Drug Class Review

Controller Medications for Asthma

Preliminary Scan Report #1

April 2013

Last Report: April 2011

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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 to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. 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 U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Report

Update #1, April 2011 (searches through September 2010)

Date of Last Preliminary Update Scan Report

None since most recent report

Scope and Key Questions

Researchers at the University of North Carolina wrote preliminary key questions and the eligibility criteria for studies based on the populations, interventions, and outcomes of interest. These were reviewed by representatives of organizations participating in the Drug Effectiveness Review Project (DERP) and posted to the DERP website for public comment. 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), other medications (drug-drug interactions), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?

Inclusion Criteria

Populations

- Adults (age >12 years) and children (age ≤12 years) with **persistent asthma**

Interventions

Table 1. Included interventions

Drug Class	Brand name Administration	Labeled indications	Strength
Beclomethasone dipropionate Inhaled corticosteroid	QVAR® HFA	Asthma (age ≥ 5)	40 mcg/puff 80 mcg/puff
	Vanceril®[a] MDI	Asthma (age ≥ 5)	42 mcg/puff 84 mcg/puff
Budesonide Inhaled corticosteroid	Pulmicort Flexhaler® DPI	Asthma (age ≥ 6)	90 mcg/dose 180 mcg/dose
	Pulmicort Respules® Inhalation suspension	Asthma (age 1-8)	0.25 mg/2ml 0.5 mg/2ml 1 mg/2ml
Ciclesonide Inhaled corticosteroid	Alvesco®[b] HFA-MDI	Asthma (age ≥ 12)	80 mcg/puff 160 mcg/puff
Flunisolide Inhaled corticosteroid	AeroBid® MDI AeroBid-M® MDI-menthol	Asthma (age ≥ 6)	250 mcg/puff
	AeroSpan® HFA	Asthma (age ≥ 6)	80 mcg/puff
	Bronalide®[a] MDI	Asthma (age ≥ 4)	250 mcg/puff
Fluticasone propionate Inhaled corticosteroid	Flovent® HFA HFA	Asthma (age ≥ 4)	44 mcg/puff 110 mcg/puff 220 mcg/puff
	Flovent Rotadisk®[a] DPI	Asthma (age ≥ 12)	50 mcg/dose 100 mcg/dose 250 mcg/dose
	Flovent Diskus® DPI	Asthma (age ≥ 4 yrs)	50 mcg/dose 100 mcg/dose 250 mcg/dose
Mometasone furoate Inhaled corticosteroid	Asmanex Twisthaler® DPI	Asthma (age ≥ 4)	110 mcg/dose 220 mcg/dose
Triamcinolone acetonide Inhaled corticosteroid	Azmacort®[a] MDI – with spacer mouthpiece	Asthma (age ≥ 6)	75 mcg/dose
Montelukast Leukotriene modifier	Singulair® Tablets Chewable tablets Granules	Asthma (age ≥ 1)	10 mg 4 mg, 5 mg 4 mg/packet
Zafirlukast Leukotriene receptor antagonist	Accolate® Tablets	Asthma (age ≥ 5 yrs in US); (age ≥ 12 yrs in Canada)	10 mg 20 mg

Drug Class	Brand name Administration	Labeled indications	Strength
Zileuton 5-lipoxygenase Inhibitor	Zyflo® Tablets Zyflo CR® Extended release tablets	Asthma (age ≥ 12 yrs)	600 mg 600 mg
Arformoterol Long-Acting Beta-2 Agonist	Brovana® Inhalation solution	Not approved for asthma (COPD only)	15 mcg/2ml
Formoterol fumarate/ Eformoterol Long-Acting Beta-2 Agonist	Foradil Aerolizer® DPI	Asthma (age ≥ 5 yrs)	12 mcg/capsule
	Oxis Turbohaler®[c] DPI	Asthma (age ≥ 6 yrs)	6 mcg/puff 12 mcg/puff
Salmeterol xinafoate Long-Acting Beta-2 Agonist	Serevent Diskus® DPI	Asthma (age ≥ 4 yrs)	50 mcg/blister
Omalizumab Anti-IgE medication	Xolair® Powder for subcutaneous injection	Asthma (age ≥ 12 yrs)	202.5 mg (delivers 150 mg/1.2ml)
Fluticasone propionate/ Salmeterol xinafoate Combination product	Advair Diskus® DPI	Asthma (age ≥ 4 yrs)	100mcg/50mcg 250mcg/50mcg 500mcg/50mcg
	Advair HFA® HFA	Asthma (age ≥ 12 yrs)	45mcg/21mcg 115mcg/21mcg 230mcg/21mcg
Budesonide/ Formoterol Combination product	Symbicort® HFA	Asthma (age ≥ 12 yrs)	80mcg/4.5mcg 160mcg/4.5mcg
Tiotropium bromide Long-acting angicholinergic	Spiriva® DPI	Not approved for asthma (COPD only)	18 mcg/capsule

Abbreviations: DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; MDI = metered dose inhaler.
[a] This product has been discontinued by the manufacturer.
[b] The FDA approved dosing regimen for ciclesonide is twice daily.
[c] This product is not available in the US.

Study designs

- For efficacy/effectiveness outcomes,
  1) randomized controlled clinical trials of at least 6 weeks duration and n ≥ 40
  2) good quality systematic reviews
- For adverse events/safety:
  1) randomized controlled clinical trials of at least 6 weeks duration and n ≥ 40
  2) observational studies of at least 6 months duration and n ≥ 100
  3) good quality systematic reviews

Comparators

- Any other asthma medication listed above
- Placebo

Efficacy and effectiveness outcomes

- Control of symptoms (e.g., days/nights/frequency of symptoms, rate of asthma exacerbations, frequency of rescue medication use, courses of oral steroids)
- Functional capacity and quality of life (missed school and missed work days, ability to participate in work/school/sports/physical activity, activity limitation, improved sleep/sleep disruption)
- Urgent care services (Emergency department visits/urgent medical care visits)
- Adherence
- Hospitalization
- Mortality

Harms/adverse events outcomes

- Any reported adverse event or harm (e.g., growth suppression, hypothalamus-pituitary-adrenal axis suppression, osteoporosis/fractures, mortality, growth retardation, bone mineral density, ocular toxicity, suppression of the HPA axis, tachycardia, anaphylaxis, death)
- Withdrawals due to adverse events

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from March 27, 2010 through April 2, 2013 using terms for included drugs. To identify trials of newly-approved drugs, we searched from database inception (i.e., did not limit the search start date) through April 2, 2013. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/). All citations were imported into an electronic database (EndNote X4) 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

New Drugs

New drugs identified in this Preliminary Update Scan

6/22/2010: Dulera®, a combination product of formoterol fumarate and mometasone furoate, was approved for the treatment of asthma in patients 12 years of age and older.

7/1/2011: Arcapta Neohaler® (indacaterol), a long-acting beta2-adrenergic agonist, was approved for the long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is not indicated to treat acute deteriorations of chronic obstructive pulmonary disease or asthma.

4/17/2013: Breo®, a combination product of fluticasone furoate and vilanterol, will be discussed by the Pulmonary-Allergy Drugs Advisory Committee for approval for the long-term maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease.

New Indications

None identified.

New Safety Alerts

Identified in this Preliminary Update Scan

None identified.

Identified in previous Preliminary Update Scan(s)

No scan since most recent report

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

None identified.

Reviews identified in previous Preliminary Update Scan(s)

No scans have been conducted since the original report.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches for randomized controlled trials resulted in 300 citations. Of those, there are 43 potentially relevant new publications, including 18 trials comparing two included medications, 20 placebo-controlled trials, and 5 subgroup or secondary analyses of trials included in existing reports (see Appendix A for abstracts). Characteristics of these trials are shown in Tables 2, 3, and 4, below.

Table 2. New head-to-head trials

Study	N, Duration	Population	Comparison	Focus
Inhaled corticosteroids				
Brown, 2012	742, 52 weeks	African American adults with moderate-to-severe asthma	Budesonide vs budesonide + formoterol	Safety and asthma control with a budesonide/ formoterol pressurized metered-dose inhaler versus budesonide over 1 year in African American patients
Hoshino, 2012	50, 24 weeks	Asthma patients	Budesonide vs budesonide + formoterol	Effects of budesonide/ formoterol versus budesonide alone on airway dimensions and inflammation in individuals with asthma
Spector, 2012	311, 12 weeks	African American adolescents with moderate to severe persistent asthma	Budesonide vs budesonide + formoterol	Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler versus budesonide dry powder inhaler in adolescent and adult black asthma patients
Zangrilli, 2011	250, 12 week	Hispanic adults with moderate to severe asthma requiring medium- to high-dose inhaled corticosteroids	budesonide vs budesonide + formoterol	Efficacy and safety of budesonide/formoterol with budesonide in an ethnically diverse group of Hispanic participants with asthma previously treated with inhaled corticosteroids
Stelmach, 2011	96, 6 months	Children with newly diagnosed atopic asthma	Budesonide vs montelukast	Effects of a medium and high dose of inhaled corticosteroid and a high-dose inhaled corticosteroid with vitamin D on bone metabolism in children with newly diagnosed atopic asthma
Korn, 2012	160, 6 weeks	Patients with moderate asthma	Ciclesonide vs fluticasone proprionate + salmeterol xinafoate	Efficacy of a newly developed fixed combination of ciclesonide and formoterol in comparison to the marketed fixed combination of fluticasone and salmeterol in patients with moderate asthma
Postma, 2011	NR, 52 weeks	Adults with mild persistent asthma	Ciclesonide vs fluticasone proprionate + salmeterol xinafoate	Benefits of first-line treatment with ciclesonide and a combination of fluticasone and salmeterol in patients with mild persistent asthma

Study	N, Duration	Population	Comparison	Focus
Katial, 2011	621, 52 weeks	Patients with persistent asthma symptomatic on open-label fluticasone propionate 100 micrograms	Fluticasone vs fluticasone proprionate + salmeterol xinafoate	Safety and efficacy of fluticasone propionate/salmeterol combination 250/50 micrograms versus fluticasone propionate 250 micrograms in subjects with persistent asthma symptomatic on open-label FP 100 micrograms
Vaessen-Verberne, 2010	158, 26 weeks	Children with symptomatic asthma	Fluticasone vs fluticasone proprionate + salmeterol xinafoate	Noninferiority of salmeterol/fluticasone propionate, 50/100 mug twice a day, in symptom control compared with fluticasone propionate, 200 mug twice a day Diskus in children with symptomatic asthma
Djukanovic, 2010	89, 12 weeks	Asthma patients uncontrolled on short-acting beta(2)-agonists	Fluticasone vs montelukast	Efficacy of adding a leukotriene modifier to an inhaled corticosteroid for clinical and/or anti-inflammatory outcomes in patients symptomatic on short-acting beta(2)-agonists
Weinstein, 2010	728, 12 weeks	Adults with uncontrolled asthma	Mometasone vs formoterol fumarate + mometasone furoate	Efficacy and safety of mometasone furoate/formoterol 400/10 microg versus MF 400 microg administered twice-daily via metered-dose inhaler in patients with asthma uncontrolled on high-dose inhaled corticosteroids
Meltzer, 2010	746, 26 weeks	Adults with not well-controlled asthma on low-dose inhaled corticosteroids	Mometasone vs formoterol vs formoterol fumarate + mometasone furoate	Effect of mometasone furoate/formoterol versus its monocomponents, each administered via metered-dose inhaler, on asthma deteriorations and lung function
Nathan, 2010	781, 12 weeks	Adults with asthma uncontrolled on medium-dose inhaled corticosteroid	Mometasone vs formoterol vs formoterol fumarate + mometasone furoate	Effect of mometasone furoate/formoterol combination, 200/10 microg, administered twice daily on asthma deteriorations and pulmonary function in patients with asthma uncontrolled on medium-dose inhaled corticosteroid
Long-acting beta-2 agonists				

Study	N, Duration	Population	Comparison	Focus
Meltzer, 2010	746, 26 weeks	Adults with not well-controlled asthma on low-dose inhaled corticosteroids	Formoterol vs mometasone vs formoterol fumarate + mometasone furoate	Effect of mometasone furoate/formoterol versus its monocomponents, each administered via metered-dose inhaler, on asthma deteriorations and lung function
Nathan, 2010	781, 12 weeks	Adults with asthma uncontrolled on medium-dose inhaled corticosteroid	Formoterol vs mometasone vs formoterol fumarate + mometasone furoate	Effect of mometasone furoate/formoterol combination, 200/10 microg, administered twice daily on asthma deteriorations and pulmonary function in patients with asthma uncontrolled on medium-dose inhaled corticosteroid
Upworth, 2013	62, 1 year	Children with persistent asthma with the homozygous Arg16 genotype	Salmeterol vs montelukast	Efficacy of using montelukast as an alternative to salmeterol as tailored second-line asthma controller therapy in children expressing the Arg(16) beta(2) receptor genotype
Bateman, 2011	388, 16 weeks	Asthmatic adults with the B16-Arg/Arg genotype	Salmeterol vs tiotropium	Efficacy and safety of the long-acting anticholinergic tiotropium with salmeterol and placebo added to an inhaled corticosteroid in B16-Arg/Arg patients with asthma that was not controlled by inhaled corticosteroids alone.
Peters, 2010	210, NR	Adults with uncontrolled asthma	Salmeterol vs tiotropium	The addition of tiotropium bromide to an inhaled glucocorticoid, as compared with a doubling of the dose of the inhaled glucocorticoid (primary superiority comparison) or the addition of the LABA salmeterol (secondary noninferiority comparison)
Leukotriene modifiers				
Stelmach, 2011	96, 6 months	Children with newly diagnosed atopic asthma	Montelukast vs budesonide	Effects of a medium and high dose of inhaled corticosteroid and a high-dose inhaled corticosteroid with vitamin D on bone metabolism in children with newly diagnosed atopic asthma
Djukanovic, 2010	89, 12 weeks	Asthma patients uncontrolled on short-acting beta(2)-agonists	Montelukast vs fluticasone	Efficacy of adding a leukotriene modifier to an inhaled corticosteroid for clinical and/or anti-inflammatory outcomes in patients symptomatic on short-acting beta(2)-agonists

Study	N, Duration	Population	Comparison	Focus
Upworth, 2013	62, 1 year	Children with persistent asthma with the homozygous Arg16 genotype	Montelukast vs salmeterol	Efficacy of using montelukast as an alternative to salmeterol as tailored second-line asthma controller therapy in children expressing the Arg(16) beta(2) receptor genotype
Anti-IgE therapy				
None				
Combination products				
Brown, 2012	742, 52 weeks	African American adults with moderate-to-severe asthma	Budesonide + formoterol vs budesonide	Safety and asthma control with a budesonide/formoterol pressurized metered-dose inhaler versus budesonide over 1 year in African American patients
Hoshino, 2012	50, 24 weeks	Asthma patients	Budesonide + formoterol vs budesonide	Effects of budesonide/formoterol versus budesonide alone on airway dimensions and inflammation in individuals with asthma
Spector, 2012	311, 12 weeks	African American adolescents with moderate to severe persistent asthma	Budesonide + formoterol vs budesonide	Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler versus budesonide dry powder inhaler in adolescent and adult black asthma patients
Zangrilli, 2011	250, 12 week	Hispanic adults with moderate to severe asthma requiring medium- to high-dose inhaled corticosteroids	Budesonide + formoterol vs budesonide	Efficacy and safety of budesonide/formoterol with budesonide in an ethnically diverse group of Hispanic participants with asthma previously treated with inhaled corticosteroids
Hozawa, 2011	40, NR	Asthmatic patients with suspected persistent airway inflammation and small airway impairment	Budesonide + formoterol vs fluticasone proprionate + salmeterol xinafoate	Effects of budesonide/formoterol delivered by a Turbuhaler® and fluticasone/salmeterol delivered by a Diskus® on small airway function and airway inflammation
Korn, 2012	160, 6 weeks	Patients with moderate asthma	Fluticasone proprionate + salmeterol xinafoate vs ciclesonide	Efficacy of a newly developed fixed combination of ciclesonide and formoterol in comparison to the marketed fixed combination of fluticasone and salmeterol in patients with moderate asthma

Study	N, Duration	Population	Comparison	Focus
Postma, 2011	NR, 52 weeks	Adults with mild persistent asthma	Fluticasone proprionate + salmeterol xinafoate vs ciclesonide	Benefits of first-line treatment with ciclesonide and a combination of fluticasone and salmeterol in patients with mild persistent asthma
Katial, 2011	621, 52 weeks	Patients with persistent asthma symptomatic on open-label fluticasone propionate 100 micrograms	Fluticasone proprionate + salmeterol xinafoate vs fluticasone	Safety and efficacy of fluticasone propionate/salmeterol combination 250/50 micrograms versus fluticasone propionate 250 micrograms in subjects with persistent asthma symptomatic on open-label FP 100 micrograms
Vaessen-Verberne, 2010	158, 26 weeks	Children with symptomatic asthma	Fluticasone proprionate + salmeterol xinafoate vs fluticasone	Noninferiority of salmeterol/fluticasone propionate, 50/100 mug twice a day, in symptom control compared with fluticasone propionate, 200 mug twice a day Diskus in children with symptomatic asthma
Maspero, 2010	404, 52 week	Adults with persistent asthma inadequately controlled on inhaled corticosteroid monotherapy	Formoterol fumarate + mometasone furoate vs fluticasone proprionate + salmeterol xinafoate	Long-term safety of mometasone furoate/formoterol administered through metered-dose inhaler in patients with persistent asthma previously on medium- to high-dose inhaled corticosteroid
Weinstein, 2010	728, 12 weeks	Adults with uncontrolled asthma	Formoterol fumarate + mometasone furoate vs mometasone	Efficacy and safety of mometasone furoate/formoterol 400/10 microg versus MF 400 microg administered twice-daily via metered-dose inhaler in patients with asthma uncontrolled on high-dose inhaled corticosteroids
Meltzer, 2010	746, 26 weeks	Adults with not well-controlled asthma on low-dose inhaled corticosteroids	Formoterol fumarate + mometasone furoate vs mometasone vs formoterol	Effect of mometasone furoate/formoterol versus its monocomponents, each administered via metered-dose inhaler, on asthma deteriorations and lung function
Nathan, 2010	781, 12 weeks	Adults with asthma uncontrolled on medium-dose inhaled corticosteroid	Formoterol fumarate + mometasone furoate vs mometasone vs formoterol	Effect of mometasone furoate/formoterol combination, 200/10 microg, administered twice daily on asthma deteriorations and pulmonary function in patients with asthma uncontrolled on medium-dose inhaled corticosteroid

Study	N, Duration	Population	Comparison	Focus
Long-acting anticholinergics				
Bateman, 2011	388, 16 weeks	Asthmatic adults with the B16-Arg/Arg genotype	Tiotropium vs salmeterol	Efficacy and safety of the long-acting anticholinergic tiotropium with salmeterol and placebo added to an inhaled corticosteroid in B16-Arg/Arg patients with asthma that was not controlled by inhaled corticosteroids alone.
Peters, 2010	210, NR	Adults with uncontrolled asthma	Tiotropium vs salmeterol	The addition of tiotropium bromide to an inhaled glucocorticoid, as compared with a doubling of the dose of the inhaled glucocorticoid (primary superiority comparison) or the addition of the LABA salmeterol (secondary noninferiority comparison)

Table 3. New placebo-controlled trials

Study	N, Duration	Population	Comparison	Focus
Inhaled corticosteroids				
Krishnan, 2012	84 and 56, 4 years	Children with mild or moderate asthma	Budesonide	Influence of adherence to study medications on treatment-related differences in outcomes
Pedersen, 2010	2073, 12 weeks	Children (6-11 years) with persistent asthma	Ciclesonide	Efficacy and safety of ciclesonide in children with persistent asthma
Bensch, 2011	218, 52 weeks	Children with mild persistent asthma ranging in age from 4 to 10 years	Flunisolide	Effect of 1 year of inhalation therapy with flunisolide hydrofluoroalkane (HFA) on growth velocity and bone maturation in children with mild persistent asthma
Bateman, 2012	598, 8 weeks	Patients with persistent asthma not controlled by short-acting beta(2) agonists	Fluticasone	Efficacy of inhaled once-daily fluticasone furoate administered in the evening in patients with persistent asthma not controlled by short-acting beta(2) agonists
Bleecker, 2012	622, 8 weeks	Adults with moderate asthma, uncontrolled on low-dose inhaled corticosteroid	Fluticasone	Efficacy and safety of fluticasone furoate administered using a dry powder inhaler in patients with moderate asthma, uncontrolled on low-dose ICS

Study	N, Duration	Population	Comparison	Focus
Busse, 2012	627, 8 weeks	Patients with persistent moderate-to-severe asthma, symptomatic on medium-dose inhaled corticosteroid therapy	Fluticasone	To determine the optimal dose(s) of fluticasone furoate for treating patients with asthma
Guilbert, 2011	NR, 2 years	Children aged 2 and 3 years with recurrent wheezing and positive modified Asthma Predictive Index scores	Fluticasone	Effect of daily inhaled corticosteroid given for 2 years on linear growth in preschool children with recurrent wheezing
Woodcock, 2011	545, 8 weeks	Persistent asthma patients maintained on inhaled corticosteroids for at least 3 months	Fluticasone	Efficacy and safety of fluticasone furoate in patients with persistent asthma
Skoner, 2011	187, 52 weeks	Children aged 4-9 years with asthma	Mometasone	Effects of long-term mometasone furoate delivered via a dry powder inhaler on growth velocity and hypothalamic-pituitary-adrenal axis function in children with asthma
Long-acting beta-2 agonists				
Chuchalin, 2007	156, 7 weeks	Asthma patients	Indacaterol	Safety and tolerability of indacaterol in asthma patients
Leukotriene modifiers				
Philip, 2011	134, 8	Adults with chronic asthma	Montelukast	Efficacy of inhaled montelukast added to inhaled mometasone
Valovirta, 2011	1771, 52 weeks	Children 6 months to 5 years of age with episodic asthma	Montelukast	Regimen-related efficacy of montelukast in treating pediatric episodic asthma
Anti-IgE therapy				
Bardelas, 2012	271, 24 weeks	Adults with persistent allergic asthma inadequately controlled with NHLBI Step 4 or above asthma therapy	Omalizumab	Effect of omalizumab on asthma control in patients with persistent allergic asthma inadequately controlled with NHLBI Step 4 or above asthma therapy
Bousquet, 2011	400, 32 weeks	Adults with severe allergic asthma	Omalizumab	Persistency of treatment responder classification in patients receiving omalizumab added to optimized asthma therapy

Study	N, Duration	Population	Comparison	Focus
Hanania, 2011	850, 48 weeks	Adults with inadequately controlled asthma despite treatment with high-dose ICS plus LABAs, with or without other controllers	Omalizumab	Efficacy and safety of omalizumab in patients with inadequately controlled severe asthma who are receiving high-dose ICS and LABAs with or without additional controller therapy
Rubin, 2012	unclear, 20 weeks	Brazilian adults with severe persistent allergic asthma inadequately controlled	Omalizumab	Impact of omalizumab as an add-on therapy to standard treatment with inhaled corticosteroids and long-acting beta-2 agonists on asthma-related quality of life in patients with severe allergic asthma
Combination products				
Sterling, 2012	75, NR	Adults with persistent asthma	Fluticasone furoate + vilanterol (Breo)	Efficacy of vilanterol used concurrently with inhaled corticosteroid in adult patients with persistent asthma
Frampton, 2012	NR, 26 weeks	Adults with persistent asthma uncontrolled on medium-dose inhaled corticosteroids	Formoterol fumarate + mometasone furoate	Effectiveness of mometasone/formoterol 200 mug/10 mug twice daily versus formoterol and placebo in patients with persistent asthma uncontrolled on medium-dose inhaled corticosteroids
Long-acting anticholinergics				
Kerstjens, 2011	107, 8 weeks	Patients with uncontrolled severe asthma	Tiotropium	Efficacy and safety of tiotropium administered through the Respimat inhaler as add-on therapy in patients with uncontrolled severe asthma despite maintenance treatment with at least a high-dose inhaled corticosteroid plus a long-acting beta(2)-agonist
Kerstjens, 2012	912, 48 weeks	Patients with asthma who were receiving inhaled glucocorticoids and LABAs	Tiotropium	Effect on lung function and exacerbations of adding tiotropium (a total dose of 5 mug) or placebo, both delivered by a soft-mist inhaler once daily for 48 weeks in patients with asthma who were receiving inhaled glucocorticoids and LABAs

Table 4. Secondary analyses of included primary trial publications

Study	N, Duration	Population	Comparison	Focus
Cohen, 2010	1041, 4 years	Children age 5 to 12 years with asthma	Budesonide vs placebo	To explore whether in utero smoke exposure is associated with increased airway responsiveness among children with asthma and whether IUS modifies the response to treatment with inhaled corticosteroids
Kelly, 2012	943, NR	Adults who has participated in the Childhood Asthma Management Program	Budesonide vs placebo	To determine whether the use of inhaled glucocorticoids causes a decrease in attained adult height.
Camargo, 2010	475, 52 weeks	African American patients with asthma	Fluticasone vs fluticasone proprionate + salmeterol xinafoate	To explore whether obesity alters the risk, impairment and response to treatment in African Americans with asthma
Wang, 2011	unclear, 48 weeks	Children with mild-to-moderate persistent asthma	Fluticasone vs montelukast	Cost-effectiveness of 2 commonly used asthma controllers, fluticasone and montelukast, with data from the Pediatric Asthma Controller Trial
Vogelmeier, 2012	404, 1 year	Asian adults with asthma	Fluticasone proprionate + salmeterol xinafoate vs budesonide + formoterol	Effectiveness of budesonide/formoterol maintenance and reliever therapy compared with salmeterol/fluticasone propionate plus as-needed salbutamol in patients enrolled across Asian countries, specifically China, Korea, Taiwan and Thailand.

Table 5. Breakdown of potentially relevant head-to-head comparisons:

	Budesonide	Ciclesonide	Fluticasone	Mometasone	Montelukast	Formoterol	Salmeterol	Tiotropium	Fluticasone/ Salmeterol	Budesonide/ Formoterol	Formoterol/ Mometasone
Budesonide					1					4	
Ciclesonide									2		
Fluticasone					1				2		
Mometasone						2					3
Montelukast	1		1				1				
Formoterol				2							2
Salmeterol					1			2			
Tiotropium							2				
Fluticasone/ Salmeterol		2	2							1	1
Budesonide/ Formoterol	4								1		
Formoterol/ Mometasone				3		2			1		

Summary and Recommendations

We identified 3 new medications and 43 new trials (18 head to head trials, 20 placebo controlled trials, and 5 subgroup or secondary analyses) published since the most recent update report. New head-to-head trials are available for 11 of the 20 included medications, including 4 studies comparing the new combination product Dulera® with mometasone or formoterol alone. New placebo controlled trials are available for 11 of the 20 included medications, including the new medications indacaterol (Arcapta®) and the two new combination products Breo® and Dulera®.

The most recent Controller Medications for Asthma update report used evidence from placebo controlled trials when head-to-head trials were not available and incorporated results of up-to-date good quality systematic reviews and meta-analyses when appropriate. Using a similar approach, a complete update at this time is likely to be large. An update that excluded studies of leukotriene modifiers (montelukast, zafirlukast, and zileuton), Anti IgE therapies (omalizumab), and long acting cholinergics (tiotropium) is also likely to be large because these medications represent only 13 of the total studies identified by the scan (5 head-to-head and 8 placebo controlled trials), and it is likely that other eligible studies exist for the medications that would remain included.

A streamlined approach that includes only new head-to-head trials and excludes placebo-controlled trials would likely be of medium size. We recommend that the Participants also consider a modified streamlined update that is limited to head-to-head trials for most of the included medications and placebo controlled trials of included medications that are being used off-label. Most of the head-to-head trials we identified were studies of combination products compared with single medications or other combinations, including the new Dulera® (but not including the new Breo®). With this scan, we identified three off-label placebo controlled trials (1 study of indacaterol and 2 studies of tiotropium). A modified streamlined update using this approach would likely be of medium size.

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

Head-to-head trials

Bateman, E. D., O. Kornmann, et al. (2011). "Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma." J Allergy Clin Immunol **128**(2): 315-22.

BACKGROUND: The efficacy and safety of inhaled long-acting beta(2)-adrenergic agonists in asthmatic patients with the B16-Arg/Arg genotype has been questioned, and the use of antimuscarinics has been proposed as an alternative in patients whose symptoms are not controlled by inhaled corticosteroids (ICSs). OBJECTIVE: We compared the efficacy and safety of the long-acting anticholinergic tiotropium with salmeterol and placebo added to an ICS in B16-Arg/Arg patients with asthma that was not controlled by ICSs alone. METHODS: In a double-blind, double-dummy, placebo-controlled trial, after a 4-week run-in period with 50 mug of twice-daily salmeterol administered through a metered-dose inhaler, 388 asthmatic patients were randomized 1:1:1 to 16 weeks of treatment with 5 mug of Respimat tiotropium administered daily in the evening, 50 mug of salmeterol administered twice daily through a metered-dose inhaler, or placebo. Patients aged 18 to 67 years demonstrated reversibility to bronchodilators, and their symptoms were uncontrolled by regular ICSs (400-1000 mug of budesonide/equivalent). ICS regimens were maintained throughout the trial. The mean weekly morning peak expiratory flow (PEF) before randomization was 358 +/- 115.7 L/min (range, 80.3-733.0 L/min). RESULTS: Changes in weekly PEF from the last week of the run-in period to the last week of treatment (primary end point: change in PEF) were -3.9 +/- 4.87 L/min (n = 128) for tiotropium and -3.2 +/- 4.64 L/min (n = 134) for salmeterol, and these were superior to placebo (-24.6 +/- 4.84 L/min, n = 125, P < .05). Tiotropium was noninferior to salmeterol (estimated difference, -0.78 L/min [95% CI, -13.096 to 11.53]; P = .002; alpha = .025, 1-sided; noninferiority, 20 L/min). Tiotropium and salmeterol were numerically superior to placebo in some patient-reported secondary outcomes. Adverse events were comparable across treatments. CONCLUSION: Tiotropium was more effective than placebo and as effective as salmeterol in maintaining improved lung function in B16-Arg/Arg patients with moderate persistent asthma. Safety profiles were comparable.

Brown, R. W., C. D. O'Brien, et al. (2012). "Long-term safety and asthma control measures with a budesonide/formoterol pressurized metered-dose inhaler in African American asthmatic patients: a randomized controlled trial." J Allergy Clin Immunol **130**(2): 362-7 e9.

BACKGROUND: Information surrounding the long-term safety of combination inhaled corticosteroid/long-acting beta(2)-adrenergic agonist medications in African American asthmatic patients is limited. OBJECTIVE: We sought to assess safety and asthma control with a budesonide/formoterol pressurized metered-dose inhaler (pMDI) versus budesonide over 1 year in African American patients. METHODS: This 52-week, randomized, double-blind, parallel-group, multicenter, phase 3B safety study (NCT00419952) was conducted in 742 self-reported African American patients 12 years or older with moderate-to-severe asthma previously receiving medium- to high-dose

inhaled corticosteroids. After 2 weeks using a 320 mug twice-daily budesonide pMDI, patients were randomized 1:1 to 320/9 mug twice-daily budesonide/formoterol pMDI or 320 mug twice-daily budesonide pMDI. RESULTS: Both treatments were well tolerated. Asthma exacerbation incidence and rate (per patient-treatment year) were lower with budesonide/formoterol versus budesonide (incidence, 7.7% vs 14.0% [P= .006]; rate ratio, 0.615 [P= .002]). Time to first asthma exacerbation was longer (P= .018) with budesonide/formoterol versus budesonide. The most common adverse events, regardless of study drug relationship, were headache (9.5% and 7.7%), nasopharyngitis (6.9% and 8.0%), sinusitis (4.0% and 6.3%), and viral upper respiratory tract infection (5.8% and 4.4%) for budesonide/formoterol and budesonide, respectively. Serious adverse events occurred in 12 and 15 patients, respectively; none were considered drug related. No substantial or unexpected patterns of abnormalities were observed in laboratory, electrocardiographic, or Holter monitoring assessments. Hospitalization caused by asthma exacerbation occurred in 0 and 4 patients in the budesonide/formoterol and budesonide groups, respectively. Pulmonary function and asthma control measures generally favored budesonide/formoterol. CONCLUSIONS: In this population budesonide/formoterol pMDI was well tolerated over 12 months, with a safety profile similar to that of budesonide; the asthma exacerbation rate was reduced by 38.5% versus budesonide.

Djukanovic, R., S. J. Wilson, et al. (2010). "Montelukast added to fluticasone propionate does not alter inflammation or outcomes." Respir Med **104**(10): 1425-35.

BACKGROUND: Airway inflammation is a key pathological feature of asthma which underlies its clinical presentation. OBJECTIVES: To examine whether adding a leukotriene modifier to an inhaled corticosteroid produces further clinical and/or anti-inflammatory benefits in patients symptomatic on short-acting beta(2)-agonists. METHODS: Patients uncontrolled on short-acting beta(2)-agonists were treated for 12 weeks with either fluticasone propionate (100mcg BD) or fluticasone propionate (100mcg BD) and montelukast (10mg QD) in a randomized, double-blind, parallel group study. Bronchoscopy with endobronchial biopsy and bronchoalveolar lavage (BAL) was performed before and after treatment to compare effects on airway inflammation. RESULTS: Of 103 subjects enrolled, 89 subjects completed treatment and 82 subjects had matched pair biopsy samples. Submucosal eosinophil counts, the primary endpoint, and asthma control improved to similar extents after both treatments (p<or=0.008). Both treatments significantly reduced submucosal mast cell, CD3+, CD4+, CD8+ and CD25+ cell counts. Submucosal mast cell reduction was greater in the fluticasone propionate plus montelukast group. There were no differences between treatments in BAL markers of inflammation or thickness of sub-epithelial collagen. CONCLUSIONS: Low-dose fluticasone propionate significantly improves clinical disease control and reduces airway inflammation in asthma patients uncontrolled with short-acting beta(2)-agonists without further improvement when montelukast is added to low-dose fluticasone propionate.

Hoshino, M.J. Ohtawa. (2012). "Effects of budesonide/formoterol combination therapy versus budesonide alone on airway dimensions in asthma." Respirology **17**(4): 639-46.

BACKGROUND AND OBJECTIVE: Combination therapy with inhaled corticosteroids and long-acting beta(2)-agonists results in improved asthma symptom control compared

with the use of inhaled corticosteroids alone. However, the effects of combination therapy on structural changes and inflammation of the airways are still unknown. The aim of this study was to compare the effects of budesonide/formoterol with those of budesonide alone on airway dimensions and inflammation in individuals with asthma. METHODS: Fifty asthmatic patients were randomized to treatment with budesonide/formoterol (200/6 microg, two inhalations bd) or budesonide (200 microg, two inhalations bd) for 24 weeks. Airway dimensions were assessed using a validated computed tomography technique, and airway wall area (WA) corrected for body surface area (BSA), percentage WA (WA%), wall thickness/Osquare root BSA, and luminal area (Ai)/BSA at the right apical segmental bronchus, were measured. The percentage of eosinophils in induced sputum, pulmonary function, and Asthma Quality of Life Questionnaires (AQLQ) were also evaluated. RESULTS: There were significantly greater decreases in WA/BSA ($P < 0.05$), WA% ($P < 0.001$) and wall thickness/square root BSA ($P < 0.05$), and increases in Ai/BSA ($P < 0.05$), in subjects treated with budesonide/formoterol compared with those treated with budesonide. The reduction in sputum eosinophils and increase in per cent of predicted forced expiratory volume in 1 s (FEV(1) %) were greater for subjects treated with budesonide/formoterol compared with those treated with budesonide alone. In the budesonide/formoterol group, the changes in WA% were significantly correlated with changes in sputum eosinophils and FEV(1%) ($r = 0.84$ and $r = 0.64$, respectively). There were improvements in the AQLQ scores after treatment with budesonide/formoterol. CONCLUSIONS: Budesonide/formoterol combination therapy is more effective than budesonide alone for reducing airway wall thickness and inflammation in individuals with asthma.

Hozawa, S., M. Terada, et al. (2011). "Comparison of budesonide/formoterol Turbuhaler with fluticasone/salmeterol Diskus for treatment effects on small airway impairment and airway inflammation in patients with asthma." Pulm Pharmacol Ther **24**(5): 571-6.

BACKGROUND: A course of combination therapy with an inhaled corticosteroid (ICS) and a long-acting beta(2) agonist (LABA) for asthma can improve lung function, asthma symptoms and reduce exacerbations. Because both medicinal substance and inhalation devices are associated with clinical efficacy, each ICS/LABA combination may have different features. This study aimed to compare the effects of two widely available formulations, budesonide/formoterol (BUD/FM) delivered by a Turbuhaler((R)), and fluticasone/salmeterol (FP/SM) delivered by a Diskus((R)), on small airway function and airway inflammation. METHODS: Asthmatic patients (n = 40) treated twice daily with FP/SM 250/50 mug with forced expiratory volume in 1 s values controlled above 80% of the predicted normal but with suspected persistent airway inflammation and small airway impairment were enrolled in the study. Patients were randomized into two groups, receiving either twice daily BUD/FM 320/9 mug or FP/SM 250/50 mug, and treatment efficacy was compared after 4 weeks. Outcomes included impulse oscillometry (IOS), fractional exhaled nitric oxide (FeNO), spirometry and Asthma Control Questionnaire (ACQ) scores. RESULTS: Patients in the BUD/FM group showed significant improvements in their IOS and spirometry parameters of small airway function, FeNO values and ACQ scores, compared with the FP/SM group. There were good correlations between IOS parameters, FeNO and ACQ score changes over the course of the treatment. CONCLUSIONS: BUD/FM twice daily significantly improved small airway impairment

and airway inflammation in asthmatic patients, leading to a reduction in asthma symptoms and achievement of good asthma control. In addition, improvement of small airway function may improve airway inflammation and/or lead to better controlled asthma.

Katial, R. K., D. Bernstein, et al. (2011). "Long-term treatment with fluticasone propionate/salmeterol via Diskus improves asthma control versus fluticasone propionate alone." Allergy Asthma Proc **32**(2): 127-36.

This 52-week study was designed to assess the safety and efficacy of fluticasone propionate/salmeterol combination (FSC) 250/50 micrograms versus fluticasone propionate (FP) 250 micrograms in subjects with persistent asthma symptomatic on open-label FP 100 micrograms. The primary objective of this study was to show that FSC 250/50 micrograms was superior to FP 250 micrograms at increasing pulmonary function as measured by forced expiratory volume in 1 second over a 52-week treatment period. A secondary objective was to compare the rate of asthma attacks defined as (1) a sustained 2-day decrease in morning peak expiratory flow or increase in albuterol use for 2 consecutive days, (2) an asthma exacerbation requiring systemic corticosteroids, or (3) an unscheduled clinic or hospital visit for acute asthma symptoms. Three hundred six subjects received FSC 250/50 micrograms and 315 subjects received FP 250 micrograms. Both treatments were administered twice daily. Treatment with FSC 250/50 micrograms resulted in a significant improvement in lung function compared with FP 250 micrograms ($p < 0.001$). Additionally, treatment with FSC 250/50 micrograms resulted in a reduction in the rate of exacerbations of asthma (i.e., requiring systemic corticosteroids or unscheduled urgent care intervention) compared with FP 250 micrograms (0.170 versus 0.273, respectively; $p = 0.017$). There was no differentiation between treatments for less severe attacks of asthma. FSC 250/50 micrograms showed consistently greater improvement in lung function, symptom control, and decreased albuterol use. In addition, FSC 250/50 micrograms-treated subjects experienced fewer severe asthma exacerbations than subjects treated with FP 250 micrograms.

Korn, S.R. Buhl. (2012). "Efficacy of a fixed combination of ciclesonide and formoterol: the EXCITED-study." Respir Med **106**(1): 57-67.

Recommended treatment for moderate to severe asthma is the combination of an inhaled corticosteroid and a long-acting beta2-agonist. The present study was designed to evaluate the efficacy of a newly developed fixed combination of ciclesonide and formoterol in comparison to the marketed fixed combination of fluticasone and salmeterol in patients with moderate asthma. This was a phase II, multi-centre, randomized, parallel-group, double-blind, double-dummy study. After a 2-week run-in period, 160 patients with moderate asthma were randomized to a 6-week treatment with ciclesonide/formoterol 320/9 mug bid (CIC/F) or fluticasone propionate/salmeterol 250/50 mug bid (FP/S), both delivered as powder formulations. The primary outcome FEV1 increased during treatment by 0.356 L in the CIC/F group and by 0.288 L in the FP/S group ($p < 0.0001$). The increases were statistically significant and clinically relevant. The between-treatment analysis demonstrated non-inferiority of CIC/F to FP/S treatment ($p < 0.0001$). A significant improvement from baseline in lung function, symptom score and rescue medication use was observed in both groups at all time points.

No differences were observed between treatments in the frequency of adverse events and overnight urinary cortisol/creatinine ratio. The studied fixed combination of ciclesonide/formoterol is not inferior to the marketed fixed combination of fluticasone/salmeterol in terms of efficacy and tolerability.

Lipworth, B. J., K. Basu, et al. (2013). "Tailored second-line therapy in asthmatic children with the Arg(16) genotype." Clin Sci (Lond) **124**(8): 521-8.

The Arg(16) beta(2) receptor genotype confers increased susceptibility to exacerbations in asthmatic children taking regular LABA (long-acting beta(2) agonists). We therefore evaluated using montelukast as an alternative to salmeterol as tailored second-line asthma controller therapy in children expressing this susceptible genotype. A total of 62 persistent asthmatic children with the homozygous Arg16 genotype were randomized to receive salmeterol (50 mug, b.i.d.) or montelukast (5 or 10 mg, once daily) as an add-on to inhaled fluticasone for 1 year. School absences (the primary outcome) were reduced with montelukast compared with salmeterol {difference in score=-0.40 [95% CI (confidence interval), -0.22 to -0.58]; P=0.005}. Salbutamol use was also reduced with montelukast compared with salmeterol [difference in score=-0.47 (95% CI, -0.16 to -0.79); P<0.0001]. Greater improvements occurred in both symptom and quality of life scores with montelukast against salmeterol, whereas there was no difference in FEV(1) (forced expiratory volume in 1 s). In conclusion, montelukast may be suitable as tailored second-line controller therapy instead of salmeterol in asthmatic children expressing the susceptible Arg(16) genotype, a move towards a personalized medicine approach to management.

Maspero, J. F., H. Nolte, et al. (2010). "Long-term safety of mometasone furoate/formoterol combination for treatment of patients with persistent asthma." J Asthma **47**(10): 1106-15.

OBJECTIVE: The combination of inhaled corticosteroid (ICS) and long-acting beta(2)-agonist is recommended for treatment of patients with persistent asthma inadequately controlled on ICS monotherapy. This study was conducted to evaluate the long-term safety of mometasone furoate/formoterol (MF/F) administered through metered-dose inhaler (MDI) in patients with persistent asthma previously on medium- to high-dose ICS. METHODS: This was a 52-week, randomized, multicenter, parallel-group, open-label, evaluator-blinded study. At baseline, 404 patients (aged >/=12 years) were stratified according to their previous ICS dose (medium or high), then randomized 2:1 to receive twice-daily treatment of MF/F (200/10 or 400/10 mug) or fluticasone propionate/salmeterol (FP/S; 250/50 or 500/50 mug). The primary endpoint was the number and percentage of patients reporting any adverse event (AE). Additional safety evaluations included plasma cortisol 24-hour area under the curve (AUC(0-24 h)) and ocular changes. Pulmonary function, asthma symptoms, and use of rescue medication were monitored. RESULTS: The incidence of >/=1 treatment-emergent AE was similar across treatment groups (MF/F 200/10 mug, 77.3% [n= 109]; FP/S 250/50 mug, 82.4% [n= 56]; MF/F 400/10 mug, 79.2% [n= 103]; FP/S 500/50 mug, 76.9% [n= 50]). Rates of treatment-related AEs were also similar across treatment groups (MF/F 200/10 mug, 28.4%; FP/S 250/50 mug, 23.5%; MF/F 400/10 mug, 23.1%; FP/S 500/50 mug, 20.0%). Headache (3.7%) and dysphonia (2.7%) were the most common treatment-related AEs overall. The nature and frequency of AEs and the decreases in plasma cortisol AUC(0-24

h) observed with MF/F treatment were similar to those observed with FP/S treatment. Ocular events were rare (2-6% overall incidence among treatment groups); in particular, no posterior subcapsular cataracts were reported. Only three patients discontinued the study because of treatment-related ocular AEs (two for lens disorders in the MF/F 400/10 mug group; one for reduced visual acuity in the FP/S 250/50 mug group) and no asthma-related deaths occurred. Furthermore, MF/F showed numerical improvement in lung function and clinical benefits by reducing asthma symptoms and rescue medication use. CONCLUSIONS: One-year treatment with the new combination therapies - twice-daily MF/F-MDI 200/10 and 400/10 mug - is safe and well tolerated in patients with persistent asthma.

Meltzer, E. O., P. Kuna, et al. (2012). "Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function." Eur Respir J **39**(2): 279-89.

This study evaluated the effect of mometasone furoate (MF)/formoterol (F) versus its monocomponents, each administered via metered-dose inhaler, on asthma deteriorations and lung function. This 26-week, multicentre, double-blind, placebo-controlled study included subjects aged >/=12 yrs with not well-controlled asthma on low-dose inhaled corticosteroids. After a 2-3-week open-label run-in (MF 100 mug b.i.d.), 746 subjects were randomised to receive placebo, F 10 mug, MF 100 mug or MF/F 100/10 mug b.i.d. Co-primary end-points were time to first asthma deterioration (MF/F versus F to assess effect of MF) and change in forced expiratory volume in 1 s (FEV(1)) area under the curve of serial spirometry measurements over the 12-h period following the morning dose (AUC(0-12h)) (baseline to week 12; MF/F versus MF to assess effect of F). The therapeutic effect of MF in the combination was demonstrated by a reduction in asthma deterioration incidence with MF/F versus F and a delayed time to first asthma deterioration ($p<0.001$). Asthma deterioration incidence was also reduced with MF/F versus MF ($p=0.006$). The therapeutic effect of F in the combination was demonstrated by MF/F versus MF in FEV(1) AUC(0-12h) change (4.00 versus 2.53 L.h, respectively; $p=0.001$). MF/F treatment also resulted in a marked improvement in health-related quality of life. MF/F 100/10 mug b.i.d. treatment showed greater clinical efficacy than its individual components or placebo; both components contributed to the efficacy of MF/F.

Nathan, R. A., H. Nolte, et al. (2010). "Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids." Allergy Asthma Proc **31**(4): 269-79.

Asthma is a heterogeneous condition characterized by reduced lung function, chronic inflammation, and periodic asthma deteriorations. This study was performed to evaluate the effect of mometasone furoate (MF)/formoterol (F) combination, 200/10 microg, administered twice daily (b.i.d.) on asthma deteriorations and pulmonary function in patients with asthma uncontrolled on medium-dose inhaled corticosteroid (ICS). After 2- to 3-week open-label run-in with MF 200 microg b.i.d., patients (>or=12 years) were randomized to 26 weeks of treatment with MF/F 200/10 microg, MF 200 microg, F 10 microg, or placebo b.i.d. Coprimary end points were time to first asthma deterioration (MF/F versus F) and bronchodilation, assessed by the area under the curve of the change in forced expiratory volume in 1 second 0-12 hours (FEV(1) AUC(0-12h); MF/F versus

MF). A total of 781 patients were randomized. Treatment with MF/F 200/10 microg reduced asthma deteriorations and clinically judged deteriorations (i.e., deterioration resulting in emergency treatment, hospitalization, or treatment with additional excluded asthma medication [i.e., systemic corticosteroids]). The proportion of patients experiencing asthma deteriorations was MF/F, 30.4%; MF, 33.9%; F, 54.0%; placebo, 55.6% ($p < 0.001$, MF/F versus F and placebo). There was a sixfold reduction in clinically judged deteriorations with MF/F versus F and placebo ($p < 0.001$). Lung function improved more rapidly with MF/F than MF and placebo. Mean change from baseline FEV(1) AUC(0-12h) at week 12 was MF/F, 11.7% versus MF, 5.7%; F, 8.5%; and placebo, 3.9% ($p < 0.001$). Treatment-related AEs were rare and similar across groups. Treatment with MF/F 200/10 microg was effective in reducing the risk of asthma deteriorations. MF/F was safe and provided rapid and sustained bronchodilation in patients with asthma.

Peters, S. P., S. J. Kunselman, et al. (2010). "Tiotropium bromide step-up therapy for adults with uncontrolled asthma." N Engl J Med **363**(18): 1715-26.

BACKGROUND: Long-acting beta-agonist (LABA) therapy improves symptoms in patients whose asthma is poorly controlled by an inhaled glucocorticoid alone. Alternative treatments for adults with uncontrolled asthma are needed. METHODS: In a three-way, double-blind, triple-dummy crossover trial involving 210 patients with asthma, we evaluated the addition of tiotropium bromide (a long-acting anticholinergic agent approved for the treatment of chronic obstructive pulmonary disease but not asthma) to an inhaled glucocorticoid, as compared with a doubling of the dose of the inhaled glucocorticoid (primary superiority comparison) or the addition of the LABA salmeterol (secondary noninferiority comparison). RESULTS: The use of tiotropium resulted in a superior primary outcome, as compared with a doubling of the dose of an inhaled glucocorticoid, as assessed by measuring the morning peak expiratory flow (PEF), with a mean difference of 25.8 liters per minute ($P<0.001$) and superiority in most secondary outcomes, including evening PEF, with a difference of 35.3 liters per minute ($P<0.001$); the proportion of asthma-control days, with a difference of 0.079 ($P=0.01$); the forced expiratory volume in 1 second (FEV1) before bronchodilation, with a difference of 0.10 liters ($P=0.004$); and daily symptom scores, with a difference of -0.11 points ($P<0.001$). The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and increased the prebronchodilator FEV1 more than did salmeterol, with a difference of 0.11 liters ($P=0.003$). CONCLUSIONS: When added to an inhaled glucocorticoid, tiotropium improved symptoms and lung function in patients with inadequately controlled asthma. Its effects appeared to be equivalent to those with the addition of salmeterol. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00565266.).

Postma, D. S., P. M. O'Byrne, et al. (2011). "Comparison of the effect of low-dose ciclesonide and fixed-dose fluticasone propionate and salmeterol combination on long-term asthma control." Chest **139**(2): 311-8.

BACKGROUND: Patients with mild persistent asthma constitute about 70% of the asthma population; thus, it is important to know which first-line treatment is best for the management of mild asthma. We compared benefits of first-line treatment with

ciclesonide and a combination of fluticasone and salmeterol in patients with mild asthma. METHODS: Patients aged 12 to 75 years with mild persistent asthma were enrolled in a randomized, double-blind, placebo-controlled study. After run-in, patients were randomized to ciclesonide 160 mug once daily (CIC160), fluticasone propionate/salmeterol 100/50 mug bid (FP200/S100), or placebo for 52 weeks. The primary variable was time to first severe asthma exacerbation; the coprimary variable was the percentage of poorly controlled asthma days. Patients recorded asthma symptoms and salbutamol use in electronic diaries and completed a standardized version of the Asthma Quality of Life Questionnaire. RESULTS: Compared with placebo, the time to first severe asthma exacerbation was prolonged, and lung function was improved with FP200/S100 treatment (P = .0002) but not with CIC160. Both CIC160 and FP200/S100 provided significantly fewer poorly controlled asthma days than placebo (P </= .0016 for both active treatments). Moreover, both active treatments provided significantly more asthma symptom-free days (P </= .0001), rescue medication-free days (P = .0005, one-sided), and days with asthma control (P </= .0033). Overall Asthma Quality of Life Questionnaire scores were significantly higher in both active treatment groups than placebo (P </= .0017). CONCLUSIONS: In mild asthma, FP200/S100 prolonged time to first severe asthma exacerbation, and CIC160 and FP200/S100 were clinically equieffective for most measures of asthma control. Trial registry: ClinicalTrials.gov; No.: NCT00163358; URL: www.clinicaltrials.gov.

Spector, S. L., U. J. Martin, et al. (2012). "Budesonide/formoterol pressurized metered-dose inhaler versus budesonide: a randomized controlled trial in black patients with asthma." J Asthma **49**(1): 70-7.

OBJECTIVE: Concerns exist that responses to long-acting beta(2)-adrenergic agonists in black patients may differ from the general population. The efficacy and safety of budesonide/formoterol (BUD/FM) pressurized metered-dose inhaler (pMDI) versus budesonide dry powder inhaler (BUD DPI) were evaluated in adolescent and adult black asthma patients. METHODS: This 12-week, randomized, double-blind, multicenter, phase IV US study was conducted in 311 self-reported black patients aged >/=12 years with moderate to severe persistent asthma, previously receiving medium- to high-dose inhaled corticosteroid. After 2 weeks on BUD 90 mug x 2 inhalations twice daily (bid), symptomatic patients were randomized to BUD/FM 160/4.5 mug x 2 inhalations bid or BUD 180 mug x 2 inhalations bid. RESULTS: Improvement in predose forced expiratory volume in 1 second from baseline to the treatment mean (primary variable) was greater with BUD/FM versus BUD (0.16 vs. 0.07 L; p = .008); this effect was also observed at weeks 2, 6, and end of treatment (p </= .032). Greater improvements (p < .001) in peak expiratory flow with BUD/FM versus BUD were seen at first measurement and maintained during 12 weeks (morning: 25.34 vs. 7.53 L/minute, respectively; evening: 21.61 vs. 7.67 L/minute, respectively); greater improvements in daily asthma symptom score and rescue medication use were also observed (p </= .039). Both treatments were well tolerated, with similar safety profiles. CONCLUSIONS: In this population of black asthma patients, BUD/FM pMDI resulted in greater improvements in pulmonary function and asthma control versus BUD DPI, with similar safety profiles.

Stelmach, I., M. Olszowiec-Chlebna, et al. (2011). "Inhaled corticosteroids may have a beneficial effect on bone metabolism in newly diagnosed asthmatic children." Pulm Pharmacol Ther **24**(4): 414-20.

BACKGROUND: The adverse effect of inhaled corticosteroids (ICS) treatment on bone metabolism in children with asthma is still controversial, and a possible beneficial effect of vitamin D added to ICS on bone turnover is uncertain. OBJECTIVE: We conducted a randomized, double-blind, parallel-group, 6-month trial to assess the effects of a medium and high dose of ICS and a high-dose ICS with vitamin D on bone metabolism in children with newly diagnosed atopic asthma. METHODS: 96 children were equally randomized to 4 groups receiving the following doses of inhaled budesonide [mug/day]: 400 (ICS 400 group), 800 (ICS 800 group), 800 with oral vitamin D (ICS 800 with vit D group), and montelukast as a control (control group). Markers of bone production (osteocalcin, alkaline phosphatase) and bone degradation (amino-terminal cross-linked telopeptide of type I collagen--NTx, carboxy-terminal telopeptides of type I collage), and also concentration of 25-hydroxycholecalciferol (25OH D) and calcium-phosphorus balance (calcium, phosphorus, parathormon-PTH) in serum and/or urine were assessed twice: before and after 6 months of treatment. RESULTS: We obtained a significant decrease in phosphorus and PTH serum levels in ICS 400 and ICS 800 with vit D groups compared to control group, and a significant decrease of NTx urine level in ICS 800 with vit D group. CONCLUSIONS: Medium doses of inhaled corticosteroids exert an advantageous effect on bone metabolism in newly diagnosed asthmatic children. Vitamin D together with a high dose of inhaled corticosteroids has a beneficial effect on both calcium-phosphorus balance and collagen turnover.

Vaessen-Verberne, A. A., N. J. van den Berg, et al. (2010). "Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma." Am J Respir Crit Care Med **182**(10): 1221-7.

RATIONALE: For children with symptomatic asthma despite low to moderate doses of inhaled corticosteroids, evidence is still lacking whether to add a long-acting bronchodilator or to increase the dose of inhaled corticosteroids. OBJECTIVE: To evaluate whether salmeterol/fluticasone propionate (SFP), 50/100 mug twice a day, is noninferior regarding symptom control compared with fluticasone propionate (FP), 200 mug twice a day Diskus in children with symptomatic asthma. METHODS: A multicenter, randomized, parallel-group, double-blind study was performed comparing SFP and FP treatment during 26 weeks on asthma control and lung function. MEASUREMENTS AND MAIN RESULTS: A total of 158 children, 6-16 years old, still symptomatic on FP, 100 mug twice a day, during a 4-week run-in period, were included. Percentage of symptom-free days during the last 10 weeks of the treatment period did not differ between treatment groups (per protocol analysis: adjusted mean difference [FP minus SFP] 2.6%; 95% confidence interval, -8.1 to 13.4). Both groups showed substantial improvements of about 25 percent points in symptom-free days (both $P < 0.001$ from baseline). Lung function measurements (FEV(1), FVC, PEF rate, and maximal expiratory flow) did not differ between groups except for a slight advantage in maximal expiratory flow in the SFP group at 1 week. No differences were found between FP and SFP regarding exacerbation rates, adverse events, or growth. CONCLUSIONS: In our study the efficacy on symptom control and lung function of the combination of a

long-acting bronchodilator with inhaled corticosteroid is equal to doubling the dose of the inhaled corticosteroid in children still symptomatic on a moderate dose of inhaled corticosteroid.

Weinstein, S. F., J. Corren, et al. (2010). "Twelve-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg and 400/10 microg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids." Allergy Asthma Proc **31**(4): 280-9.

A significant unmet medical need exists in patients with uncontrolled asthma. The purpose of this study was to evaluate the efficacy and safety of mometasone furoate/formoterol (MF/F) 400/10 microg versus MF 400 microg administered twice-daily (b.i.d.) via metered-dose inhaler in patients with asthma uncontrolled on high-dose inhaled corticosteroids (ICS). In a 12-week, randomized, multicenter, double-blind, parallel-group study, patients (>or=12 years of age) were randomized to MF/F 200/10 microg, MF/F 400/10 microg, or MF 400 microg, b.i.d. after a 2- to 3-week open-label run in with MF 400 microg b.i.d. The primary end point was mean change in area under the curve from 0 to 12 hours in forced expiratory volume in 1 second (FEV(1) AUC(0-12h)) from baseline to week 12 for MF/F 400/10 microg versus MF 400 microg. Effects of MF/F on asthma control and symptoms were evaluated and adverse events recorded. Seven hundred twenty-eight patients were randomized. Significant improvement from baseline to week 12 occurred for mean change in FEV(1) AUC(0-12h) with MF/F 400/10 microg (4.19 L x hour) versus MF 400 microg (2.04 L x hour; $p < 0.001$). Both MF/F doses resulted in rapid (5 minutes) and sustained improvement in lung function throughout 12 weeks. Both MF/F doses were superior to MF in improving asthma control and reducing nocturnal awakenings due to asthma requiring short-acting beta(2)-agonist use. All treatments were well tolerated. Asthma patients who were poorly controlled on high-dose ICS experienced significant improvement in asthma control, lung function, and symptoms when treated with MF/F compared with MF.

Zangrilli, J., L. E. Mansfield, et al. (2011). "Efficacy of budesonide/formoterol pressurized metered-dose inhaler versus budesonide pressurized metered-dose inhaler alone in Hispanic adults and adolescents with asthma: a randomized, controlled trial." Ann Allergy Asthma Immunol **107**(3): 258-65 e2.

BACKGROUND: Few clinical trials in asthma have focused on Hispanic populations. OBJECTIVE: To compare the efficacy and safety of budesonide/formoterol (BUD/FM) with BUD in an ethnically diverse group of Hispanic participants with asthma previously treated with inhaled corticosteroids (ICS). METHODS: This 12-week, randomized, double-blind, active-controlled study (NCT00419757) was designed to enroll Hispanic participants (self-reported) (>/=12 years of age) with moderate to severe asthma requiring medium- to high-dose ICS. After a 2-week run-in period (low-dose BUD pressurized metered-dose inhaler [pMDI] 80 mug x 2 inhalations [160 mug] twice daily), participants with a symptom score greater than 0 (scale: 0-3) on 3 or more of 7 run-in days and forced expiratory volume in 1 second (FEV(1)) 45%-85% predicted were randomized to BUD/FM pMDI 160/4.5 mug x 2 inhalations (320/9 mug) twice daily or BUD pMDI 160 mug x 2 inhalations (320 mug) twice daily. RESULTS: Randomized participants (n = 127 BUD/FM; n = 123 BUD) were predominately Mexican (51%) or Puerto Rican

(21%). During low-dose ICS run-in, the mean symptom score was 1.0; however, mean predose FEV(1) improved (2.10-2.21 L). During randomized treatment, small, but not statistically significant, improvements favored BUD/FM vs BUD (am peak expiratory flow [PEF; primary efficacy variable] 25.4 vs 19.9 L/min; pm PEF 20.6 vs 15.8 L/min; predose FEV(1) 0.16 vs 0.11 L; rescue medication use -0.7 vs -0.6 inhalations/d). Most adverse events were mild or moderate in intensity. CONCLUSIONS: Improvement in clinically relevant control end points occurred in both BUD/FM and BUD groups; both treatments were well tolerated in this Hispanic asthma population but were not significantly differentiated.

Placebo-controlled trials

Bardelas, J., M. Figliomeni, et al. (2012). "A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma." J Asthma **49**(2): 144-52.

OBJECTIVE: The 2007 National Heart, Lung, and Blood Institute (NHLBI) asthma guidelines shifted the focus of care from asthma severity to ongoing assessment of asthma control using the components of impairment and risk. We evaluated the effect of omalizumab on asthma control in patients with persistent allergic asthma inadequately controlled with NHLBI Step 4 or above asthma therapy. METHODS: In this double-blind, placebo-controlled study, patients >/=12 years (n = 271) received omalizumab (n = 136) or placebo (n = 135) every 2 or 4 weeks for 24 weeks. The primary efficacy variable, change from baseline in Asthma Control Test (ACT) total score, and Investigator's Global Evaluation of Treatment Effectiveness (IGETE, secondary efficacy variable) were evaluated at week 24. RESULTS: ACT score improved more with omalizumab compared with placebo (least squares means [LSMs]: 5.01, 4.36); however, the difference was not significant (p = .1779). Similarly, IGETE was not significantly different (p = .1177), but more patients treated with omalizumab (26/127, 20%) compared with placebo (19/131, 15%) had IGETE rated as "Excellent." Significant benefits were observed for omalizumab compared with placebo for change in ACT score (LSMs: 6.66, 5.27; p = .0334) and IGETE (p = .0321) at week 24 in a subgroup of patients with very poorly controlled asthma (ACT </= 15) at baseline. There were no significant differences for the subgroup of patients with forced expiratory volume in 1 second </= 80% predicted at baseline. Adverse events (AEs) were similar between groups with no drug-related serious AEs or deaths. CONCLUSIONS: For allergic asthma patients with NHLBI Step 4 or above asthma therapy, omalizumab consistently improved asthma control; however, compared with placebo, differences were not significant. Placebo-treated patients had substantial improvement in their ACT score, which may have limited the ability to detect differences between treatment groups. Subgroup analyses showed significant improvements with omalizumab versus placebo in patients with very poorly controlled asthma.

Bateman, E. D., E. R. Bleecker, et al. (2012). "Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial." Respir Med **106**(5): 642-50.

BACKGROUND: This randomized, double-blind, multicenter study was designed to evaluate the efficacy of inhaled once-daily fluticasone furoate (FF) administered in the

evening in patients with persistent asthma not controlled by short-acting beta(2) agonists, and to determine the dose(s) suitable for further development. METHODS: Of 1459 patients screened, 598 received one of six treatments: placebo, FF (25 mug, 50 mug, 100 mug or 200 mug) once daily each evening, or fluticasone propionate (FP) 100 mug twice daily for 8 weeks. The primary endpoint was change from baseline in pre-dose evening forced expiratory volume in 1 s (FEV(1)). RESULTS: A dose-response effect was observed for once-daily FF 25-200 mug including ($p < 0.001$) and excluding placebo ($p = 0.03$). FF 50-200 mug once daily significantly increased FEV(1) from baseline ($p < 0.05$ vs placebo), by >200 mL for FF 100 mug and 200 mug. Significant improvements were also achieved for peak expiratory flow, and percentage symptom-free and rescue-free 24 h periods. The magnitude of effect was at least as good as twice-daily FP. Overall, once-daily FF was well tolerated with no systemic corticosteroid effects. CONCLUSION: FF 50-200 mug/day once daily in the evening demonstrated dose-related efficacy in asthma with 100-200 mug appearing to be the optimal doses for further evaluation. ClinicalTrials.gov: NCT00603382.

Bensch, G. W., L. S. Greos, et al. (2011). "Linear growth and bone maturation are unaffected by 1 year of therapy with inhaled flunisolide hydrofluoroalkane in prepubescent children with mild persistent asthma: a randomized, double-blind, placebo-controlled trial." Ann Allergy Asthma Immunol **107**(4): 323-9.

BACKGROUND: Inhaled corticosteroids (ICS) are the preferred long-term therapy for subjects with persistent asthma. However, concerns remain about potential effects of long-term ICS use on growth in children. OBJECTIVE: To determine the effect of 1 year of inhalation therapy with flunisolide hydrofluoroalkane (HFA) on growth velocity and bone maturation in children with mild persistent asthma. METHODS: In this double-blind, placebo-controlled study, 218 prepubescent (Tanner Stage 1) children with mild persistent asthma ranging in age from 4 to 10 years were evaluated. After a 2-week run-in period, subjects were randomized (1:1) to 2 puffs flunisolide HFA twice daily (85 mug/puff) or placebo for 52 weeks. Height was assessed by stadiometry at each visit. Growth velocity (cm/52 weeks) was estimated by the slope of the linear regression of height over time. An independent assessor scored hand and wrist radiographs for bone development pretreatment and at week 52. Analysis of covariance was used for all efficacy endpoints. RESULTS: The 2 treatment groups were similar at baseline for sex, race, age, weight, and height. At the end of double-blind treatment, mean growth velocity was 6.01 +/- 1.84 cm/52 weeks for flunisolide HFA (n = 106) and 6.19 +/- 1.30 cm/52 weeks for placebo (n = 112) (P = .425). Mean advancement in bone age during the 1-year study was similar for the 2 groups: 0.93 +/- 0.46 years for flunisolide HFA (n = 70) and 1.01 +/- 0.41 years for placebo (n = 75) (P = .128). CONCLUSIONS: In this study, flunisolide HFA did not suppress growth or bone maturation at the highest approved dose for children with persistent asthma.

Bleecker, E. R., E. D. Bateman, et al. (2012). "Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids." Ann Allergy Asthma Immunol **109**(5): 353-8 e4.

BACKGROUND: Fluticasone furoate (FF) is an inhaled corticosteroid (ICS) with 24-hour activity in development as a once-daily treatment for the long-term management of

asthma. OBJECTIVE: To assess the efficacy and safety of 4 doses of once-daily FF administered using a dry powder inhaler in patients (>/=12 years) with moderate asthma, uncontrolled on low-dose ICS (fluticasone propionate [FP] 200 mug/day or equivalent). METHODS: This double-blind, placebo-controlled, dose-ranging study randomized 622 patients to 1 of 6 treatments: FF (100, 200, 300, or 400 mug) once daily in the evening, FP 250 mug twice daily (active control), or placebo for 8 weeks. The primary endpoint was the change from baseline in predose evening forced expiratory colume in 1 second (FEV1) at week 8. RESULTS: At week 8, relative to placebo, all doses of FF once daily and FP twice daily demonstrated significantly (P < .001) greater increases from baseline and greater than 200-mL increases in predose FEV1. There was no evidence of a dose-response relationship between FF doses. Improvement with once-daily FF was similar to or greater than that for twice-daily FP. Secondary efficacy endpoint findings generally supported the efficacy of FF 100 to 400 mug once daily, although statistically significant improvements versus placebo in symptom-free 24-hour periods were only reported for FF 400 mug. There were few withdrawals due to lack of efficacy. Oral candidiasis was reported in 0 to 4% of patients; 24-hour urinary cortisol excretion ratios were similar across active treatment groups and not significantly different from placebo. CONCLUSION: FF 100 to 400 mug once daily in the evening is effective and well tolerated in patients with asthma uncontrolled on low-dose ICS, with 100 mug and 200 mug, considered the most applicable doses in this asthma population. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00603278.

Bousquet, J., Z. Siergiejko, et al. (2011). "Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma." Allergy **66**(5): 671-8.

BACKGROUND: The physician's global evaluation of treatment effectiveness (GETE) at 16 weeks has been shown to be the most effective assessment of response to omalizumab (XOLAIR(R)). This randomized, open-label, parallel-group study evaluated the persistency of treatment responder classification in patients receiving omalizumab added to optimized asthma therapy (OAT). METHODS: Patients (12-75 years, n = 400) with severe allergic asthma, uncontrolled despite Global Initiative for Asthma 2004 Step 4 therapy, received OAT and omalizumab (n = 272) or OAT (n = 128) for 32 weeks. Response or nonresponse was evaluated at Weeks 16 and 32. Response was defined as an investigator's (physician's) GETE rating of excellent or good; nonresponse was defined as a rating of moderate, poor or worsening. RESULTS: Three hundred and forty-nine patients had GETE ratings available at Weeks 16 and 32 (omalizumab n = 258, OAT n = 91). Omalizumab responders of about 171/187 (91.4%)and 44/71 (62.0%) omalizumab nonresponders at Week 16 persisted as responders or nonresponders at Week 32. The investigator's GETE at Week 16 predicted persistency of response or nonresponse to omalizumab at Week 32 for 83.3% (215/258) of patients. OAT patients showed a lower persistency of response (18/28 [64.3%]) and a higher persistency of nonresponse (57/63 [90.5%]) than omalizumab patients. Excellent and good GETE ratings in omalizumab-treated patients were reflected by improvements in exacerbation rates (P < 0.001), severe exacerbation rates (P = 0.023), hospitalizations (P = 0.003), total emergency visits (P = 0.026) and Asthma Control Questionnaire overall score (P < 0.001). CONCLUSION: Response to omalizumab, as assessed by a physician's GETE at 16 weeks, is an effective predictor of continuing persistent response to omalizumab for the majority of patients.

Busse, W. W., E. R. Bleecker, et al. (2012). "Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial." Thorax **67**(1): 35-41.

BACKGROUND: Fluticasone furoate (FF) is a novel inhaled corticosteroid with 24 h activity. FF is being developed as a once-daily treatment in combination with the long-acting beta(2) agonist vilanterol trifenatate for asthma and chronic obstructive pulmonary disease. OBJECTIVES: To determine the optimal dose(s) of FF for treating patients with asthma. METHODS: An 8-week multicentre, randomised, double-blind study. 627 patients with persistent moderate-to-severe asthma, symptomatic on medium-dose inhaled corticosteroid therapy, were randomised to placebo, FF 200, 400, 600 or 800 mug (once daily in the evening using a novel dry powder inhaler), or fluticasone propionate 500 mug twice daily (via Diskus/Accuhaler). The primary efficacy measure was mean change from baseline in pre-dose evening forced expiratory volume in one second (FEV(1)). Other endpoints included morning and evening peak expiratory flow, and rescue/symptom-free 24 h periods. RESULTS: Each dose was significantly superior to placebo for the primary endpoint ($p<0.001$) with efficacy at least similar to that reported with fluticasone propionate. There was no dose-response relationship across the FF doses studied. Peak expiratory flow improved in all groups ($p<0.001$ vs placebo), and there were significant treatment effects on rescue/symptom-free 24 h periods with all active treatments. FF was generally well tolerated. The incidence of oral candidiasis was higher with FF 800 mug than placebo; pharmacokinetic and 24 h urinary cortisol analyses confirmed a higher systemic exposure of FF at this highest dose level. CONCLUSIONS: FF doses <800 mug have a favourable therapeutic index. The absence of an efficacy dose response suggests that 200 mug is an appropriate dose in patients with moderate persistent asthma. CLINICALTRIALS.GOV IDENTIFIER: NCT00603746.

Chuchalin, A. G., A. N. Tsoi, et al. (2007). "Safety and tolerability of indacaterol in asthma: a randomized, placebo-controlled 28-day study." Respir Med **101**(10): 2065-75.

The safety and tolerability of indacaterol, a novel once-daily beta(2)-agonist bronchodilator with a fast onset of action, were assessed in 156 asthma patients in a multicentre, randomized, double-blind, placebo-controlled study. Patients received indacaterol 200, 400 or 600 microg or placebo once daily for 28 days. Adverse events (AEs), laboratory assessments, vital signs, electrocardiograms, spirometry and physical examinations were monitored. Indacaterol pharmacokinetics were assessed. There was no evidence of dose-related increases in AE incidence or clinically significant hypokalaemia or hyperglycaemia in indacaterol-treated patients. Mean pulse rate changes were minor in any group, with maximum 1-h post-dose changes from baseline of -3.7, -3.3 and -2.2 bpm for indacaterol 200, 400 and 600 microg, respectively, and -2.9 bpm for placebo. Mean QTc interval was similar between groups; change from baseline >60 ms occurred in only two patients. Mean FEV(1) increased after the first indacaterol dose; baseline-adjusted pre-dose (trough) values remained >or=166 mL higher than placebo at all subsequent visits, supporting a 24-h bronchodilator effect. Pre-dose (but not post-dose) serum indacaterol concentrations indicated a slight trend for accumulation. Once-daily indacaterol 200-600 microg has a favourable therapeutic index. It is well tolerated, and is

not associated with any adverse cardiac or metabolic effects, while providing effective 24-h bronchodilation.

Frampton, J. E. (2012). "Mometasone/formoterol inhalation aerosol: in asthma uncontrolled on medium- or high-dose inhaled corticosteroids." Drugs **72**(9): 1229-41.

The corticosteroid mometasone and the long-acting beta(2)-selective adrenoreceptor agonist formoterol have been combined in a single pressurized metered-dose inhaler for use in patients aged >/=12 years with asthma. In a 26-week well designed trial in patients with persistent asthma uncontrolled on medium-dose inhaled corticosteroids (ICS), mometasone/formoterol 200 mug/10 mug twice daily (bid) was more effective than placebo or the same nominal dosage of formoterol alone in reducing the incidence of asthma deteriorations, as well as in improving lung function, asthma control, asthma symptoms and asthma-related quality-of-life outcomes. The combination was also more effective than the same nominal dosage of mometasone alone in improving lung function and asthma control. Similarly, in a 12-week well designed trial in patients with persistent asthma uncontrolled on high-dose ICS, mometasone/formoterol 400 mug/10 mug bid was more effective than the same nominal dosage of mometasone alone in improving lung function, asthma control and asthma symptoms. Treatment with a lower dosage of the combination (200 mug/10 mug bid) yielded similar results and, moreover, significantly reduced the incidence of asthma deteriorations compared with mometasone alone. Mometasone/formoterol was generally well tolerated in clinical trials of 12-52 weeks' duration. The adverse event profile of the combination was consistent with that of its individual components; no new or unexpected safety signals were detected.

Guilbert, T. W., D. T. Mauger, et al. (2011). "Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone." J Allergy Clin Immunol **128**(5): 956-63 e1-7.

BACKGROUND: The effect on linear growth of daily long-term inhaled corticosteroid therapy in preschool-aged children with recurrent wheezing is controversial. OBJECTIVE: We sought to determine the effect of daily inhaled corticosteroid given for 2 years on linear growth in preschool children with recurrent wheezing. METHODS: Children aged 2 and 3 years with recurrent wheezing and positive modified Asthma Predictive Index scores were randomized to a 2-year treatment period of chlorofluorocarbon-delivered fluticasone propionate (176 mug/d) or masked placebo delivered through a valved chamber with a mask and then followed for 2 years off study medication. Height growth determined by means of stadiometry was compared between treatment groups. RESULTS: In the study cohort as a whole, the fluticasone group did not have significantly less linear growth than the placebo group (change in height from baseline difference, -0.2 cm; 95% CI, -1.1 to 0.6) 2 years after discontinuation of study treatment. In post hoc analyses children 2 years old who weighed less than 15 kg at enrollment and were treated with fluticasone had less linear growth compared with those treated with placebo (change in height from baseline difference, -1.6 cm; 95% CI, -2.8 to -0.4; P = .009). CONCLUSION: Linear growth was not significantly different in high-risk preschool-aged children with recurrent wheezing treated with 176 mug/d chlorofluorocarbon-delivered fluticasone compared with placebo 2 years after fluticasone is discontinued. However, post hoc subgroup analyses revealed that children who are

younger in age and of lesser weight relative to the entire study cohort had significantly less linear growth, possibly because of a higher relative fluticasone exposure.

Hanania, N. A., O. Alpan, et al. (2011). "Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial." Ann Intern Med **154**(9): 573-82.

BACKGROUND: Inhaled corticosteroids (ICS) and long-acting beta(2)-agonists (LABAs) are recommended in patients with asthma that is not well-controlled; however, many patients continue to have inadequately controlled asthma despite this therapy. OBJECTIVE: To evaluate the efficacy and safety of omalizumab in patients with inadequately controlled severe asthma who are receiving high-dose ICS and LABAs, with or without additional controller therapy. DESIGN: Prospective, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial. (ClinicalTrials.gov registration number: NCT00314575). SETTING: 193 investigational sites in the United States and 4 sites in Canada. PATIENTS: 850 patients aged 12 to 75 years who had inadequately controlled asthma despite treatment with high-dose ICS plus LABAs, with or without other controllers. Intervention: Omalizumab (n = 427) or placebo (n = 423) was added to existing medication regimens for 48 weeks. MEASUREMENTS: The primary end point was the rate of protocol-defined exacerbations over the study period. Secondary efficacy end points included the change from baseline to week 48 in mean daily number of puffs of albuterol, mean total asthma symptom score, and mean overall score on the standardized version of the Asthma Quality of Life Questionnaire (AQLQ[S]). Safety end points included the frequency and severity of treatment-emergent adverse events. RESULTS: During 48 weeks, the rate of protocol-defined asthma exacerbations was significantly reduced for omalizumab compared with placebo (0.66 vs. 0.88 per patient; P = 0.006), representing a 25% relative reduction (incidence rate ratio, 0.75 [95% CI, 0.61 to 0.92]). Omalizumab improved mean AQLQ(S) scores (0.29 point [CI, 0.15 to 0.43]), reduced mean daily albuterol puffs (-0.27 puff/d [CI, -0.49 to -0.04 puff/d]), and decreased mean asthma symptom score (-0.26 [CI, -0.42 to -0.10]) compared with placebo during the 48-week study period. The incidence of adverse events (80.4% vs. 79.5%) and serious adverse events (9.3% vs. 10.5%) were similar in the omalizumab and placebo groups, respectively. LIMITATIONS: The results are limited by early patient discontinuation (20.8%). The study was not powered to detect rare safety events or the treatment effect in the oral corticosteroid subgroup. CONCLUSION: In this study, omalizumab provided additional clinical benefit for patients with severe allergic asthma that is inadequately controlled with high-dose ICS and LABA therapy. Primary Funding Source: Genentech and Novartis Pharmaceuticals.

Kerstjens, H. A., M. Engel, et al. (2012). "Tiotropium in asthma poorly controlled with standard combination therapy." N Engl J Med **367**(13): 1198-207.

BACKGROUND: Some patients with asthma have frequent exacerbations and persistent airflow obstruction despite treatment with inhaled glucocorticoids and long-acting beta-agonists (LABAs). METHODS: In two replicate, randomized, controlled trials involving 912 patients with asthma who were receiving inhaled glucocorticoids and LABAs, we compared the effect on lung function and exacerbations of adding tiotropium (a total dose of 5 mug) or placebo, both delivered by a soft-mist inhaler once daily for 48 weeks. All the patients were symptomatic, had a post-bronchodilator forced expiratory volume in 1

second (FEV(1)) of 80% or less of the predicted value, and had a history of at least one severe exacerbation in the previous year. RESULTS: The patients had a mean baseline FEV(1) of 62% of the predicted value; the mean age was 53 years. At 24 weeks, the mean (+/-SE) change in the peak FEV(1) from baseline was greater with tiotropium than with placebo in the two trials: a difference of 86+/-34 ml in trial 1 (P=0.01) and 154+/-32 ml in trial 2 (P<0.001). The predose (trough) FEV(1) also improved in trials 1 and 2 with tiotropium, as compared with placebo: a difference of 88+/-31 ml (P=0.01) and 111+/-30 ml (P<0.001), respectively. The addition of tiotropium increased the time to the first severe exacerbation (282 days vs. 226 days), with an overall reduction of 21% in the risk of a severe exacerbation (hazard ratio, 0.79; P=0.03). No deaths occurred; adverse events were similar in the two groups. CONCLUSIONS: In patients with poorly controlled asthma despite the use of inhaled glucocorticoids and LABAs, the addition of tiotropium significantly increased the time to the first severe exacerbation and provided modest sustained bronchodilation. (Funded by Boehringer Ingelheim and Pfizer; ClinicalTrials.gov numbers, NCT00772538 and NCT00776984.).

Kerstjens, H. A., B. Disse, et al. (2011). "Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial." J Allergy Clin Immunol **128**(2): 308-14.

BACKGROUND: Some patients with severe asthma remain symptomatic and obstructed despite maximal recommended treatment. Tiotropium, a long-acting inhaled anticholinergic agent, might be an effective bronchodilator in such patients. OBJECTIVE: We sought to compare the efficacy and safety of 2 doses of tiotropium (5 and 10 mug daily) administered through the Respimat inhaler with placebo as add-on therapy in patients with uncontrolled severe asthma (Asthma Control Questionnaire score, >/= 1.5; postbronchodilator FEV(1), </= 80% of predicted value) despite maintenance treatment with at least a high-dose inhaled corticosteroid plus a long-acting beta(2)-agonist. METHODS: This was a randomized, double-blind, crossover study with three 8-week treatment periods. The primary end point was peak FEV(1) at the end of each treatment period. RESULTS: Of 107 randomized patients (54% female patients; mean, 55 years of age; postbronchodilator FEV(1), 65% of predicted value), 100 completed all periods. Peak FEV(1) was significantly higher with 5 mug (difference, 139 mL; 95% CI, 96-181 mL) and 10 mug (difference, 170 mL; 95% CI, 128-213 mL) of tiotropium than with placebo (both P < .0001). There was no significant difference between the active doses. Trough FEV(1) at the end of the dosing interval was higher with tiotropium (5 mug: 86 mL [95% CI, 41-132 mL]; 10 mug: 113 mL [95% CI, 67-159 mL]; both P < .0004). Daily home peak expiratory flow measurements were higher with both tiotropium doses. There were no significant differences in asthma-related health status or symptoms. Adverse events were balanced across groups except for dry mouth, which was more common on 10 mug of tiotropium. CONCLUSION: The addition of once-daily tiotropium to asthma treatment, including a high-dose inhaled corticosteroid plus a long-acting beta(2)-agonist, significantly improves lung function over 24 hours in patients with inadequately controlled, severe, persistent asthma.

Krishnan, J. A., B. G. Bender, et al. (2012). "Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial." J Allergy Clin Immunol **129**(1): 112-8.

BACKGROUND: Information comparing subjective and objective measurements of adherence to study medications and the effects of adherence on treatment-related differences in asthma clinical trials are limited. OBJECTIVE: We sought to compare subjective and objective measurements of children's adherence to inhaled corticosteroids or placebo and to determine whether adherence to study medications modified treatment-related differences in outcomes. METHODS: In an ancillary study conducted in 3 of 8 Childhood Asthma Management Program Clinical Centers, adherence was assessed by using self-reported and objective data in 5- to 12-year-old children with mild or moderate asthma who were randomly assigned to 200 mug of inhaled budesonide twice per day (n = 84) or placebo (n = 56) for 4 years. The kappa statistic was used to evaluate agreement between self-reported adherence (daily diary cards) and objectively measured adherence (number of doses left in study inhalers). Multivariable analyses were used to determine whether adherence to study treatment modified treatment-related differences in outcomes. RESULTS: Adherence of less than 80% was seen in 75% of 140 children when adherence was measured objectively but only in 6% of children when measured by means of self-report. There was poor agreement between objective and subjective measurements of adherence of at least 80% (kappa = 0.00; 95% CI, -0.05 to 0.04); self-reported adherence over the 4-year period generally overestimated objectively measured adherence (93.6% vs 60.8%, P < .0001). There was little evidence to indicate that adherence modified treatment-related differences in outcomes. CONCLUSION: Researchers should use objective rather than self-reported adherence data to identify clinical trial participants with low levels of adherence to study treatment.

Pedersen, S., P. Potter, et al. (2010). "Efficacy and safety of three ciclesonide doses vs placebo in children with asthma: the RAINBOW study." Respir Med **104**(11): 1618-28.

OBJECTIVE: To evaluate the efficacy and safety of three doses of ciclesonide (with or without spacer) in children with persistent asthma. PATIENTS AND METHODS: This was a multicentre, double-blind, placebo-controlled, 12-week study of ciclesonide 40, 80 or 160 mug (once daily pm). Children (6-11 years) were randomised 1:1 to treatment via a metered dose inhaler (MDI) or MDI plus spacer. The primary variable was change from baseline in mean morning peak expiratory flow (PEF). Secondary variables included: time to first lack of efficacy (LOE), asthma control, forced expiratory volume in 1 s (FEV(1)), asthma symptom score and quality of life (QoL). Safety assessments included: adverse events (AEs), urinary cortisol excretion and body height. RESULTS: In total, 1073 children received treatment. At endpoint, mean morning PEF significantly improved with all doses of ciclesonide vs. placebo. There was no difference over placebo in time to first LOE, but ciclesonide was superior to placebo on asthma control, symptom score, FEV(1) and QoL. There were no differences between the spacer or non-spacer subgroups. The incidences of AEs were comparable between treatment groups (approximately 35%) and there were no between-group differences in body height or urinary cortisol. CONCLUSIONS: Ciclesonide 40-160 mug once daily is effective and well tolerated in children with persistent asthma; its efficacy and safety are unaffected by the use of a spacer. clinicaltrials.gov registration number: NCT00384189.

Philip, G., C. Villaran, et al. (2011). "The efficacy and tolerability of inhaled montelukast plus inhaled mometasone compared with mometasone alone in patients with chronic asthma." J Asthma **48**(5): 495-502.

BACKGROUND: The efficacy of oral montelukast in chronic asthma is well established. Montelukast is also an effective adjunctive therapy to inhaled corticosteroids (ICS) in asthma uncontrolled on ICS alone. Inhaled montelukast was recently shown to provide significant bronchodilation compared with placebo in patients with chronic asthma. The purpose of this study was to evaluate the efficacy of inhaled montelukast added to inhaled mometasone. METHODS: This was an 8-week, multicenter, randomized, double-blind, placebo-controlled study comparing once-daily inhaled montelukast 1 mg plus inhaled mometasone 220 mug (delivered by separate dry powder inhalers) with placebo plus inhaled mometasone 220 mug. Men and women aged 15-85 years with chronic asthma, forced expiratory volume in 1 second (FEV(1)) 50-80% of the predicted value, and beta-agonist reversibility >/=12% were eligible. Patients were required to meet a minimum symptom threshold while receiving open-label inhaled mometasone during a 3-week prestudy/run-in period. Patients received blinded (montelukast vs. placebo) treatment for 2 weeks, entered a 1-week washout period, then crossed over to the other treatment for 2 weeks. The primary endpoint was the average change from baseline in FEV(1) over the 2-week treatment period. Secondary endpoints included daytime and nighttime symptom scores. Other endpoints included short-acting beta-agonist (SABA) use, asthma exacerbations, asthma control, peak expiratory flow (PEF), and blood eosinophil count. RESULTS: A total of 134 patients were randomized. For the primary endpoint, change from baseline in FEV(1), inhaled montelukast plus inhaled mometasone was significantly more effective than placebo plus inhaled mometasone (least squares mean 0.22 L vs. 0.17 L; p = .033 [two-sided at alpha = 0.05]). Inhaled montelukast plus inhaled mometasone was also significantly more effective than placebo plus inhaled mometasone in improving daytime asthma symptom scores (p = .005) and nighttime asthma symptom scores (p = .015), increasing the percentage of days with asthma control (p = .004), decreasing the percentage of days with asthma exacerbations (p </= .001), and decreasing the blood eosinophil count (p = .013). Differences were not significant on AM or PM PEF or SABA use, although the latter approached significance (p = .073). Both treatments were well tolerated. CONCLUSION: Inhaled montelukast plus inhaled mometasone was significantly more effective than placebo plus inhaled mometasone in improving FEV(1), symptoms, asthma control, and blood eosinophil count.

Rubin, A. S., A. Souza-Machado, et al. (2012). "Effect of omalizumab as add-on therapy on asthma-related quality of life in severe allergic asthma: a Brazilian study (QUALITX)." J Asthma **49**(3): 288-93.

OBJECTIVE: To assess the impact of omalizumab as an add-on therapy to standard treatment with inhaled corticosteroids (ICS) and long-acting beta-2 agonists (LABA) on asthma-related quality of life (QoL) in patients with severe allergic asthma. METHODS: This was a 20-week, randomized, open-label, study involving Brazilian patients (>12 years) with severe persistent allergic asthma inadequately controlled despite regular treatment with, at least, ICS (>/=500 mug/day fluticasone or equivalent) + LABA. The primary objective was to assess the mean change from baseline in overall Asthma-related

Quality of Life Questionnaire (AQLQ) score in omalizumab-treated patients compared with the control group. Secondary outcome measures included rescue medication use, incidence of asthma exacerbations, perception of treatment efficacy among patients, mean change from baseline in AQLQ score, and >1.5-point increase in overall AQLQ score. RESULTS: In the omalizumab group, overall AQLQ score was 3.2 (0.9) (mean [SD]) at baseline and 4.4 (1.3) at week 20 versus 3.0 (1.0) at baseline and 3.0 (1.1) at week 20 in the control group. Mean change from baseline on overall AQLQ score at week 20 in the omalizumab group was 1.2 (0.2) versus 0 (0.1) in the control group, showing a significant increase in scores from baseline in the omalizumab group ($p < .001$). There was also a statistically significant difference ($p < .001$) in the number of patients who showed a >1.5-point increase from baseline in overall AQLQ score after 20 weeks, thus indicating a better QoL in the omalizumab group. There was no significant difference with respect to the use of rescue medication, incidence of asthma exacerbation, and adverse events between treatment groups. The global evaluation of treatment effectiveness was significantly better for omalizumab ($p < .001$). CONCLUSION: Omalizumab was well tolerated and significantly improved the overall AQLQ score. Hence, it is a potential add-on therapy for severe persistent allergic asthma not controlled by standard prescribed treatment in Brazilian patients.

Skoner, D. P., E. O. Meltzer, et al. (2011). "Effects of inhaled mometasone furoate on growth velocity and adrenal function: a placebo-controlled trial in children 4-9 years old with mild persistent asthma." J Asthma **48**(8): 848-59.

OBJECTIVE: To assess the effects of long-term mometasone furoate delivered via a dry powder inhaler (MF-DPI) on growth velocity and hypothalamic-pituitary-adrenal axis function in children with asthma. STUDY DESIGN: Children aged 4-9 years with asthma (n = 187) were randomized to MF-DPI 100 mug (delivered dose; actuated dose is 110 mug) once daily in the morning (QD AM), 100 mug twice daily (BID), 200 mug QD AM, or placebo for 52 weeks followed by a 3-month follow-up period. The primary outcome was growth velocity calculated from stadiometric heights recorded at each visit. Secondary outcomes included serum and 12-h urinary cortisol, serum osteocalcin, and urinary N-telopeptide. RESULTS: MF-DPI 100 mug QD AM treatment did not significantly affect growth velocity compared with placebo (-0.10 +/- 0.31 cm/y, $p = 0.76$). When the effect of a total daily dose of 200 mug MF-DPI on growth velocity was examined, no significant effect was demonstrated for MF-DPI 100 mug BID compared with placebo (-0.64 +/- 0.39 cm/y, $p = 0.10$), although the change in mean growth velocity with MF-DPI 200 mug QD AM reached statistical significance (-0.70 +/- 0.29 cm/y, $p = 0.02$). The effects of all examined doses of MF-DPI on mean plasma cortisol levels were similar to cortisol changes seen in the placebo group, suggesting an absence of drug-related effects. No differences in 12-h urinary cortisol or other outcomes were observed between groups. CONCLUSIONS: One year of treatment with a total daily dose of 100 mug of MF-DPI in the morning resulted in no significant difference, whereas a total daily dose of 200 mug of MF-DPI was associated with some changes in growth velocity when compared with placebo. The differences in growth velocity, and the absence of drug-related cortisol effects, support the use of a total daily dose of 100 mug of MF-DPI in children aged 4-9 years with mild persistent asthma.

Sterling, R., J. Lim, et al. (2012). "Efficacy and optimal dosing interval of the long-acting beta(2) agonist, vilanterol, in persistent asthma: a randomised trial." Respir Med **106**(8): 1110-5.

BACKGROUND: Vilanterol (VI) is a novel once-daily long-acting beta(2) agonist with inherent 24-h activity. The aim of this study was to evaluate the efficacy of three once-daily doses and one twice-daily dose of VI used concurrently with ICS in adult patients (>/=18 years) with persistent asthma. Safety was also assessed. METHODS: Multicentre, randomised, double-blind, placebo-controlled, five-period crossover study consisting of 7-day treatment periods separated by 7-day wash-out periods. Seventy-five patients, maintained on ICS, received VI 6.25, 12.5 and 25 mcg once-daily (evening), VI 6.25 mcg twice-daily (morning/evening), and placebo. The primary endpoint was trough forced expiratory volume in 1 s (FEV(1)) (mean of 23 h and 24 h post evening dose) on Day 7; secondary endpoint was weighted mean 24-h serial FEV(1) on Day 7. RESULTS: All VI groups demonstrated statistically significant increases in trough FEV(1) versus placebo ($p < 0.001$). There was a statistically significant increase in weighted mean 24-h FEV(1) for each VI group versus placebo ($p < 0.001$). The effects of once-daily VI on trough FEV(1) and weighted mean 24-h FEV(1) were dose dependent. The incidence of adverse events (AEs) was low in each VI treatment group and was not dose dependent (5-9%; placebo = 18%); no drug-related AEs or serious AEs were reported. CONCLUSION: Once-daily treatment with VI was well tolerated and associated with improvements in lung function. The VI 6.25 mcg twice-daily dose showed the greatest change in trough FEV(1), however, similar changes in weighted mean 24-h FEV(1) with VI 12.5 mcg once-daily were observed. Although our study was not powered to demonstrate non-inferiority of once- versus twice-daily dosing of VI, the data suggest no advantage over a 24-h period of twice-daily over once-daily dosing for the same total daily dose. ClinicalTrials.gov: NCT00980200.

Valovirta, E., M. L. Boza, et al. (2011). "Intermittent or daily montelukast versus placebo for episodic asthma in children." Ann Allergy Asthma Immunol **106**(6): 518-26.

BACKGROUND: No standard, optimal treatment exists for severe intermittent (ie, episodic) asthma in children. However, evidence suggests that both daily and episode-driven montelukast are effective for this phenotype. OBJECTIVE: To assess the regimen-related efficacy of montelukast in treating pediatric episodic asthma. METHODS: A multicenter, randomized, double-blind, double-dummy, parallel-group, 52-week study was performed in children 6 months to 5 years of age comparing placebo with two regimens of montelukast 4 mg: (1) daily; or (2) episode-driven for 12 days beginning with signs/symptoms consistent with imminent cold or breathing problem. The main outcome measure was the number of asthma episodes (symptoms requiring treatment) culminating in an asthma attack (symptoms requiring physician visit, emergency room visit, corticosteroids, or hospitalization). RESULTS: Five hundred eighty-nine patients were randomized to daily montelukast, 591 to intermittent montelukast, and 591 to placebo. Compared with placebo, no significant difference was seen between daily montelukast ($P = .510$) or intermittent montelukast ($P = .884$) in the number of asthma episodes culminating in an asthma attack over 1 year. Daily montelukast reduced symptoms over the 12-day treatment period of asthma episodes compared with placebo ($P = .045$). Beta-agonist use was reduced with both daily ($P = .048$) and intermittent montelukast ($P = .028$) compared with placebo. However, because of prespecified rules

for multiplicity adjustments (requiring a positive primary endpoint), statistical significance for secondary endpoints cannot be concluded. All treatments were well tolerated. CONCLUSIONS: Montelukast did not reduce the number of asthma episodes culminating in an asthma attack over 1 year in children 6 months to 5 years of age, although numerical improvements occurred in some endpoints.

Woodcock, A., E. D. Bateman, et al. (2011). "Efficacy in asthma of once-daily treatment with fluticasone furoate: a randomized, placebo-controlled trial." Respir Res **12**(132.

BACKGROUND: Fluticasone furoate (FF) is a novel long-acting inhaled corticosteroid (ICS). This double-blind, placebo-controlled randomized study evaluated the efficacy and safety of FF 200 mcg or 400 mcg once daily, either in the morning or in the evening, and FF 200 mcg twice daily (morning and evening), for 8 weeks in patients with persistent asthma. METHODS: Asthma patients maintained on ICS for >/= 3 months with baseline morning forced expiratory volume in one second (FEV(1)) 50-80% of predicted normal value and FEV(1) reversibility of >/= 12% and >/= 200 ml were eligible. The primary endpoint was mean change from baseline FEV(1) at week 8 in pre-dose (morning or evening [depending on regimen], pre-rescue bronchodilator) FEV(1). RESULTS: A total of 545 patients received one of five FF treatment groups and 101 patients received placebo (intent-to-treat population). Each of the five FF treatment groups produced a statistically significant improvement in pre-dose FEV(1) compared with placebo ($p < 0.05$). FF 400 mcg once daily in the evening and FF 200 mcg twice daily produced similar placebo-adjusted improvements in evening pre-dose FEV(1) at week 8 (240 ml vs. 235 ml). FF 400 mcg once daily in the morning, although effective, resulted in a smaller improvement in morning pre-dose FEV(1) than FF 200 mcg twice daily at week 8 (315 ml vs. 202 ml). The incidence of oral candidiasis was low (0-4%) and UC excretion was comparable with placebo for all FF groups. CONCLUSIONS: FF at total daily doses of 200 mcg or 400 mcg was significantly more effective than placebo. FF 400 mcg once daily in the evening had similar efficacy to FF 200 mcg twice daily and all FF regimens had a safety tolerability profile generally similar to placebo. This indicates that inhaled FF is an effective and well tolerated once-daily treatment for mild-to-moderate asthma. TRIAL REGISTRATION: NCT00398645.

Secondary analyses of included primary trial publications

Camargo, C. A., Jr., E. R. Sutherland, et al. (2010). "Effect of increased body mass index on asthma risk, impairment and response to asthma controller therapy in African Americans." Curr Med Res Opin **26**(7): 1629-35.

OBJECTIVE: To explore whether obesity alters the risk, impairment and response to treatment in African Americans with asthma. METHODS: The data used for this secondary analysis are from a 1-year study in African American subjects comparing fluticasone propionate/salmeterol 100/50 microg combination (FSC) and fluticasone propionate 100 microg (FP). Subjects were retrospectively stratified by body mass index (BMI) <20 [underweight], 20-24.9 [normal weight], 25-29.9 [overweight], 30-34.9 [obese I], 35-39.9 [obese II], and >or=40 [obese III] kg/m(2). Outcomes studied included impairment domains: FEV(1), morning and evening peak expiratory flow (AM and PM PEF), daily albuterol use, daily symptom scores and future risk domain: exacerbations.

CLINICAL TRIAL REGISTRATION: www.clinicaltrials.gov; NCT00102765. RESULTS: There were 475 subjects evenly distributed between FSC and FP by baseline parameters. There were 207 subjects with a BMI >or=30, including 70 subjects with a BMI >or=40. Baseline BMI >or=40 was associated with numerically lower baseline AM and PM PEF. There was an attenuation of response to both treatments for only PM PEF ($p < 0.05$). By contrast, subjects with lower degrees of obesity or overweight did not differ from those with normal weight. The total population exacerbation rate was 2-fold greater in obese III subjects (39%) compared with subjects in other BMI categories (16-21%) ($p < 0.05$). A potential study limitation is the retrospective analysis of existing data. DISCUSSION: Response to treatment was attenuated for PM PEF for subjects with BMI >or=40 and was also associated with an increased rate of asthma exacerbations.

Cohen, R. T., B. A. Raby, et al. (2010). "In utero smoke exposure and impaired response to inhaled corticosteroids in children with asthma." J Allergy Clin Immunol **126**(3): 491-7.

BACKGROUND: Few studies have examined the effects of in utero smoke exposure (IUS) on lung function in children with asthma, and there are no published data on the impact of IUS on treatment outcomes in children with asthma. OBJECTIVES: To explore whether IUS exposure is associated with increased airway responsiveness among children with asthma and whether IUS modifies the response to treatment with inhaled corticosteroids (ICSs). METHODS: To assess the impact of parent-reported IUS exposure on airway responsiveness in childhood asthma, we performed a repeated-measures analysis of methacholine PC(20) data from the Childhood Asthma Management Program, a 4-year, multicenter, randomized, double-masked, placebo-controlled trial of 1041 children age 5 to 12 years comparing the long-term efficacy of ICS with mast cell stabilizing agents or placebo. RESULTS: Although improvement was seen in both groups, children with asthma and IUS exposure had on average 26% less of an improvement in airway responsiveness over time compared with unexposed children (P = .01). Moreover, while children who were not exposed to IUS who received budesonide experienced substantial improvement in PC(20) compared with untreated children (1.25-fold increase; 95% CI, 1.03-1.50; P = .02), the beneficial effects of budesonide were attenuated among children with a history of IUS exposure (1.04-fold increase, 95% CI, 0.65-1.68; P = .88). CONCLUSION: In utero smoke exposure reduces age-related improvements in airway responsiveness among children with asthma. Moreover, IUS appears to blunt the beneficial effects of ICS use on airways responsiveness. These results emphasize the importance of preventing this exposure through smoking cessation counseling efforts with pregnant women.

Kelly, H. W., A. L. Sternberg, et al. (2012). "Effect of inhaled glucocorticoids in childhood on adult height." N Engl J Med **367**(10): 904-12.

BACKGROUND: The use of inhaled glucocorticoids for persistent asthma causes a temporary reduction in growth velocity in prepubertal children. The resulting decrease in attained height 1 to 4 years after the initiation of inhaled glucocorticoids is thought not to decrease attained adult height. METHODS: We measured adult height in 943 of 1041 participants (90.6%) in the Childhood Asthma Management Program; adult height was determined at a mean (+/-SD) age of 24.9+/-2.7 years. Starting at the age of 5 to 13 years, the participants had been randomly assigned to receive 400 mug of budesonide, 16 mg of

nedocromil, or placebo daily for 4 to 6 years. We calculated differences in adult height for each active treatment group, as compared with placebo, using multiple linear regression with adjustment for demographic characteristics, asthma features, and height at trial entry. RESULTS: Mean adult height was 1.2 cm lower (95% confidence interval [CI], -1.9 to -0.5) in the budesonide group than in the placebo group (P=0.001) and was 0.2 cm lower (95% CI, -0.9 to 0.5) in the nedocromil group than in the placebo group (P=0.61). A larger daily dose of inhaled glucocorticoid in the first 2 years was associated with a lower adult height (-0.1 cm for each microgram per kilogram of body weight) (P=0.007). The reduction in adult height in the budesonide group as compared with the placebo group was similar to that seen after 2 years of treatment (-1.3 cm; 95% CI, -1.7 to -0.9). During the first 2 years, decreased growth velocity in the budesonide group occurred primarily in prepubertal participants. CONCLUSIONS: The initial decrease in attained height associated with the use of inhaled glucocorticoids in prepubertal children persisted as a reduction in adult height, although the decrease was not progressive or cumulative. (Funded by the National Heart, Lung, and Blood Institute and the National Center for Research Resources; CAMP ClinicalTrials.gov number, NCT00000575.).

Vogelmeier, C., I. Naya, et al. (2012). "Budesonide/formoterol maintenance and reliever therapy in Asian patients (aged >/=16 years) with asthma: a sub-analysis of the COSMOS study." Clin Drug Investig **32**(7): 439-49.

BACKGROUND: The combination of an inhaled corticosteroid (ICS), budesonide, and a rapid long-acting beta(2)-agonist (LABA), formoterol, in a single inhaler for use as maintenance and reliever therapy (Symbicort Turbuhaler SMART) effectively achieves a high level of asthma control and reduces exacerbations and asthma-related hospitalizations. The COSMOS study, a multinational, 12-month study (N = 2143), compared budesonide/formoterol maintenance and reliever therapy with salmeterol/fluticasone propionate plus as-needed salbutamol, allowing physicians to modify maintenance doses of both combinations according to routine clinical practice. OBJECTIVE: The aim of this post hoc sub-group analysis of the COSMOS study is to provide focused data on budesonide/formoterol maintenance and reliever therapy compared with salmeterol/fluticasone propionate plus as-needed salbutamol in patients (aged >/=16 years) enrolled across Asian countries, specifically China, Korea, Taiwan and Thailand. METHODS: This sub-analysis of the COSMOS study concerns all 404 randomized patients >/=16 years of age (mean forced expiratory volume in 1 second [FEV(1)] 69.1%) who were recruited from Asian countries. Patients received either budesonide/formoterol (Symbicort Turbuhaler SMART, n = 198), starting dose 160 mg/4.5 mg two inhalations twice daily (bid) [plus additional as-needed inhalations], or salmeterol/fluticasone propionate (Seretide((R)) Diskus((R)), n = 206), starting dose 50 mg/250 mg bid (plus salbutamol [Ventolin((R))] as needed). Maintenance doses could be titrated by clinicians after the first 4 weeks (budesonide/formoterol maintenance plus as needed, n = 198; salmeterol/fluticasone propionate plus salbutamol, n = 206). To allow for free adjustment in maintenance doses in both arms, the trial was performed open-label; maintenance doses could be titrated by clinicians after the first 4 weeks. The time to first severe exacerbation (defined as deterioration in asthma resulting in hospitalization/emergency room treatment, oral corticosteroids for >/=3 days or unscheduled visit leading to treatment change) was the primary variable. RESULTS: The

time to first severe exacerbation was prolonged in patients using maintenance plus as-needed budesonide/formoterol compared with salmeterol/fluticasone propionate plus salbutamol (log-rank p = 0.024). The risk of a first exacerbation was reduced by 44% (hazard ratio 0.56; 95% confidence interval [CI] 0.32, 0.95; p = 0.033) in patients using the adjusted budesonide/formoterol regimen versus titrated salmeterol/fluticasone propionate. The overall exacerbation rates were 0.16 versus 0.26 events/patient-year, respectively, with a 38% reduction (rate ratio 0.62/patient/year; 95% CI 0.41, 0.94; p = 0.024) in favour of the budesonide/formoterol regimen. Compared with baseline, both regimens provided clinically relevant improvements in asthma control, quality of life and FEV(1); no statistically significant differences between the treatment groups were observed. Mean adjusted (standard deviation) ICS dose (expressed as beclomethasone dose equivalents) during treatment, including as-needed budesonide doses, was 944 (281) and 1034 (394) mug/day, respectively, in patients using maintenance plus as-needed budesonide/formoterol compared with salmeterol/fluticasone propionate. CONCLUSION: In patients (aged >/=16 years) enrolled from Asian countries as part of the COSMOS study, the budesonide/formoterol maintenance and reliever regimen was associated with a lower future risk of exacerbations versus the physicians' free choice of salmeterol/fluticasone propionate dose plus salbutamol. Single inhaler combination treatment with maintenance plus as-needed budesonide/formoterol was also at least as efficacious as salmeterol/fluticasone propionate dose plus salbutamol in improving current asthma control.

Wang, L., C. S. Hollenbeak, et al. (2011). "Cost-effectiveness analysis of fluticasone versus montelukast in children with mild-to-moderate persistent asthma in the Pediatric Asthma Controller Trial." J Allergy Clin Immunol **127**(1): 161-6, 6 e1.

BACKGROUND: Cost-effectiveness analyses of asthma controller regimens for adults exist, but similar evaluations exclusively for children are few. OBJECTIVE: We sought to compare the cost-effectiveness of 2 commonly used asthma controllers, fluticasone and montelukast, with data from the Pediatric Asthma Controller Trial. METHODS: We compared the cost-effectiveness of low-dose fluticasone with that of montelukast in a randomized, controlled, multicenter clinical trial in children with mild-to-moderate persistent asthma. Analyses were also conducted on subgroups based on phenotypic factors. Effectiveness measures included (1) the number of asthma-control days, (2) the percentage of participants with an increase over baseline of FEV(1) of 12% or greater, and (3) the number of exacerbations avoided. Costs were analyzed from both a US health care payer's perspective and a societal perspective. RESULTS: For all cost-effectiveness measures studied, fluticasone cost less and was more effective than montelukast. For example, fluticasone treatment cost $430 less in mean direct cost (P < .01) and resulted in 40 more asthma-control days (P < .01) during the 48-week study period. Considering sampling uncertainty, fluticasone cost less and was more effective at least 95% of the time. For the high exhaled nitric oxide (eNO) phenotypic subgroup (eNO >/=25 ppb) and more responsive PC(20) subgroup (PC(20) <2 mg/mL), fluticasone was cost-effective compared with montelukast for all cost-effectiveness measures, whereas not all the effectiveness measures were statistically different for the other 2 phenotypic subgroups. CONCLUSION: For children with mild-to-moderate persistent asthma, low-dose fluticasone had lower cost and higher effectiveness compared with montelukast,

especially in those with more airway inflammation, as indicated by increased levels of eNO and more responsivity to methacholine.