma not previously receiving maintenance corticosteroids." *Clin Drug Investig* 28(3): 169-181.

BACKGROUND and objective: The efficacy and safety of twice-daily inhaled salmeterol/fluticasone propionate combination (SFC) therapy have been well established in the treatment of adults and adolescents with asthma. Once-daily administration of SFC could also be appropriate in patients with mild persistent asthma. This study aimed to investigate whether once-daily SFC 50 microg/100 microg was at least as effective as fluticasone propionate (FP) 100 microg twice daily, and more effective than twice-daily placebo, over 52 weeks as initial maintenance therapy in patients with mild persistent asthma. **METHODS:** This was a randomized, double-blind, double-dummy, placebo-controlled, multicentre, parallel-group study carried out in primary and secondary care. Patients aged between 12 and 79 years with a documented clinical history of asthma for $>$ or $=$ 6 months who were currently receiving inhaled short-acting beta(2)-adrenoceptor agonists only were enrolled. Patients were randomized to receive either once-daily inhaled SFC 50 microg/100 microg, twice-daily inhaled FP 100 microg (i.e. twice the dose of FP compared with SFC) or placebo for 52 weeks. The primary efficacy endpoints were mean morning peak expiratory flow (PEF), as recorded by patients prior to the use of bronchodilator or study medication, and the rate of investigator-recorded asthma exacerbations. **RESULTS:** Patients receiving twice-daily FP and once-daily SFC showed greater improvements in mean morning PEF compared with those receiving placebo (FP, difference in means 20.1 L/min; 95% CI 14.7, 25.5; $p < 0.001$; SFC, difference in means 14.8 L/min; 95% CI 9.4, 20.2; $p < 0.001$). The difference in adjusted mean PEF between once-daily SFC and twice-daily FP was -5.3 L/min (95% CI -9.1, -1.6). PEF results showed that once-daily SFC was non-inferior to twice-daily FP. Over 52 weeks, there was a 35% reduction in exacerbation rates with once-daily SFC, which in this respect demonstrated superiority over placebo ($p < 0.001$). Non-inferiority between once-daily SFC and twice-daily FP with respect to exacerbation rates was not shown. Once-daily SFC significantly improved clinic forced expiratory flow between 25% and 75% of forced vital capacity (difference in means 0.129 L/s; $p < 0.001$) and clinic PEF (difference in means 10.8 L/min; $p < 0.001$) compared with twice-daily FP. Both treatments were well tolerated and the safety profile of each was similar to that seen with placebo. **CONCLUSION:** In patients with mild persistent asthma not previously receiving maintenance

therapy, once-daily SFC 50 microg/100 microg is an effective treatment compared with placebo, and was non-inferior to twice-daily FP 100 microg with respect to mean morning PEF. However, in this study, once-daily SFC was not as efficacious as twice-daily FP in reducing asthma exacerbation rates. This study confirms the benefits of regular maintenance treatment in patients with mild persistent asthma.

Covar, R. A., S. J. Szefler, et al. (2008). "Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children." *J Allergy Clin Immunol* 122(4): 741-747 e744.

BACKGROUND: Asthma exacerbations are a common cause of critical illness in children. **OBJECTIVE:** To determine factors associated with exacerbations in children with persistent asthma. **METHODS:** Regression modeling was used to identify historical, phenotypic, treatment, and time-dependent factors associated with the occurrence of exacerbations, defined by need for oral corticosteroids or emergency or hospital care in the 48-week Pediatric Asthma Controller Trial study. Children age 6 to 14 years with mild-to-moderate persistent asthma were randomized to receive either fluticasone propionate 100 microg twice daily (FP monotherapy), combination fluticasone 100 microg AM and salmeterol twice daily, or montelukast 5 mg once daily. **RESULTS:** Of the 285 participants randomized, 48% had 231 exacerbations. Using a multivariate analysis, which included numerous demographic, pulmonary, and inflammatory parameters, only a history of an asthma exacerbation requiring a systemic corticosteroid in the past year (odds ratio [OR], 2.10; $P < .001$) was associated with a subsequent exacerbation during the trial. During the trial, treatment with montelukast versus FP monotherapy (OR, 2.00; $P = .005$), season (spring, fall, or winter vs summer; $P < \text{or} = .001$), and average seasonal 5% reduction in AM peak expiratory flow (OR, 1.21; $P = .01$) were each associated with exacerbations. Changes in worsening of symptoms, beta-agonist use, and low peak expiratory flow track together before an exacerbation, but have poor positive predictive value of exacerbation. **CONCLUSION:** Children with mild-to-moderate persistent asthma with previous exacerbations are more likely to have a repeat exacerbation despite controller treatment. Inhaled corticosteroids are superior to montelukast at modifying the exacerbation risk. Available physiologic measures and biomarkers and diary card tracking are not reliable predictors of asthma exacerbations.

Edin, H. M., L. B. Andersen, et al. (2009). "Effects of fluticasone propionate and salmeterol hydrofluoroalkane inhalation aerosol on asthma-related quality of life." *Ann Allergy Asthma Immunol* 102(4): 323-327.

BACKGROUND: Current asthma guidelines emphasize domains of impairment and risk for assessing severity and control, noting the need to consider separately the effects of asthma on asthma quality of life and functional capacity. Proper treatment to control asthma should result in improvements in patient well-being and functional status. **OBJECTIVE:** To assess asthma-related quality of life after treatment with combination fluticasone propionate and salmeterol delivered via hydrofluoroalkane 134a metered-dose inhaler compared with the individual components alone. **METHODS:** Asthma-related quality of life was assessed as part of two 12-week, randomized, double-blind, placebo-controlled clinical trials comparing the fluticasone propionate-salmeterol combination administered via a single metered-dose inhaler with

salmeterol, fluticasone propionate, and placebo administered via traditional chlorofluorocarbon metered-dose inhaler. The Asthma Quality of Life Questionnaire was completed at baseline and end point. Score changes, overall and for the 4 separate domains, were compared within and among the treatment groups. RESULTS: A total of 720 of 725 patients completed a baseline Asthma Quality of Life Questionnaire and were included in the analyses. In both studies, all mean scores improved significantly from baseline with the fluticasone propionate-salmeterol combination, with significantly greater improvement in the overall score compared with salmeterol alone, fluticasone propionate alone, and placebo groups. Improvements with the combination were also clinically meaningful compared with changes with salmeterol and placebo in both studies and with fluticasone propionate in study 1. CONCLUSIONS: Treatment with combination fluticasone propionate and salmeterol delivered via hydrofluoroalkane metered-dose inhaler resulted in significantly greater improvements in asthma-related quality of life compared with individual components and placebo administered via traditional chlorofluorocarbon metered-dose inhaler.

Godard, P., P. Greillier, et al. (2008). "Maintaining asthma control in persistent asthma: comparison of three strategies in a 6-month double-blind randomised study." *Respir Med* 102(8): 1124-1131.

In patients controlled with SFC250 Diskus bd, this double-blind, randomised 6-month study compared continuing SFC250 to stepping down to either SFC100 bd or FP250 bd. Six hundred and three patients previously using 1,000 microg BDP (or equivalent) daily +LABA and controlled according to investigator's judgement were recruited. Patients received SFC250 bd during an 8-week open run-in period. Four hundred and seventy six patients (mean age=43 years, mean FEV₁=2.9+/-1.0) who fulfilled the randomisation criterion ('Well-controlled' asthma according to the GOAL weekly definition for the last 2 weeks of the run-in period) entered a 24-week treatment period. The statistical hypothesis was based on a non-inferiority of SFC100 or FP250 compared to SFC250. The main criterion was the change from baseline in morning PEF over weeks 1-12 in the per-protocol population. The non-inferiority limit was -15 L/min. At inclusion, the three treatment groups were well balanced. Mean morning PEF was 476, 470 and 465 L/min in the SFC250, SFC100 and FP250 groups, respectively. The adjusted mean change in morning PEF over weeks 1-12 was +1.76+/-2.43 L/min for SFC250, -3.07+/-2.32 L/min for SFC100 and -16.51+/-2.46 L/min for FP250. SFC100 was at least as effective as SFC250 (treatment difference -4.83 [-12.39; 2.72], p=0.151) whereas FP250 was not (treatment difference -18.27 [-26.05; -10.49], p<0.001). Similar results were observed over weeks 13-24 in morning PEF (SFC100-SFC250=-4.54+/-3.84, p=0.238; FP250-SFC250=-20.11+/-3.92, p<0.0001). Secondary endpoints showed a similar pattern. Over weeks 1-12, SFC250 was significantly more effective than FP250 on evening PEF, daily symptoms and bronchodilator use. There was no difference between SFC100 and SFC250. The mean annual rate of moderate exacerbations was 0.16 in both SFC 250 and SFC 100 groups, and 0.21 in FP 250 group (ns, Poisson analysis). All treatments were well tolerated. CONCLUSION: In patients achieving asthma control with SFC250, stepping treatment down with SFC100 was at least as effective on lung function and symptoms as continuing SFC250, whereas FP250 was not.

Harnest, U., D. Price, et al. (2008). "Comparison of mometasone furoate dry powder inhaler and fluticasone propionate dry powder inhaler in patients with moderate to severe persistent asthma requiring high-dose inhaled corticosteroid therapy: findings from a noninferiority trial." *J Asthma* 45(3): 215-220.

BACKGROUND: Inhaled corticosteroids (ICSs) are one of the suggested first-line therapies for patients with persistent asthma of moderate severity. **METHODS:** The efficacy and safety of mometasone furoate (MF) 400 microg twice daily (BID) and fluticasone propionate (FP) 500 microg BID administered for 12 weeks via dry powder inhaler (DPI) were compared in a noninferiority trial, in adults with moderate-to-severe persistent asthma. The primary variable was the change from baseline in am peak expiratory flow rate (PEFR). PM PEFR, forced expiratory volume in 1 second (FEV(1)), asthma symptoms, rescue medication use, response to therapy, exacerbation rates, and adverse events were also assessed. **RESULTS:** The lower bound of 95% CIs for treatment differences in the primary variable ranged from 2.6% to 5.6% throughout the 12-week study and were within the prespecified noninferiority range. No significant between-group differences were observed in lung function, rescue medication use, response to therapy, exacerbation rates, or adverse events. At most of the weeks assessed, there were no between-group differences in asthma symptoms. Most adverse events were mild-to-moderate. **CONCLUSION:** MF-DPI 400 microg BID was therapeutically equivalent to FP-DPI 500 microg BID in patients with moderate-to-severe persistent asthma.

Huchon, G., H. Magnussen, et al. (2009). "Lung function and asthma control with beclomethasone and formoterol in a single inhaler." *Respir Med* 103(1): 41-49.

BACKGROUND: Lung deposition is crucial for asthma treatment. However, there is no study comparing the potential role of lung co-deposition of combination therapy (inhaled corticosteroid and long-acting beta2 agonist) in the same inhaler. In moderate to severe asthmatics, an extra-fine hydrofluoroalkane combination of beclomethasone dipropionate and formoterol given via a single pressurised metered-dose inhaler (pMDI) was compared with beclomethasone dipropionate chlorofluorocarbon (CFC) pMDI and formoterol dry powder inhaler (DPI) given via separate inhalers. **METHODS:** In a double-blind, double-dummy, 24-week randomised clinical trial, 645 patients with moderate to severe asthma uncontrolled by regular treatment with inhaled corticosteroids received regular treatment with extra-fine fixed combination beclomethasone dipropionate 200 microg/formoterol 12 microg bid, or beclomethasone dipropionate (500 microg bid) via CFC pMDI and formoterol (12 microg bid) via DPI, or beclomethasone dipropionate (500 microg bid) via CFC pMDI. The primary outcome was morning peak expiratory flow (PEF). Secondary outcomes included lung function measured at clinic, asthma symptoms and control, exacerbations. **RESULTS:** Beclomethasone dipropionate/formoterol combination via single inhaler or via separate inhalers improved morning PEF. However, the combination via single inhaler was more effective than given via separate inhalers for asthma control. Both combination treatments were superior to beclomethasone dipropionate alone in improving lung function and asthma control. All treatments were well tolerated. **INTERPRETATION:** In patients with moderate to severe asthma, beclomethasone dipropionate/formoterol in a single inhaler was as effective as beclomethasone dipropionate plus formoterol and superior to beclomethasone dipropionate alone in improving lung function. For the first time with a single inhaler, beclomethasone dipropionate/formoterol was significantly superior to separate components for asthma control.

Humbert, M., W. Berger, et al. (2008). "Add-on omalizumab improves day-to-day symptoms in inadequately controlled severe persistent allergic asthma." *Allergy* 63(5): 592-596.

BACKGROUND: Omalizumab is efficacious in the treatment of moderate-to-severe and severe persistent allergic (immunoglobulin E-mediated) asthma, reducing exacerbations, emergency visits and improving quality of life (QoL). However, as exacerbations are relatively infrequent, assessment of efficacy on day-to-day symptoms is warranted. **AIMS:** To investigate the effect of add-on omalizumab on day-to-day symptoms, and how they correlate with QoL in severe persistent asthma. **METHODS:** The correlation between asthma symptom scores and QoL [Asthma Quality of Life Questionnaire (AQLQ)] was assessed. Symptom-free days (total symptom score = 0) and symptom-controlled days (definition 1: total symptom score ≤ 1 ; and definition 2: morning peak expiratory flow $\geq 90\%$ of baseline, daytime asthma score ≤ 1 and night-time asthma score = 0) were compared between the omalizumab-treated group, omalizumab responders and placebo. **RESULTS:** Four hundred and nineteen patients (omalizumab, n = 209; placebo, n = 210) were included in the efficacy analyses, and 61% (118/195) of patients with response data were classified as responders. Total symptom score strongly correlated with AQLQ overall and symptom scores and individual domains. AQLQ overall score correlated well with symptom scores. Responders had significantly more symptom-free days than the omalizumab-treated and placebo groups (45.8%, 37.2% and 22.6% respectively), and more symptom-controlled days (definition 1: 56.1%, 47.9% and 35.3%, respectively, and definition 2: 50.8%, 43.9% and 28.0%, respectively). **CONCLUSIONS:** In patients with inadequately controlled severe persistent asthma, day-to-day symptoms correlate well with QoL. Add-on omalizumab significantly improves day-to-day symptoms compared with placebo. Further improvement in responders confirms the physician's assessment as a response measure.

Kerwin, E. M., R. A. Nathan, et al. (2008). "Efficacy and safety of fluticasone propionate/salmeterol 250/50 mcg Diskus administered once daily." *Respir Med* 102(4): 495-504.

BACKGROUND: The twice daily administration of an inhaled corticosteroid (ICS) and long-acting beta(2)-agonist (LABA) has been shown to be effective in achieving asthma control. The once daily administration of an ICS/LABA may be a treatment option for some patients. **OBJECTIVE:** To assess the effectiveness of fluticasone propionate (FP)/salmeterol via a single inhaler (FSC) administered once daily compared with FP once daily, FSC twice daily, or placebo. **METHODS:** A 12-week, randomized, double-blind multicenter study conducted in 844 patients ≥ 12 years of age who were symptomatic while using a short-acting beta(2)-agonist alone. Blinded treatments included: FSC 250/50 mcg once daily in the evening (FSC 250/50 QD), FP 250 mcg once daily in the evening (FP 250 QD), FSC 100/50 mcg twice daily (FSC 100/50 mcg BID), or placebo. All treatments were delivered via the Diskus device. **RESULTS:** All treatments demonstrated greater improvements in efficacy measures compared with placebo. Overall, the greatest improvements were observed in the patients receiving FSC, either once or twice daily, compared with the FP 250 QD group. The two FSC treatments were similar except that QD dosing did not maintain improvements in lung function for 24h compared with twice daily dosing. All treatments were well tolerated. No suppression of HPA axis, as assessed by 24-

h urinary cortisol excretion, was observed in any of the active treatment groups. CONCLUSION: In patients symptomatic on a short-acting beta(2)-agonist alone, FSC 100/50 mcg BID was shown to provide better efficacy than a higher strength (FSC 250/50 mcg) administered once daily. However, a once daily regimen was effective and may be a valuable treatment option for some patients. Registered at (<http://ctr.gsk.co.uk/welcome.asp>) (SAS30022).

Kerwin, E. M., J. J. Oppenheimer, et al. (2009). "Efficacy and tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler in adults and adolescents with asthma previously stable with twice-daily budesonide/ formoterol dosing." *Ann Allergy Asthma Immunol* 103(1): 62-72.

BACKGROUND: The goal of asthma therapy is to control symptoms using minimal pharmacologic intervention. **OBJECTIVE:** To evaluate the efficacy and tolerability of once-daily budesonide/formoterol vs once-daily budesonide in patients stable with twice-daily budesonide/formoterol. **METHODS:** This double-blind, 12-week study enrolled 619 patients 12 years and older with mild to moderate asthma. After 4 to 5 weeks of twice-daily budesonide/formoterol pressurized metered-dose inhaler (pMDI), 80/4.5 microg x 2 inhalations (320/18 microg/d), stable patients were randomized 1:1:1:1 to 2 inhalations twice daily of budesonide/formoterol pMDI, 80/4.5 microg (320/18 microg/d), or 2 inhalations once daily (evening) of budesonide/formoterol pMDI, 160/4.5 microg or 80/4.5 microg (320/9 microg or 160/9 microg/d), or budesonide pMDI, 160 microg (320 microg/d). **RESULTS:** All budesonide/formoterol groups maintained significantly more favorable evening predose forced expiratory volume in 1 second (FEV1), morning peak expiratory flow (PEF), daytime/nighttime asthma symptoms, nighttime rescue medication use, and rescue medication-free days vs budesonide. Variables evaluated during the end of the once-daily dosing interval (evening predose FEV1, evening PEF, daytime asthma symptoms, and daytime rescue medication use) significantly favored twice-daily budesonide/formoterol vs all treatments. Twice-daily budesonide/formoterol demonstrated significantly more favorable results for symptom-free and asthma control days vs all treatments and awakening-free nights vs budesonide. Asthma Quality of Life Questionnaire and Asthma Control Questionnaire results significantly favored twice-daily budesonide/formoterol vs budesonide ($P < \text{or} = .018$). All treatments were well tolerated. **CONCLUSIONS:** Pulmonary function and asthma control were more effectively maintained with all budesonide/formoterol regimens vs once-daily budesonide and with twice-daily budesonide/formoterol at twice the daily formoterol dose vs both once-daily budesonide/formoterol doses.

Koenig, S. M., J. J. Murray, et al. (2008). "Does measuring BHR add to guideline derived clinical measures in determining treatment for patients with persistent asthma?" *Respir Med* 102(5): 665-673.

RATIONALE: Little is known about the use of biomarkers in guiding treatment decisions in routine asthma management. The objective of this study was to determine whether adding a LABA to an ICS would control bronchial hyperresponsiveness (BHR) at an overall lower dose of ICS when titration of medication was based upon the assessment of routine clinical measures with or without the measurement of BHR. **METHODS:** After a 2-week run-in period, subjects ($> \text{or} = 12$ years) were randomized to one of three treatment groups. Two groups followed a BHR

treatment strategy (based on clinical parameters [lung function, asthma symptoms, and bronchodilator use] and BHR) and were treated with either fluticasone propionate/salmeterol (FSC(BHR) group) or fluticasone propionate (FP(BHR) group) (n=156 each). The third group followed a clinical treatment algorithm (based on clinical parameters alone) and were treated with fluticasone propionate (FP(REF) group; n=154). All treatments were administered via Diskus. Treatment doses were adjusted as needed every 8 weeks for 40 weeks according to the subject's derived severity class, which was based on clinical measures of asthma control with or without BHR. RESULTS: The mean total daily inhaled corticosteroids (ICS) dose during the double-blind treatment period was lower, although not statistically significant, in the FSC(BHR) group compared with the FP(BHR) group (a difference of -42.9 mcg; p=0.07). Compared with the FP(REF) group, the mean total daily ICS dose was higher in the FSC(BHR) group (a difference of 85.2 mcg) and was significantly higher in the FP(BHR) group (a difference of 131.2 mcg, p=0.037). CONCLUSION: This study demonstrated that for most subjects, control of BHR was maintained when treatment was directed toward control of clinical parameters. In addition, there was a trend towards control of BHR and clinical measures at a lower dose of ICS when used concurrently with salmeterol.

Koenig, S. M., N. Ostrom, et al. (2008). "Deterioration in asthma control when subjects receiving fluticasone propionate/salmeterol 100/50 mcg Diskus are "stepped-down"." *J Asthma* 45(8): 681-687.

In this study, 647 subjects stable on fluticasone propionate/salmeterol Diskus 100/50 mcg BID (FSC) were randomized to continue FSC 100/50 mcg BID or "step down" to either fluticasone propionate (FP) 100 mcg BID, salmeterol (SAL) 50 mcg BID, or montelukast (MON) 10 mg once daily for 16 weeks. Overall asthma control significantly improved in the FSC group; whereas, "stepping down" to FP, SAL, or MON resulted in deterioration in asthma control, as determined by decreased measures of lung function and clinical features. This study provides support that treatment of both inflammation and smooth muscle dysfunction may be necessary to achieve and maintain asthma control in patients uncontrolled on ICS.

Kooi, E. M., S. Schokker, et al. (2008). "Fluticasone or montelukast for preschool children with asthma-like symptoms: Randomized controlled trial." *Pulm Pharmacol Ther* 21(5): 798-804.

RATIONALE: Beneficial effects of anti-inflammatory therapy such as fluticasone propionate (FP) and montelukast (Mk) have been demonstrated in preschool children with asthma. However, comparative studies are lacking in this age group. Therefore, we conducted a study to evaluate and compare the effect of FP and Mk in preschool children with asthma-like symptoms. METHODS: In this multicenter, randomized, placebo-controlled, double-blind, double-dummy trial, children aged 2-6 years with asthma-like symptoms were included. In total, 63 children were randomly allocated to receive FP (25), Mk (18) or placebo (20) for 3 months. The primary outcome was the daily symptom score (wheeze, cough, shortness of breath) as recorded by caregivers in a symptom diary card. Secondary endpoints were rescue medication free days, blood eosinophils and lung function (interrupter technique and forced oscillation technique (FOT)). RESULTS: During the 3 months study period, symptoms improved in all 3 groups, with a statistically significant difference between FP and placebo in favor of the FP group (p=0.021). A significant reduction in circulating eosinophils after 3 months of treatment

was found in the Mk group only ($p=0.008$), which was significantly different from the change found in the placebo group ($p=0.045$). With the exception of frequency dependence (measured by FOT), which showed a difference between FP and Mk after 3 months of treatment in favor of the FP group ($p=0.048$), no differences in lung function within or between groups were found. CONCLUSIONS: In spite of a lack of power, our results suggest that FP has a beneficial effect on symptoms and Mk on blood eosinophil level as compared to placebo. Except for a difference in one lung function parameter after 3 months between FP and Mk in favor of the FP group, this study revealed no differences between FP and Mk.

Kopp, M. V., E. Hamelmann, et al. (2009). "Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma." *Clin Exp Allergy* 39(2): 271-279.

BACKGROUND: The treatment of allergic asthma by specific immunotherapy (SIT) is hampered by potential side-effects. OBJECTIVE: The aim of this study was to study the effect of omalizumab, a monoclonal anti-IgE antibody, in combination with SIT in patients with seasonal allergic rhinoconjunctivitis (SAR) and co-morbid seasonal allergic asthma (SAA) incompletely controlled by conventional pharmacotherapy. METHODS: A randomized, double-blind, placebo-controlled, multi-centre trial was performed to assess the efficacy and safety of omalizumab (Xolair) vs. placebo in combination with depigmented SIT (Depigoid) during the grass pollen season. Omalizumab or placebo was started 2 weeks before SIT; the whole treatment lasted 18 weeks. Primary endpoint was daily 'symptom load', the sum of daily scores for symptom severity and rescue medication use. RESULTS: A total of 140 patients (age 11-46 years) were randomized; and a total of 130 finished the study. Combination therapy reduced the symptom load by 39% ($P=0.0464$, Wilcoxon test) over SIT monotherapy. This difference was mainly due to reduced symptom severity ($P=0.0044$), while rescue medication use did not change significantly. Combination therapy also improved asthma control (Asthma Control Questionnaire, $P=0.0295$) and quality of life in the case of asthma (Asthma Quality of Life Questionnaire, $P=0.0293$) and rhinoconjunctivitis (Rhinoconjunctivitis Quality of Life Questionnaire, $P=0.0537$). Numbers of patients with 'excellent or good' treatment efficacy according to ratings of investigators (75.0% vs. 36.9%) or patients (78.5% vs. 46.1%) were markedly higher in the combination group than under SIT alone. CONCLUSION: Combination of omalizumab with SIT for treatment of patients with SAR and co-morbid SAA was safe and reduced the symptom load in a statistically significant and clinically meaningful manner.

Lu, S., N. Liu, et al. (2009). "A randomized study comparing the effect of loratadine added to montelukast with montelukast, loratadine, and beclomethasone monotherapies in patients with chronic asthma." *J Asthma* 46(5): 465-469.

BACKGROUND: Loratadine added to montelukast has been suggested to improve endpoints of asthma. OBJECTIVE: This study investigated the additive effects of concomitant montelukast and loratadine when compared with montelukast, loratadine, and inhaled beclomethasone monotherapies in asthma. Methods. Patients ($N = 406$) were 15 to 65 years of age with a forced expiratory volume in 1 second (FEV(1))-predicted of 50% to 85%, FEV(1) reversibility \geq 15%, and a minimal level of daytime symptoms and beta-agonist use. This three-part 2X2 crossover-study consisted of two double-blind 6-week treatment periods where

patients were administered once daily oral montelukast 10 mg, loratadine 10 mg, montelukast 10 mg + loratadine 10 mg, or twice daily inhaled beclomethasone 200 µg. A subsequent 48-week extension study compared montelukast + loratadine with beclomethasone. The primary endpoint was the percentage change from baseline in FEV₁. RESULTS: Over 6 weeks of double-blind treatment, significant improvements ($p < 0.05$) in the primary endpoint of FEV₁ were seen for montelukast + loratadine versus loratadine (least-square mean percentage-point difference of 5.8%), beclomethasone versus montelukast + loratadine (2.35%), montelukast versus loratadine (5.94%), and beclomethasone versus montelukast (4.65%); a numerical improvement ($p = 0.054$) was seen for montelukast + loratadine versus montelukast (1.60%). Significant improvements for montelukast + loratadine versus montelukast were seen in some secondary endpoints (evening peak expiratory flow, nocturnal asthma symptom score, nocturnal awakenings, and asthma-specific quality of life) but not others. Significant improvements in most endpoints except daytime asthma symptoms score were seen for montelukast + loratadine versus loratadine. In the extension study, both montelukast + loratadine and beclomethasone improved several endpoints. All treatments were generally comparable in the percentage of patients with clinical and laboratory adverse experiences. CONCLUSION: In this study, the addition of loratadine to montelukast produced a small numerical, but not statistically significant, improvement in FEV₁ and, in general, no consistent improvement in other asthma endpoints. No improvement of montelukast + loratadine versus beclomethasone was seen in any endpoint.

Lundback, B., E. Ronmark, et al. (2009). "Asthma control over 3 years in a real-life study." *Respir Med* 103(3): 348-355.

This was a 3-year "real-life" study, during which patients' medication was increased and decreased to achieve sustained asthma control. Patients (282) were randomised to receive treatment with SAL 50µg, FP 250µg, or SFC 50/250µg via a Diskustride mark inhaler, bid. A 12-month double-blind period was followed by a 2-year open phase. The physician increased or decreased patients' medication to achieve and maintain asthma control at regular clinical assessments using criteria based on the asthma treatment guidelines. On completion 73% (168/229) of the subjects were receiving SFC to maintain control of their asthma, compared with 21% (49/229) receiving FP and 5% (12/229) receiving SAL. Odds ratio for requiring increased treatment were 2.66 ($p=0.002$) for patients initially randomised to FP and 9.38 ($p<0.0001$) SAL, compared with SFC. Time until 25% of patients first required an increase in study medication was 6months for patients initially treated with SAL compared to 12months for FP and 21months for SFC. Symptoms and use of rescue medication improved first, followed rapidly by PEF with the greatest improvements occurring over the first year. Airway hyperresponsiveness continued to improve throughout the study. The majority of patients achieved and maintained control of asthma over a 3-year period with physician-driven medication changes. Patients treated with SFC were more likely to achieve control than patients treated with FP or SAL alone. Continuing improvements in airway hyperresponsiveness indicate the importance of maintaining treatment after clinical control of symptoms and lung function are achieved.

Maspero, J., F. Guerra, et al. (2008). "Efficacy and tolerability of salmeterol/fluticasone propionate versus montelukast in childhood asthma: A prospective, randomized, double-blind, double-dummy, parallel-group study." *Clin Ther* 30(8): 1492-1504.

BACKGROUND: Asthma control remains suboptimal in adults and children worldwide. Inhaled salmeterol/fluticasone propionate combination (SFC) and oral montelukast (MON) are 2 treatments available for childhood asthma. **OBJECTIVE:** This study, the PEdiatric Asthma Control Evaluation (PEACE), investigated the efficacy and tolerability of SFC compared with MON for the control of persistent asthma in children. **METHODS:** Children with asthma (forced expiratory volume in 1 second [FEV(1)] 55%-80% predicted; reversibility $\geq 12\%$) aged 6 to 14 years who were receiving only short-acting beta(2)-agonists entered a 2-week run-in period. Symptomatic patients (rescue use or symptoms during 4 of the last 7 days) were randomized to double-blind, double-dummy treatment with SFC 50/100 microg BID via multidose dry powder inhaler or MON 5-mg tablet QD for 12 weeks. The primary end point was change from baseline in morning peak expiratory flow (PEF). Efficacy assessments included lung function, asthma symptoms, rescue medication use, and asthma control. Tolerability was assessed by recording the number and type of adverse events (AEs) and the number of asthma exacerbations. **RESULTS:** Of 607 patients screened, 548 were randomized to treatment. The SFC group contained 281 patients and the MON group included 267. Demographic characteristics and baseline data were similar for both groups (mean age, 9.3 years for both groups; mean [SD] FEV(1), 1.49 [0.43] L in the SFC group and 1.48 [0.43] L in the MON group). There were more males in the MON group (179 [67%]) than in the SFC group (156 [56%]). The adjusted mean (SE) changes from baseline in morning PEF were 45.88 (2.82) L/min with SFC and 28.7 (2.86) L/min with MON (treatment difference, 17.16 L/min; 95% CI, 9.23-25.08; $P < 0.001$). Compared with MON, the SFC group had significantly more asthma symptom-free days (odds ratio [OR], 1.74; 95% CI, 1.07-2.82; $P = 0.025$), more rescue-free days (OR, 3.24; 95% CI, 2.09-5.02; $P < 0.001$), and more asthma-controlled weeks (difference in treatment medians over weeks 1-12, 16.77%; 95% CI, 8.3-16.77; $P < 0.001$). Both treatments were well tolerated, with a similar number of patients reporting AEs (SFC group, 155/281 [55%]; MON group, 153/267 [57%]); the most common AE in both groups was headache (SFC group, 66 [23%]; MON group, 72 [27%]). The mean exacerbation rates over 12 weeks (post hoc analysis) were 0.12 in the SFC group and 0.30 in the MON group (SFC/MON ratio, 0.40; 95% CI, 0.29-0.57; $P < 0.001$). **CONCLUSIONS:** In these children with uncontrolled asthma previously on short-acting beta(2)-agonist monotherapy (% predicted FEV(1) $< 80\%$, frequent asthma symptoms and rescue medication use), treatment with SFC was significantly more effective in improving morning PEF and other measures of asthma control and in decreasing exacerbation rates (in a post hoc analysis) than treatment with MON. The 2 drugs were both well tolerated, with similar numbers and types of AEs reported.

Menezes, M. B., A. L. Teixeira, et al. (2008). "Inflammatory and functional effects of increasing asthma treatment with formoterol or double dose budesonide." *Respir Med* 102(10): 1385-1391.

Adding a long-acting beta(2)-agonist to inhaled corticosteroids (ICS) for asthma treatment is better than increasing ICS dose in improving clinical status, although there is no consensus about the impact of this regimen on inflammation. In this double-blind, randomized, parallel group study, asthmatics with moderate to severe disease used budesonide (400 mcg/day) for 5 weeks (run-in period); then they were randomized to use budesonide (800 mcg/day--BUD

group) or budesonide plus formoterol (400 mcg and 24 mcg/day, respectively--FORMO group) for 9 weeks (treatment period). Home PEF measurements, symptom daily reporting, spirometry, sputum induction (for differential cell counts and sputum cell cultures), and hypertonic saline bronchial challenge test were performed before and after treatments. TNF-alpha, IL-4 and eotaxin-2 levels in the sputum and cell culture supernatants were determined. Morning and night PEF values increased in the FORMO group during the treatment period ($p < 0.01$), from 435 ± 162 to 489 ± 169 and 428 ± 160 to 496 ± 173 L/min, respectively. The rate of exacerbations in the FORMO group was lower than in the BUD group ($p < 0.05$). Neutrophil counts in sputum increased in both groups ($p < 0.05$) and leukocyte viability after 48 h-culture increased in the FORMO group ($p < 0.05$). No other parameter changed significantly in either group. This study showed that adding formoterol to budesonide improved home PEF and provided protection from exacerbations, although increase of leukocyte viability in cell culture may be a matter of concern and needs further investigation.

Murphy, K., H. Nelson, et al. (2008). "The effect of budesonide and formoterol in one pressurized metered-dose inhaler on patient-reported outcomes in adults with mild-to-moderate persistent asthma." *Curr Med Res Opin* 24(3): 879-894.

OBJECTIVE: To determine the effects of budesonide and formoterol administered via one pressurized metered-dose inhaler (budesonide/formoterol pMDI) on patient-reported outcomes (PROs) and to determine the contributions of budesonide and formoterol to those effects in adults with asthma. **RESEARCH DESIGN AND METHODS:** A 12-week, randomized, double-blind, double-dummy, placebo-controlled, multicenter study was conducted in 480 patients aged ≥ 12 years with mild-to-moderate persistent asthma. After a 2-week run-in period during which current asthma therapy was discontinued, patients were randomized to receive two inhalations twice daily of budesonide/formoterol pMDI 80/4.5 microg (160/9 microg), budesonide pMDI 80 microg (160 microg), formoterol via dry powder inhaler (DPI) 4.5 microg (9 microg), or placebo. **MAIN OUTCOME MEASURES:** Analyses included a subpopulation of 405 patients aged ≥ 18 years. PROs included the standardized Asthma Quality of Life Questionnaire (AQLQ(S)), the Medical Outcomes Study (MOS) Sleep Scale, the Patient Satisfaction with Asthma Medication (PSAM) questionnaire, and asthma control variables (recorded via electronic diaries), such as asthma symptoms, rescue medication use, and nighttime awakenings due to asthma. Patient and physician global assessments were collected at the end of the study. **RESULTS:** Patients aged ≥ 18 years receiving budesonide/formoterol pMDI reported significantly greater improvements from baseline in AQLQ overall and domain scores, MOS Sleep Scale domain scores, and asthma control variables than patients receiving placebo ($p \leq 0.033$). Improvements from baseline in AQLQ(S) overall and domain scores, daily asthma symptoms scores, percentage of symptom-free days, percentage of rescue medication-free days, and percentage of asthma control days were significantly greater in patients receiving budesonide/formoterol pMDI versus formoterol DPI ($p \leq 0.042$). Patients receiving budesonide/formoterol pMDI reported significantly greater PSAM scores than did patients in all other treatment arms ($p \leq 0.004$). Study limitations may include the fact that the formoterol-alone arm used a different device and formulation than the other active arms as well as the absence of a treatment arm with budesonide and formoterol administered concomitantly in separate inhalers. In addition, these results may not be generalized to all patients with asthma, as this analysis included only patients aged ≥ 18 years.

CONCLUSIONS: Patients receiving treatment with budesonide/formoterol pMDI experienced significantly greater improvements from baseline in asthma-related quality of life, quality of sleep, and asthma control and greater satisfaction with treatment than patients receiving placebo. The combination of budesonide and formoterol in one pMDI is beneficial in improving how a patient feels and functions as a result of treatment.

Niven, R., K. F. Chung, et al. (2008). "Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: an open-label study." *Respir Med* 102(10): 1371-1378.

BACKGROUND: In a 1-year, randomized, open-label study in patients with moderate-to-severe allergic (immunoglobulin E (IgE)-mediated) asthma, adding omalizumab to best standard care (BSC) significantly improved efficacy outcomes compared with BSC alone (control). We assessed the efficacy of omalizumab in the subgroup of patients with inadequately controlled severe persistent allergic asthma despite high-dose inhaled corticosteroids (ICS) plus a long-acting beta(2)-agonist (LABA), which reflects the European Union (EU) label population. **METHODS:** Efficacy outcomes included annual asthma exacerbation rate, annual asthma deterioration-related incident (ADRI) rate, % predicted forced expiratory volume in 1 s (FEV(1)), asthma symptoms (Wasserfallen score) and quality of life (Mini Asthma Quality of Life Questionnaire (Mini-AQLQ)), which were compared in the omalizumab and control groups. Outcomes were also determined for omalizumab-treated patients judged to have responded to therapy (> or = 0.5-point improvement in Mini-AQLQ overall score at 27 weeks). **RESULTS:** In total, 164 patients (omalizumab, n=115; control, n=49) were receiving high-dose ICS plus a LABA. Annual asthma exacerbation rate was significantly reduced by 59% in the omalizumab group vs. control (1.26 vs. 3.06; P<0.001). ADRI rate was significantly reduced by 40% in the omalizumab group compared with control (5.61 vs. 9.40; P<0.05). Significant improvements were also seen in % predicted FEV(1) (71% vs. 60%; P<0.001), change from baseline in asthma symptom scores (-6.7 vs. 0.5; P<0.05) and Mini-AQLQ overall score (1.32 vs. 0.17; P<0.001). In omalizumab-treated patients, 71/102 (70%) were judged to have responded to therapy. In these Mini-AQLQ-assessed responders, exacerbation rate was reduced by 64% vs. control (1.12 vs. 3.06; P<0.001), ADRI rate was reduced by 50% vs. control (4.71 vs. 9.40; P<0.01). Percent predicted FEV(1) (73% vs. 60%; P<0.001), change from baseline in asthma symptom scores (-8.1 vs. 0.5; P<0.001) and Mini-AQLQ overall score (1.81 vs. 0.17; P<0.001) were also further significantly improved vs. control. **CONCLUSIONS:** Adding omalizumab to BSC is efficacious in patients with inadequately controlled severe persistent allergic asthma despite high-dose ICS plus a LABA (EU label population), with further efficacy observed in patients judged to have responded to therapy which may more accurately illustrate the actual benefit of omalizumab therapy in clinical practice. The naturalistic setting of this study confirms the benefits observed in double-blind randomized clinical trials.

Noonan, M., J. Leflein, et al. (2009). "Long-term safety of mometasone furoate administered via a dry powder inhaler in children: Results of an open-label study comparing mometasone furoate with beclomethasone dipropionate in children with persistent asthma." *BMC Pediatr* 9: 43.

BACKGROUND: To assess the long-term pediatric safety of 2 doses of mometasone furoate administered via a dry powder inhaler (MF-DPI) for mild-to-moderate persistent asthma

and compare them with that of beclomethasone dipropionate administered via a metered dose inhaler (BDP-MDI) in the treatment of persistent asthma. Both MF-DPI doses tested are twice the approved pediatric dosage of 100 microg once-daily (QD) for children aged 4-11 years. METHODS: Children (N = 233) aged 4-11 years were randomized to 52 weeks of treatment with MF-DPI 200 microg QD AM, MF-DPI 100 microg twice daily (BID), or BDP-MDI 168 microg BID. Patients had used inhaled corticosteroids (ICSs) daily for > or = 30 days before the screening visit and were on stable ICS doses for > or = 2 weeks before screening. The primary safety variable was the incidence of adverse events. Secondary safety variables were laboratory tests (including cortisol concentrations), vital signs, and physical examination. RESULTS: The incidence of adverse events was similar in all 3 treatment groups. The most frequently reported adverse event was upper respiratory tract infection, reported by 47%-49% of the MF-DPI-treated patients and 51% of the BPD-treated patients. Most adverse events were considered unrelated to study drug. The most frequently reported related adverse events were headache (MF-DPI 200 microg QD AM, 8%; MF-DPI 100 microg BID, 4%; BDP-MDI 168 microg BID, 2%) and oral candidiasis (4% in each treatment group). No clinically relevant changes in laboratory values, including plasma cortisol, vital signs, or physical examinations were noted in any treatment group. CONCLUSION: Both MF-DPI doses were well tolerated, with no unusual or unexpected adverse events or safety concerns, and had a similar adverse event profile to that of BDP-MDI 168 microg BID.

O'Byrne, P. M., I. P. Naya, et al. (2008). "Increasing doses of inhaled corticosteroids compared to adding long-acting inhaled beta2-agonists in achieving asthma control." *Chest* 134(6): 1192-1199.

BACKGROUND: Combination therapy with inhaled corticosteroids (ICSs) and long-acting beta(2)-agonists (LABAs), or treatment with high doses of ICSs alone improves asthma control when therapy with low-dose ICSs is not sufficient. However, it is not known which of these treatment options is more effective in sustaining asthma control. **OBJECTIVES:** To evaluate the effect of increasing the ICS dosage vs adding LABAs on the time spent with well-controlled asthma or poorly controlled asthma. **METHODS:** Post hoc analysis of the Formoterol and Corticosteroid Establishing Therapy study, which compared a fourfold increase in the budesonide dose with and without formoterol. **RESULTS:** Time with well-controlled asthma was improved by 19% (95% confidence interval [CI], 3 to 35%; $p = 0.017$) by adding formoterol, 24 microg/d, to therapy with budesonide, 200 microg/d, compared to 2% (95% CI, -9 to 12%; $p = 0.76$) with therapy with budesonide, 800 microg/d, alone. Time with well-controlled asthma was further improved by 29% (95% CI, 13 to 47%; $p < 0.001$) by adding formoterol to therapy with budesonide, 800 microg/d. Time with poorly controlled asthma was significantly reduced using the same interventions by 43% (95% CI, 25 to 57%), 22% (95% CI, 7 to 44%), and 50% (95% CI, 30 to 64%), respectively. Adding formoterol to budesonide was significantly more effective in increasing time with well-controlled asthma when compared to increasing the budesonide dose fourfold (increase, 16%; 95% CI, 1 to 33%; $p = 0.035$), with a trend for a greater reduction in time with poor control (decrease, 21%; 95% CI, -5 to 42%). **CONCLUSION:** The addition of formoterol to therapy with low-dose budesonide increases the probability of well-controlled asthma compared to a substantial increase in the dose of an ICS.

Sears, M. R., L. P. Boulet, et al. (2008). "Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma." *Eur Respir J* 31(5): 982-989.

The aim of the present study was to compare the effectiveness, safety and health economics of budesonide/formoterol maintenance and a novel reliever therapy with conventional best practice in patients with persistent asthma in Canada. After 2 weeks of usual therapy, 1,538 patients were randomised for 6 months to open-label budesonide/formoterol maintenance and reliever therapy 160/4.5 microg twice daily and as needed, or to guideline-based conventional best practice. Severe asthma exacerbations, reliever medication use and total inhaled corticosteroid dose were analysed in all patients and airway inflammation was assessed in a sub-study of 115 patients. No differences were seen in time to first severe exacerbation and severe asthma exacerbation rate. There were numerically fewer emergency room visits or hospitalisations with budesonide/formoterol maintenance and reliever therapy (4.4 versus 7.5 events per 100 patients x yr(-1), 41% reduction); however, this did not reach statistical significance. Mean total inhaled corticosteroid dose, reliever use, asthma medication costs and total annual costs per patient were all significantly lower with budesonide/formoterol maintenance and reliever therapy. Mean sputum eosinophil cell counts remained in the range for controlled inflammation in both groups. In conclusion, budesonide/formoterol maintenance and reliever therapy achieved similar or improved clinical control compared with conventional best practice, with significantly lower total inhaled corticosteroid dose and lower cost, while maintaining similar control of eosinophilic inflammation.

Slavin, R. G., C. Ferioli, et al. (2009). "Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing IgE and decreasing pharmacokinetic concentrations." *J Allergy Clin Immunol* 123(1): 107-113 e103.

BACKGROUND: Physicians have questioned whether omalizumab can be discontinued or the dose reduced after clinical improvement is seen in patients with severe asthma. **OBJECTIVES:** To examine the relationships among omalizumab, free IgE, and clinical outcomes in a randomized, placebo-controlled trial in patients with severe persistent allergic asthma following a posology based on pretreatment total IgE and body weight. **METHODS:** A pharmacokinetic-pharmacodynamic binding model was used to calculate free IgE, omalizumab, and total IgE concentrations during the 28-week treatment and 16-week follow-up of the INvestigation of Omalizumab in seVere Asthma TrEatment (INNOVATE) study. These were plotted against the mean changes in the total asthma symptom score, morning peak expiratory flow, and rescue medication use for physician-defined treatment responders and nonresponders. **RESULTS:** The model accurately fitted omalizumab and free and total IgE, allowing reconstruction of the entire time course for each patient. Free IgE was rapidly suppressed below the 50 ng/mL (20.8 IU/mL) target, although there was a notable period before clinical measures stabilized. After treatment cessation, free IgE and omalizumab returned toward baseline and, after a delay, asthma symptoms re-emerged. Model-derived omalizumab and free IgE concentrations correlated well with changes in clinical outcomes, particularly in omalizumab-treated responders. Asthma symptoms exhibited different correlations during response onset compared with response offset (hysteresis), indicative of physiological time delays between changes in IgE levels and pulmonary function. **CONCLUSION:** Omalizumab and free IgE correlated well with clinical symptoms. Reducing omalizumab doses below those in the dosing

table cannot be recommended; the resulting increase in free IgE would cause a deterioration in asthma control.

Sovani, M. P., C. I. Whale, et al. (2008). "Poor adherence with inhaled corticosteroids for asthma: can using a single inhaler containing budesonide and formoterol help?" *Br J Gen Pract* 58(546): 37-43.

BACKGROUND: Poor adherence with inhaled corticosteroids is an important problem in asthma management. Previous approaches to improving adherence have had limited success. **AIM:** To determine whether treatment with a single inhaler containing a long-acting beta(2)-agonist and a corticosteroid for maintenance treatment and symptom relief can overcome the problem of poor adherence with inhaled corticosteroids. **DESIGN OF STUDY:** Randomised, parallel group, open-label trial. **SETTING:** Forty-four general practices in Nottinghamshire. **METHOD:** Participants who used less than 70% of their prescribed dose of inhaled corticosteroid and had poorly controlled asthma were randomised to budesonide 200 microg one puff twice daily plus their own short-acting beta(2)-agonist as required (control group), or budesonide/formoterol 200/6 microg one puff once daily and as required (active group) for 6 months. The primary outcome was inhaled corticosteroid dose. **RESULTS:** Seventy-one participants (35 control, 36 active group) were randomised. Adherence with budesonide in the control group was approximately 60% of the prescribed dose. Participants in the active group used approximately 80% more budesonide than participants in the control group (448 versus 252 microg/day, mean difference 196 mug, 95% confidence interval 113 to 279; $P < 0.001$) and were less likely to withdraw from the study (3 versus 13; $P < 0.01$). No safety issues were identified. **CONCLUSION:** Using a single inhaler for both maintenance treatment and symptom relief approximately doubled the dose of inhaled corticosteroid taken, suggesting this could be a useful strategy to overcome the problems related to poor adherence with inhaled corticosteroids.