Evidence Table 11. Pharmacologic Therapy: Inhaled Corticosteroids—Combination Therapy

Abbreviations used in table:

AE	**adverse event**
AM	**morning**
ECP	**eosinophil cationic protein**
FEV_1	**forced expiratory volume in 1 sec**
ICS	**inhaled corticosteroid**
ITT	**intent-to-treat**
LABA	**long-acting beta$_2$-agonist**
LTRA	**leukotriene receptor antagonist**
OCS	**oral corticosteroids**
OR	**odds ratio**
PEF	**peak expiratory flow**
RR	**relative risk**
SABA	**short-acting beta$_2$-agonist**
SAE	**serious adverse event**
SMD	**standardized mean difference**
95% CI	**95 percent confidence interval**
WMD	**weighted mean difference**

*** indicates primary outcome**

Evidence Table 11. Pharmacologic Therapy: Inhaled Corticosteroids—Combination Therapy

ICS + LABA vs. ICS

Citation (Sponsor)	Study Design	Purpose/ Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (If Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Run-in/Intervention/ Off-Treatment Follow-up	Lung Function	Exacerbations/Symptoms	Safety
Lemanske et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol. JAMA 2001;285(20):2594–2603. (National Heart, Lung, and Blood Institute)	Multicenter, randomized, controlled, triple-blinded, double-dummy, parallel group (6 National Institutes of Health-sponsored, university-based ambulatory care centers)	To determine whether ICS therapy can be reduced or eliminated in patients with persistent asthma after adding a long-acting beta$_2$-agonist to their treatment regimen	175 (167)	(at end of salmeterol introduction phase) Age: 12–65 yr, mean = 35 yr Gender: 49% male, 51% female Ethnicity: 64% White, 22% Black, 8% Hispanic, 6% other	(at end of salmeterol introduction phase) Persistent asthma FEV_1 mean = 2.5 L before salmeterol FEV_1 % pred. mean = 73.6 before salmeterol Morning PEF mean = 431.2 L/min Evening PEF mean = 437.5 L/min PEF variability mean = 0.12	Arm 1: Triamcinolone + salmeterol xinafoate, (n=154; 148 completed and randomized to Arms 1a and 1b) Arm 1a: Triamcinolone + salmeterol (S+), (n=74); 71 completed and continued with triamcinolone + salmeterol, (69 completed) Arm 1b: Triamcinolone + salmeterol (S–), (n=74); 71 completed and assigned to placebo triamcinolone + salmeterol), (n=66 completed) Arm 2: Triamcinolone + placebo salmeterol, (n=21); 19 completed and assigned to triamcinolone + placebo salmeterol (P–); 18 completed and assigned to placebo triamcinolone + placebo salmeterol	Arm 1: 400/42 mcg twice daily Arm 1a: 400/42 mcg twice daily Arm 1b: 200/42 mcg twice daily Arm 2: 42 mcg twice daily salmeterol, 400 mcg twice daily triamcinolone, placebo	2-week salmeterol introduction phase, 8-week triamcinolone reduction phase, and 8-week triamcinolone elimination phase after a 6-week run-in period Albuterol used for rescue therapy as needed. Randomization at Phase II was by ethnic group, sex, and age.		*For reduction phase, proportion of treatment failures was 2.8% (95% CI 0% to 7%) in S+ group and 8.3% (95% CI 2% to 15%) in the S– group. At end of elimination phase, treatment failure occurred in 46.3% (95% CI 34% to 59%) of S– group and 13.7% (95% CI 5% to 22%) of S+ group. RR of treatment failure during reduction phase for S– vs. S+ was 2.2 (95% CI 0.5 to 9.2, p = 0.27; Cox regression model), and during the elimination phase, RR was 4.3 (95% CI 2.0 to 9.2, p <0.001).	
Ni et al. Addition of inhaled long-acting beta$_2$-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults. Cochrane Database Syst Rev 2005;(2): CD005307.	Meta-analysis of randomized controlled trials; 4 rated as high quality, 3 as moderate quality, and 1 as poor quality	To compare the efficacy of initiating anti-inflammatory therapy using the combination of ICS+LABA as compared to ICS alone in steroid-naïve children and adults with persistent asthma	8 trials with 1,061 subjects (1 trial had 2 control and 2 intervention groups and was counted as 2 trials, resulting in 9 trials for the meta-analysis).	Age Mean ranged from 12–77 yr. Note: None of the 5 trials indicated the proportions who were 12–18 years of age. Gender Males ranged from 25% to 61%.	Mild (5 trials) to moderate (4 trials) airway obstruction Mean FEV_1 % pred. ranged from 66% to 96%. Naïve to both LABA and ICS	Arm 1 ICS+LABA Arm2 ICS	ICS dose included 200–400 mcg/day of beclomethasone or equivalent (5 trials) and 800–1,000 mcg/day of beclomethasone or equivalent (4 trials). ICS was beclomethasone (2 trials), triamcinolone (1 trial), or fluticasone (4 trials). LABA was salmeterol xinafoate 50 mcg twice daily (7 trials) and formoterol 12 mcg twice daily (2 trials).	Duration was 4–8 weeks (4 trials), 12 weeks (2 trials), 24 weeks (1 trial), and 52 weeks (2 trials).	Difference favored LABA for improvement from baseline in FEV_1 in standard deviation units (SMD 0.29, 95% CI 0.17 to 0.42; 0.42, p <0.00001; 6 trials), in mL (WMD 210 mL, 95% CI 120 to 300; 5 trials), and in morning PEF (WMD 21.4 L/min, 95% CI 15.36 to 27.45, p <0.0001; 5 trials). No difference in change in PEF variability occurred (SMD –0.04, 95% CI –0.50 to 0.41; 4 trials).	*No difference occurred in risk of exacerbation requiring systemic corticosteroids (RR 1.19, 95% CI 0.75 to 1.88; 3 trials). Reduction in symptom score occurred for ICS+LABA vs. ICS (SMD –0.31, 95% CI –0.48 to –0.13; p = 0.02; 4 trials), and improvement occurred in percentage of symptom-free days (WMD 10.74%, 95% CI 1.86 to 19.62; p=0.02; 3 trials). No difference was found in use of rescue SABAs.	No difference was found between groups in risk of withdrawal, withdrawal due to poor asthma control, risk of AE, and withdrawal due to AE.

Citation (Sponsor)	Study Design	Purpose/Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (If Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Exacerbations/Symptoms	Safety
Ni et al. Long-acting beta$_2$-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Cochrane Database Syst Rev 2005;(4):CD0055355. (Canadian Cochrane Network, McGill University, Canada)	Meta-analysis of randomized controlled trials; 24 were parallel group designs and 2 were crossover studies. (23 of the 26 trials rated of high quality using Jadad scale.)	To assess the safety and clinical benefit on asthma control resulting from the addition of LABAs to ICSs in asthmatic patients and to examine whether the benefit was influenced by age, severity of airway obstruction, dose of ICSs, use of 1 or 2 devices to deliver combination therapy, the dose and type of LABA, and the duration of intervention	26 trials with 31 comparisons; sample sizes ranged from 16 to 663, with 8,147 total participants.	Age In 18 adult trials, mean ages ranged from 35 to 48 yr; in 8 pediatric studies, mean age ranged from 8.5 to 14 yr. Gender Males ranged from 30% to 71%.	Moderate (17 trials) or mild (8 trials); unreported in 1 trial In 23 trials, participants had inadequate control; in 3 trials, participants were asymptomatic and well-controlled. FEV_1 % pred. mean ranged from 51% to 79% in 17 trials; mean was $\geq$80% in 8 trials and unreported in 1 trial.	Arm 1 LABA + ICS Salmeterol (14 comparisons) or and formoterol (17 comparisons). Arm 2 ICS alone Budesonide (7 trials), beclomethasone (3 trials), budesonide or beclomethasone (1 trial), and uticasone propionate (4 trials); 11 trials failed to specify the ICS.	Most trials used a usual dose of LABA (salmeterol, 50 mcg twice daily; or formoterol, 6 or 12 mcg twice daily). Three trials used 100 mcg twice daily of salmeterol or 24 mcg twice daily of formoterol. One comparison used the 2 options only once daily. Twelve used low-dose ICS (200–400 mcg/day of beclomethasone or equivalent, 8 used a medium dose of ICS (401–799 mcg/day of beclomethasone or equivalent), and 3 comparisons used a high dose of ICS (800 mcg/day of beclomethasone or equivalent).	Nineteen trials used 2 inhaler devices, 5 comparisons used 1 device, 1 tested both 1 and 2 devices, and 1 trial failed to report the number of devices. Duration of intervention was 12–16 weeks (13 trials), 4–8 weeks (6 trials), or 24–54 weeks (7 trials).	Addition of LABA improved FEV_1 (WMD 170 mL, 95% CI 110 to 240, p <0.001).	*Addition of LABA reduced the risk of experiencing $\geq$1 exacerbations requiring systemic corticosteroids (RR 0.81, 95% CI 0.73 to 0.90, p <0.00005) and increased the proportion of symptom-free days (WMD 17%, 95% CI 12 to 22, p=0.00001; 6 trials) and rescue-free days (WMD 19%, 95% CI 12 to 26, p <0.001; 2 trials). Every 10% increase in baseline FEV_1 was associated with a 14% increased protection (RR 0.86, 95% CI 0.74 to 1.0) from exacerbations with LABA over placebo.	No difference was found in risk of overall AE (RR 0.98, 95% CI 0.92 to 1.05) or withdrawals due to AE (RR 1.29, 95% CI 0.96 to 1.75).
Weiler et al. Effect of fluticasone/salmeterol administered via a single device on exercise-induced bronchospasm in patients with persistent asthma. Ann Allergy Asthma Immunol 2005;94(1):65–72. (GlaxoSmithKline)	Multicenter, randomized, double-blind, parallel-group design (40 sites in US)	To evaluate the effectiveness of regular treatment with fluticasone/salmeterol (F/S) vs. fluticasone alone (F) administered via Diskus on preventing exercise-induced bronchospasm in symptomatic adolescents and adults receiving moderate-dose ICSs for the treatment of persistent asthma	192 (ITT analysis)	Age 12–50 yr, mean = 29 yr Gender 39% male, 61% female Ethnicity 72% White, 20% Black, 5% Hispanic, 3% other Smoking 85% had never used tobacco. None had smoked in past year. None had more than 10 pack-years of smoking.	Persistent asthma History of asthma $\geq$15 yr, 59% FEV_1 mean = 2.72L FEV_1 % pred. mean = 78 Maximal postexercise decline in FEV_1, mean = 31.6 Asthma-related emergency care in previous year, 15% Asthma-related hospitalization in previous year, 5% 82% were using fluticasone before enrollment.	Arm 1 Fluticasone + salmeterol (F/S) (n=102; 98 completers) Arm 2 Fluticasone (F) (n=90; 87 completers)	250/50 mcg twice daily via Diskus 250 mcg twice daily via Diskus	4 weeks after 2- to 5 week run-in Albuterol as reliever medication	*At day 1, 1 and 8.5 hr after first dose, maximal decline in FEV_1 was 11.4% and 11.6%, respectively, for F/S and 20.0% and 12.6%, respectively, for F (p <0.001 and p=0.44). At week 4, 1 and 8.5 hr after last dose, maximal decline in FEV_1 was 10.9% and 8.9%, respectively, for F/S and 18.4% and 12.9%, respectively, for F (p <0.01 for both). F/S vs. F had greater increase in morning PEF (19.2 L/min vs. 6.3 L/min, p=0.03).	F/S vs. F had greater increase in percentage of rescue-free days (15.8% vs. 7.6%, p = 0.02).	7% of F/S group and 4% of F group reported AE that was considered drug-related. No SAE was reported.

ICS + LTRA vs. ICS

Citation (Sponsor)	Study Design	Purpose/Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (If Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Post-Intervention/DB Treatment Followup	Lung Function	Vital Signs/Cardiovascular/Clinical Laboratory Values	Exacerbations/Symptoms	Safety
Robinson et al. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomized double-blind placebo-controlled trial. Lancet 2001; 357(9273):2007-2011.	Randomized, double-blind, placebo-controlled crossover	To assess whether montelukast, an LTRA, can improve symptoms or lung function in patients with chronic asthma with symptoms already taking corticosteroids	100 (72)	Age 22–79 yr, mean = 52.3 yr Gender 38% male, 62% female Ethnicity Not reported Smoking 3% current smokers, 20% exsmokers, 67% never smokers	Moderate or severe asthma FEV_1 % pred. median = 59.7 FVC % pred., median = 89.9 PEF % pred., 63.6 23% had some irreversible airflow obstruction. All were taking ICS: 12% beclomethasone propionate, 23% budesonide, 54% fluticasone propionate.	Arm 1 Montelukast followed by placebo (n=53; 50 completers) Arm 2 Placebo followed by montelukast (n=47; 41 completers)	10 mg montelukast sodium and matched placebo capsules	2 weeks followed by crossover, with no washout period	No effects for morning or evening PEF or diurnal variation in PEF No difference in FEV_1 measured at the clinic		No differences in symptom scores or use of rescuer inhaled $beta_2$-agonist use There were 4 responders to montelukast and 7 responders to placebo, defined as ≥15% in mean peak flow readings.	31% reported AE: 18% while on active treatment and 14% while on placebo.
Simons et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. J Pediatr 2001; 128(5):694–698. (Merck & Co., Inc.)	Multicenter, randomized, double-blind, crossover design	To test the hypothesis that adding montelukast to budesonide would improve asthma control in children with inhaled glucocorticoid-dependent persistent asthma.	279 (251)	Age 5–15 yr, mean = 10.4 yr Gender 67% male, 33% female Ethnicity 83% White, 10% Asian, 6% Hispanic, 1% other Height 109–182 cm, mean = 144 cm	Persistent asthma FEV_1 = 1.8 L FEV_1 % pred. mean = 77.7 FEV_1 reversibility mean = 18.1% FVC % pred. median = 89.9 Morning PEF mean = 315 L/min Mean $beta_2$-agonist use = 2.9 puffs/day Treated with inhaled glucocorticoid for ≥6 weeks	Arm 1 Montelukast + budesonide followed by placebo + budesonide Arm 2 Placebo + budesonide followed by montelukast + budesonide (study n=279 randomized; n=264 completers)	5 mg chewable montelukast tablet or matching placebo, 1 daily at bedtime + 200 mcg budesonide twice daily	Two 4-week periods with no washout period During 4-week run-in, received open-label 200 mcg budesonide twice daily	*Mean increase in FEV_1 was 4.6% during montelukast treatment and 3.3% during placebo (diff 1.3%, 95% CI –0.1 to 2.7, p=0.062). Over last 14 days of each period, montelukast vs. placebo difference was 9.7 L/min for morning PEF (95% CI 1.4 to 18.1, p=0.023) and 10.7 L/min for evening PEF (95% CI 2.4 to 19.0, p=0.012).	Blood eosinophil decreased by 15% for montelukast group vs. 7% for placebo group (p <0.001).	Decrease in $beta_2$-adrenergic agonist use was greater for montelukast vs. placebo (p=0.013). Percent of asthma exacerbation days was lower during montelukast than placebo treatment (12.2% vs. 15.9%, p <0.001). Montelukast and placebo did not differ in quality of life measurement.	No difference occurred in incidence of possible drug-related AE (3% montelukast and 3% placebo treatment).

ICS + LABA vs. ICS + LTRA

Citation (Sponsor)	Study Design	Purpose/Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Exacerbations/Symptoms	Safety
Vaquerizo et al. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. Thorax 2003; 58(3):204–210. (Merck Sharp & Dohme, Spain)	Multicenter, randomized, double-blind, parallel group design (80 hospital centers in Spain)	To evaluate the efficacy of adding oral montelukast to a constant dose of inhaled budesonide for treating adult patients with mild to moderate asthma	639 (573 completed; ITT analysis based on 625)	Age 18–79 yr, mean = 43 yr Gender 62% male, 38% female Ethnicity Not reported Smoking All nonsmokers, 33% exsmokers	Mild-to-moderate asthma Duration mean = 13.8 yr FEV_1 mean = 2.5L FEV_1 % pred. mean = 81 PEF mean = 369 L/min Daily beta-agonist use, 3.2 puffs/day Budesonide, mcg/day: 400–800, 67% 801–1,200, 5% 1,201–1,600, 27%	Arm 1 Montelukast (n=313; 308 completers) Arm 2 Placebo (n=326; 317 completers)	10 mg at bedtime	16 weeks after 2-week single-blind placebo run-in Randomization was by stratified budesonide dose level. Salbutamol was used as needed throughout.	Morning PEF changed 11.3 in placebo and 16.9 in montelukast groups (p=0.05). FEV_1 increased 2.49% in placebo and 2.63% in montelukast groups (p=0.91).	*Median asthma exacerbation days were lower with montelukast vs. placebo (3.1% vs. 4.8%, p=0.03), with relative reduction in risk 21.9% (95%CI 20.1 to 23.6). Median asthma-free days were greater with montelukast than placebo (66.1% vs. 42.3%, p=0.001) with relative reduction in risk for "day not free" of 18% (95% CI 16.8 to 19.2). Percent of patients with nocturnal awakenings was lower with montelukast (25.6% vs. 32.2%, p=0.01). Decrease in $beta_2$-agonist use was lower in the montelukast group on the 1st day compared with placebo and remained so over the 16 weeks (p=0.05).	Eight patients in placebo group and 6 in the montelukast group discontinued treatment because of clinical AE. Incidence of AE did not differ between groups (40.6% with placebo and 44.2% with montelukast, p=0.37).
Nelson et al. Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. J Allergy Clin Immunol 2000; 106(6):1088–1095. (GlaxoWellcome Inc.)	Multicenter, randomized, double-blind, double-dummy, parallel group (39 sites in United States)	To compare the efficacy and safety of fluticasone propionate/salmeterol combination (FP/S) through the Diskus inhaler versus montelukast added to fluticasone propionate (FP/M) in patients whose symptoms were suboptimally controlled with ICS therapy	487 (ITT analysis)	Age 15–83 yr, mean = 41.6 yr Gender 39% male, 61% female Ethnicity 87% White, 13% other	Asthma for ≥6 months Taking low-to-moderate doses of ICS for ≥30 days before screening FEV_1, mean = 2.39 L FEV_1 % pred., mean = 70.4 Morning PEF, mean = 395 L/min Evening PEF, mean = 415 L/min Average use of ≥4 puffs/day of albuterol	Arm 1 Fluticasone propionate + salmeterol + placebo montelukast (FP/S) (n=222; 198 completers) Arm 2 Fluticasone propionate + montelukast (FP/M) (n=225; 196 completers)	100/50 mcg in 1 inhalation twice daily 100 mcg in 1 inhalation twice daily + 10 mg once daily	12 weeks after 3-week run-in Albuterol was used for relief of symptoms.	*Overall morning PEF improved in FP/S vs. FP/M (+24.9 L/min vs. +13.0 L/min, p <0.001). Evening PEF improved in FP/S vs. FP/M (+18.9 L/min vs. +9.6 L/min, p <0.001). FEV_1 improved in FP/S vs. FP/M (+0.34 vs. +0.20, p <0.001).	Greater increase occurred in percentage of days with no albuterol use in FP/S group vs. FP/M group (+26.3 vs. +19.1, p=0.032). Reduction occurred in total albuterol use occurred for FP/S group vs. FP/M group (–1.55 vs. –1.14 puffs/day, p=0.014).	AE profiles were similar. Three SAE, occurred, but none were drug-related.
Fish et al. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. Chest 2001;120(2): 423–430. (GlaxoWellcome Inc.)	Multicenter, randomized, double-blind, double-dummy, parallel group (2 trials at 71 clinical centers in United States and Puerto Rico)	To compare the long-acting bronchodilator salmeterol with the LTRA montelukast as add-on therapy for patients who remain symptomatic while receiving low-to-intermediate dosages of ICSs	948 (948)	Age 15–83 yr, mean = 39.7 yr Gender 38.8% male, 61.2% female Ethnicity 85.0% White, 7.5% Black, 5.6% American Hispanic, 1.9% other	Mild-to-moderate persistent asthma for ≥6 months Duration, 24.7% <10 yr, 75.3% ≥10 yr FEV_1, mean = 2.3 L FEV_1 % pred., mean = 68.3 Symptomatic >6 weeks prior to screening Constant dosage of ICS for 30 days prior to screening Mean (range) ICS use: 482 mcg (44–1,760) fluticasone, 552 mcg (100–1,600) triamcinolone, 265 mcg (84–672) beclomethasone, 651 mcg (84–1,200) budesonide, 1,077 mcg (250–2,000) flunisolide	Arm 1 Salmeterol xinafoate via multidose powder inhaler + ICS (S) (n=476) Arm 2 Montelukast + ICS (M) (n=472)	50 mcg via multidose powder inhaler + usual dose ICS 10 mg/day orally + usual dose ICS	12 weeks after 7-day to 14-day run-in period Albuterol inhaler for relief of breakthrough symptoms	*S group had greater increase in morning PEF vs. M (35.0 L/min vs. 21.7 L/min, p <0.001). Improvements were noted within 1st week and remained over 12 treatment weeks.	S group had greater increase in percentage of symptom-free days vs. M group (24% vs. 16%, p <0.001). Daytime symptom scores decreased by 39% in S group vs. 31% in M group (p=0.039). Supplemental albuterol use was less in S group vs. M group (42% vs. 35% for daytime; 51% vs. 40% for nighttime; p <0.012). Greater reduction in nighttime awakenings/ week occurred in S group vs. M group (1.42 vs. 1.32, p=0.015).	Patients with drug-related AE were 7% in S group and 6% in M group. No drug-related SAE occurred.

Citation (Sponsor)	Study Design	Purpose/Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (If Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Vital Signs/Cardiovascular/Clinical Laboratory Values	Exacerbations/Symptoms	Safety
Nelson et al. Comparison of inhaled salmeterol and oral zafirlukast in asthmatic patients using concomitant inhaled corticosteroids. MedGenMed 2001;3(4):3.	Multicenter, randomized, double-blind, double-dummy, parallel-group, clinical trial (data from 2 trials) (54 clinical centers)	To compare the effects of the addition of salmeterol vs. the addition of zafirlukast to a regimen of ICSs	429 (429)	Age 12–89 yr, mean = 40 yr Gender 44% male, 56% female Ethnicity 87.9% Caucasian, 6.3% Black, 1.4% Asian, 4.4% American Hispanic	Mild to moderate persistent asthma Diagnosis for ≥6 months Duration of asthma: 24% <10 yr, 76% ≥10 yr FEV_1 before bronchodilation, mean = 2.27 L FEV_1 % pred., 66.2 Stable dose of ICS taken for at least 30 days; dosages were not recorded.	Arm 1 Salmeterol xinafoate (S) (n=214) Arm 2 Oral zafirlukast (Z) (n=215)	42 mcg (2 puffs) twice daily via metered dose inhaler + stable dose of ICS 20 mg twice daily + stable dose of ICS	4 weeks after 7- to 14-day run-in period Albuterol inhaler was used on an as-needed basis.	*S produced greater increase in mean morning PEF (28.8 L/min) and evening PEF (21.8 L/min) vs. Z (13.0 L/min and 11.2 L/min, p <0.001 and p=0.004, respectively). Decrease in mean PEF differential was greater for S vs. Z (–8.1 L/min vs. –3.7 L/min, p=0.022). Greater improvement in PEF occurred for S group vs. Z group at all treatment weeks. Increase in mean predose FEV_1 was greater for S group vs. Z group at week 1 (0.23 vs. 0.16, p <0.05); no difference occurred at week 4.		Daytime symptom scores decreased by 35% in S group vs. 21% in Z group (p=0.002). S group vs. Z group had greater increase in percentage of symptom-free days (20% vs. 9%, p <0.001) and greater reduction in sleep symptoms (45% vs. 27%, p=0.003) and nighttime awakenings (45% vs. 25%, p=0.021). Daytime and nighttime albuterol use decreased by 41% and 42% in S group compared with 25% and 16% in Z group (p=0.019 and p <0.001, respectively). Improvement in AQLQ was greater in S group vs. Z group (p <0.009). In each group, 8 patients (3.7%) experienced exacerbations.	Percentage reporting ≥1 AE in each group was 39%. In each group, 7 patients (3.3%) withdrew due to AE; 5 AE in the Z group were study-drug related.
Bjermer et al. Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. BMJ 2003; 327(7420):891. (Merck & Co.)	Multicenter, randomized, double-dummy, double-blind, parallel group (148 sites in 37 countries)	To assess the effect of montelukast versus salmeterol added to inhaled fluticasone propionate on asthma exacerbation in patients whose symptoms are inadequately controlled with fluticasone alone	1490 (ITT analysis)	Age 15–72 yr; mean = 41.1 yr Gender 45% male, 55% female Ethnicity 77.6% White, 0.7% Black, 7.1% Asian, 14.6% other	Chronic asthma for ≥1 yr FEV_1 mean = 2.4 L FEV_1 % pred., mean = 72.0 FEV_1 % reversibility, 18.6 PEF, mean = 386 L/min Mean use of $beta_2$-agonist = 3.3 puffs/day Mean number of nocturnal awakenings = 2.6 days/week	Arm 1 Montekulast (M/F) (n=747; 83.3% completed) Arm 2 Salmeterol (S/F) (n=743; 85.2% completed)	10 mg in evening + 100 mcg fluticasone twice daily 50 mcg twice daily +100 mcg fluticasone twice daily	48 weeks after 4-week run-in period	No difference between groups in change in FEV_1 (0.11 vs. 0.19). M/F group showed smaller decrease in percent reversibility in FEV_1 (–7.54 vs. –11.26, p <0.001). S/F group showed larger increase in PEF (34.59 vs. 17.73, p <0.001).	M/F treatment reduced peripheral blood eosinophil counts from baseline (–0.04 10^3/mcL, p <0.001) but S/F treatment did not (–0.01, p >0.05).	*20.1% of M/F group vs. 19.1% of S/F group had >1 exacerbation; risk ratio, 1.05 (95% CI 0.86–1.29). No difference was found in time to 1st asthma exacerbation (p=0.599) or number per year. No difference was found in decreased nocturnal awakenings (–1.68 vs. –1.74, p=0.06).	AE were reported by 71.0% of M/F group and 72.4% of S/F group. S/F group had a higher incidence of drug-related AE (7.4% vs. 4.6%, p=0.022).

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Ringdal et al. The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. Respir Med 2003;97(3):234–241. (GlaxoSmithKline)	Multicenter, randomized, double-blind, double-dummy, parallel-group study (114 centers in 19 countries)	To compare the clinical effect of the addition of either salmeterol or montelukast to treatment with an ICS, fluticasone propionate, in adults with asthma who are symptomatic despite treatment with ICSs	806 (805 for safety population; 725 for ITT analysis)	Age 14–79 yr, mean = 43 yr Gender 45% male, 55% female Smoking 6.2% current smoker, 22.6% exsmoker, 71.2% nonsmoker	FEV_1, mean = 2.60 L FEV_1 % pred., mean = 75 Reversibility mean = 27.2% Morning PEF mean = 369 L/min All received ICS (400–1,000 mcg/day of beclomethasone dipropionate, budesonide, or flunisolide; or 200–500 mcg/day of fluticasone propionate) for at least 4 weeks before the study.	Arm 1 Fluticasone propionate + oral montelukast (FP+M) (n=369 in ITT analysis) Arm 2 Salmeterol/fluticasone propionate + oral placebo (SF) (n=356 in ITT analysis)	100 mcg twice daily + 10 mg once daily 50/100 mcg twice daily	12 weeks treatment + 2-week followup after 4-week run-in period Salbutamol was used for rescue relief as required. Other regular asthma medication continued at constant dose.	*Adjusted mean increase in morning PEF was greater in SF group vs. FP+M group over 12 weeks (36 L/min vs. 19 L/min; diff. 17 L/min, 95% CI 12 to 22 L/min, p <0.05). Onset of improvement was faster in SF group, with difference at 24 hours (diff 16.9 L/min, 95% CI 11.9 to 32 L/min, p=0.03). Increase in FEV_1 was greater for SF group vs. FP+M group (0.26 vs. 0.17; diff. 0.11 L, 95% CI 0.06 to 0.16 L, p <0.005).	SF group was more likely to have symptom-free day during study period (OR 1.32, 95% CI 1.05 to 1.65, p <0.04) and more likely to have rescue-free day (OR 1.39, 95% CI 1.02 to 1.64, p=0.03). 9.6% of SF group vs. 14.6% of FP+M group had at least 1 exacerbation (p <0.05). Time to 1st exacerbation was longer in SF group than in FP+M group (p <0.05).	Similar incidence of AE occurred (44% of SF group vs. 42% of FP+M group). No drug-related SAE occurred.
Ceylan et al. Addition of formoterol or montelukast to low-dose budesonide: an efficacy comparison in short- and long-term asthma control. Respiration 2004;71(6): 594–601.	Randomized comparison trial	To investigate whether the addition of formoterol or montelukast to a low dose of ICS was effective in the control of asthma in moderately persistent asthma cases and to determine which drug should be preferred	48 (ITT analysis)	Age ≥15 yr, mean = 36.1 yr Gender 52.5% male, 47.5% female Smoking No smokers	Moderately persistent asthma Persistent symptoms for ≥1 yr Duration of asthma, mean = 8.6 yr History of allergic rhinitis, 65% Use of ICS for ≥6 months Morning PEF, mean = 264.6 FEV_1, mean = 2.4 L FEV_1 % pred., mean = 70.5 $Beta_2$-agonist use, mean = 2.4 puffs/day	Arm 1 Formoterol + budesonide (FB) (n=20 completers) Arm 2 Montelukast + budesonide (MB) (n=20 completers)	9 mcg twice daily + 400 mcg 10 mcg once daily + 400 mcg	8 weeks after 4-week run-in period Salbutamol, 100 mcg/puff, was allowed for treatment of symptoms.	(Analysis was adjusted for gender, age, and baseline values.) *Morning PEF increased from 266.3 to 320.5 L/min in FB group vs. 262.8 to 293.3 L/min in MB group (diff. of 23.7 L/min increase, p <0.0001). Night PEF increased from 287 to 331.5 L/min in FB group and from 283 to 310 L/min in MB group (diff of 17.5 L/min increase, p <0.001). Improvements in FB group began earlier. FEV_1 change was greater in FB vs. MB group (0.36 vs. 0.19, p <0.001). FEV_1 % pred. change was greater in FB vs. MB group (10.7 vs. 5.6, p <0.001).	(Analysis was adjusted for gender, age, and baseline values.) Decrease in $beta_2$-agonist use was greater in FB group vs. MB group (1.9 vs. 0.5 puffs/day, p <0.001). Decrease in morning symptom scores was greater for FB group vs. MB group (2.6 vs. 0.8, p <0.0001).	Local AE effects potentially related to drugs occurred for 30% of FB group and 20% of MB group.

Citation (Sponsor)	Study Design	Purpose/Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (If Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Randomization/Off-Treatment Follow-up	Lung Function	Vital Signs/Cardiovascular/Clinical Laboratory Values	Exacerbations/Symptoms	Safety
Ilowite et al. Addition of montelukast or salmeterol to fluticasone for protection against asthma attacks: a randomized, double-blind, multicenter study. Ann Allergy Asthma Immunol 2004;92(6):641–648. (Sponsor)	Multicenter, randomized, double-dummy, double-blind, parallel group (132 centers in United States)	To compare montelukast and salmeterol concomitantly administered with inhaled fluticasone, according to the percentage of patients without an asthma attack for 1 year	1,473 (1,452; modified ITT analysis)	Age 14–73 yr, mean = 38.6 yr Gender 39.4% male, 60.6% female Ethnicity 84.1% White, 8.9% Black, 5.2% Hispanic, 1.8% other	Chronic asthma for ≥1 yr FEV_1 % pred., mean = 74.3 FEV_1 % reversibility, 18.6 Mean use of $beta_2$-agonist = 3.5 puffs/day Mean number of nocturnal awakenings = 1.88 days/week Used $beta_2$-agonist, on average, once/day during last 14 days of run-in period Used ICSs daily for at least 8 weeks before first study visit	Arm 1 Montelukast + fluticasone MDI (M/F) (n=743; 734 in analysis; 530 completers) Arm 2 Salmeterol MDI + fluticasone MDI (S/F) (n=730; 718 in analysis; 529 completers)	10 mg/day + 220 mcg/day fluticasone 42 mcg twice daily + 220 mcg/day fluticasone	48 weeks after 4-week run-in period	Montelukast vs. salmeterol treatment reduced % reversibility in FEV_1 (diff. = 4.78, 95% CI 3.89 to 5.67). Salmeterol vs. montelukast treatment increased FEV_1 (diff. 1.98, 95% CI 1.01 to 2.96) and PEF (diff. 14.3, 95% CI 6.4 to 22.1).	Montelukast vs. salmeterol reduced blood eosinophil counts (diff. = –0.04, 95% CI –0.05 to 0.02).	*20% of M/F group and 16.7% of S/F group had asthma attacks (RR=1.20, 95% CI 0.96 to 1.49). Salmeterol vs. montelukast treatment decreased nocturnal awakenings (diff. –0.23, 95% CI –0.36 to –0.10). Albuterol use decreased in both groups, with 0.52 puffs/day less (95% CI 0.36 to 0.68) in the salmeterol group.	Monetlukast and salmeterol groups were comparable in proportion with clinical AE that was possibly or definitely drug related (8.6% vs. 10.0%) and serious (3.0% vs. 3.7%).
Ram et al. Long-acting $beta_2$-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database of Syst Rev 2005;(1):CD003137. (NHS Research and Development UK) NOTE: Meta-analysis includes studies abstracted separately above: Bjermer et al. 2003; Fish et al. 2001; Ilowite et al. 2004; Nelson et al. 2000; and Nelson et al.	Meta-analysis of randomized controlled trials, all rated of high quality	To compare the safety and efficacy of adding LABA versus LTRA in asthmatic patients who remain symptomatic in spite of regular treatment with ICS	8 trials with 5,895 patients	Age All adults; mean ages ranged from 35 to 43	Recurrent or persistent asthma Mean duration of asthma ranged from 10 to 26 years. Moderate airway obstruction ranged from 66% to 76% FEV_1 predicted. Subjects were symptomatic at enrollment. ICS doses at enrollment were <400–560 mcg/day of beclomethasone or equivalent.	Arm 1 ICS+LABA Arm 2 ICS+LTRA	Stable dose of ICS was given throughout study period (average 400–560 mcg/day of beclomethasone or equivalent). LABA was zafirlukast 20 mg twice daily (2 trials) and montelukast 10 mg once daily (6 trials). LTRA was salmeterol 50 mcg twice daily (7 trials) and formoterol 12 mcg twice daily (1 trial).	Intervention periods of 4 weeks (1 trial), 8 weeks (1 trial), 12 weeks (4 trials), and 48 weeks (2 trials).	ICS+LABA vs. ICS+LTRA group showed greater improvement in morning PEF (WMD 15.75 L/min, 95% CI 13.0 to 18.5; 8 trials) and in evening PEF (WMD 11.86 L/min, 95% CI 8.85 to 14.86; 7 trials). Improvement in FEV_1 favored ICS+LABA group (WMD 0.08 L, 95% CI 0.06 to 0.10; 7 trials).		*Risk of exacerbation requiring systemic corticosteroids was lower with ICS+LABA vs. ICS+LTRA (RR 0.83, 95% CI 0.71 to 0.97; 6 trials). ICS+LABA vs. ICS+LTRA showed greater percentage of rescue-free days (WMD 8.96%, 95% CI 4.39 to 13.53; 4 trials), decrease in use of rescue medication with ICS+LABA vs. ICS+LTRA (WMD = –0.37 puffs/day, 95% CI –0.52 to –0.23; 6 trials), improvement in global asthma quality of life (WMD 0.11, 95% CI 0.05 to 0.17; 3 trials), symptom score (SMD –0.18, 95% CI –0.25 to –0.12; 5 trials), and fewer night awakenings (WMD 0.12, 95% CI –0.19 to –0.06; 4 trials).	Risk of withdrawal was reduced for ICS+LABA vs. ICS+LTRA (RR 0.84, 95% CI 0.74 to 0.96; 8 trials), with no difference in withdrawals due to AE (RR 1.03, 95% CI 0.80 to 1.33; 8 trials).

ICS + LTRA vs. increasing ICS

Citation (Sponsor)	Study Design	Purpose/Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (If Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Post-Intervention/Off-Treatment Followup	Lung Function	Vital Signs/Cardiovascular/Clinical Laboratory Values	Exacerbations/Symptoms	Safety
Price et al. A randomized controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. Thorax 2003;58(3): 211–216. (Merck & Co.)	Multicenter, randomized, double-blind, placebo-controlled, parallel-group noninferiority study	To compare the clinical benefits of adding montelukast to inhaled budesonide with doubling the dose of inhaled budesonide in adult patients who were symptomatic on inhaled budesonide alone	889 (843; ITT analysis)	Age 15–75 yr, mean = 43 yr Gender 40% male, 60% female Ethnicity 76.9% White, 0.7% Black, 4.9% Asian, 17.4% other Smoking All nonsmokers or exsmokers	Duration >6 months, mean = 17 yr FEV_1 mean = 2.3 L FEV_1 % pred., mean = 68.7 PEF, mean = 384 L/min Daily beta$_2$-agonist use, 2.7 puffs/day Nocturnal awakenings, median 13.3% of days Days missed from work/school due to asthma in previous year, mean = 21.5 days 41.4% used OCS in previous year.	Arm 1 Montelukast + budesonide (M/B) (n=448; 428 completers) Arm 2 Budesonide (B) (n=441; 415 completers)	Montelukast, 10 mg/day at bedtime + budesonide, 800 mcg/day Budesonide, 800 mcg/day, twice daily	12 weeks after 4-week run-in period SABAs were used on as-needed basis.	*Improvement in morning PEF over last 10 weeks with M/B was as effective as B (33.5 L/min vs. 30.1 L/min, 95% CI –12.9 to 4.8 for difference). Change during first 3 days in morning PEF was greater in M/B group than in B group (20.1L/min vs. 9.6 L/min; 95% CI –17.6 to –4.3, p <0.001).	Groups did not differ in change in peripheral blood eosinophil count (–0.05 vs. –0.07 x 10^9, p=0.387).	Groups did not differ in change in beta$_2$-agonist use (p=0.51), nocturnal awakenings (p=0.353), median days with exacerbations (6.7% vs. 6.3%, p=0.78), median asthma-free days (86.7% vs. 82.2%, p=0.37), or proportion requiring oral steroids or admission to hospital (1.6% vs. 2.3%, p=0.47).	No difference was found between groups in number with AE, drug-related AE, SAE, or discontinuing because of AE.
Jenkins et al. Salmeterol/fluticasone propionate combination therapy 50/250 microg twice daily is more effective than budesonide 800 microg twice daily in treating moderate to severe asthma. Respir Med 2000;94(7):715–723. (GlaxoWellcome)	Multisided, randomized, double-blind, double-dummy, parallel group (multinational study in 44 centers)	To compare the efficacy and tolerability of this salmeterol plus fluticasone propionate combination with a threefold higher microgram dose of ICS in patients with moderate-to-severe persistent asthma who remain symptomatic on a moderate-to-high corticosteroid dose	353 (ITT analysis)	Age 14–80 yr, mean = 46 yr Gender 50% male, 50% female Ethnicity Not reported	Moderate-to-severe asthma Duration: 6%. 0 to <1 yr; 18%, 1 to <5 yr; 17%, 5 to <10 yr; 60%, ≥10 yr FEV_1 % pred., 33–109, mean = 70 Corticosteroid therapy: 24% using fluticasone propionate (median 500 mcg/day), 48% using budesonide (median 800 mcg/day), 29% using beclomethasone dipropionate (median 1,000 mcg/day)	Arm 1 Salmeterol + fluticasone propionate (SFC) (n=180, 151 completers) Arm 2 Budesonide (B) (n=173; 143 completers)	50/250 mcg plus placebo twice daily 800 mcg plus placebo twice daily	24 weeks after 2-week run-in Rescue salbutamol was used as needed throughout.	*Significant difference in morning PEF (adjusted for age, gender, country, and baseline) was found for SFC vs. B treatment (406 L/min vs. 380 L/min, diff. 25 L/min, 95% CI 15 to 35, p <0.001). Greater improvement occurred in adjusted evening PEF for SFC vs. B group (416 L/min vs. 398 L/min, p <0.001). Adjusted mean diurnal variation in PEF was lower in SFC vs. B group (p <0.003) but was not clinically meaningful.		Percentage of symptom-free days over 24 weeks was greater in SFC group vs. B group (95% CI 2 to 11, p <0.001). SFC group had greater reduction than B group in rescue medication use (p <0.001).	14% of SFC group and 18% of B group reported treatment-related AE. No treatment-related SAE occurred.

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Matz et al. Addition of salmeterol to low-dose fluticasone versus higher-dose fluticasone: an analysis of asthma exacerbations. J Allergy Clin Immunol 2001; 107(5):783–789. (GlaxoWellcome Inc.)	Retrospective analysis of 2 identical, multicenter, randomized, double-dummy, double-blind, parallel-group studies (71 research centers)	To compare the rates and characteristics of asthma exacerbations in patients after adding salmeterol to low-dose fluticasone propionate (S/F) with the rates and characteristics of exacerbations in patients receiving higher dose fluticasone propionate (F)	925 (ITT analysis)	Age ≥12 yr Gender Not reported Ethnicity Not reported	Persistent asthma	Arm 1 Salmeterol + fluticasone (S/F) (n=467) Arm 2 Fluticasone (F) (n=458)	42 mcg/88 mcg twice daily 220 mcg twice daily	24 weeks, after 2- to 4-week screening period Albuterol was used to relieve break-through symptoms.	Changes in morning PEF during exacerbation were comparable in the 2 groups.	*8.8% of S/F group vs. 13.8% of F group had ≥1 exacerbation (p=0.017). Characteristics of those with exacerbations were similar in the 2 groups. Mean duration of exacerbation was 8.4 days in S/F group and 10.5 days in F group (p=0.17) and required 6.6 days vs. 7.5 days of treatment (p=0.12). Time to 1st exacerbation favored S/F group (p=0.049). Rescue albuterol use did not differ between the 2 groups.	
O'Byrne et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med 2001;164(8 Pt 1):1392–1397.	Multicenter, randomized, double-blind, parallel group (198 centers in 17 countries)	To determine whether regular treatment with low doses of inhaled budesonide with or without low doses of inhaled formoterol would reduce severe asthma exacerbations and improve asthma control compared with placebo	Group A: 900 Group B: 1,625	Group A Age ≥12 yr, mean = 30.8 yr Gender 40% male, 60% female Ethnicity Not reported Group B Age ≥12 yr, mean = 37.2 yr Gender 43% male, 57% female Ethnicity Not reported	Group A Mild asthma No ICS for ≥3 mo FEV_1 % pred., mean = 89.7 Morning PEF, mean = 418 L/min Days with symptoms, mean = 39.8% Nights with awakenings, mean = 11.0% Group B Mild asthma ≤400 mcg/day budesonide or its equivalent for ≥3 mo FEV_1 % pred., mean = 86.5 Morning PEF, mean = 4,189 L/min Days with symptoms, mean = 37.8% Nights with awakenings, mean = 6.7%	Group A Arm 1 Budesonide (B) (n=228) Arm 2 Budesonide + formoterol (BF) (n=231) Arm 3 Placebo (P) (n=239) Group B Arm 1 Budesonide (100B) (n=228) Arm 2 Budesonide + formoterol (100BF) (n=231) Arm 3 Budesonide (200B) (n=239) Arm 4 Budesonide + formoterol (200BF)	100 mcg twice daily 100/4.5 mcg twice daily placebo 100 mcg twice daily 100/4.5 mcg twice daily 200 mcg twice daily 200/4.5 mcg twice daily	1 year after 4-week run-in (Group A took placebo; Group B took budesonide, 100 mcg twice daily) No additional treatments were allowed. If a patient had a severe exacerbation, medications were at the physician's discretion.	Group A (adjusted for baseline) BF vs. B treatment increased FEV_1 % pred. (5.87 vs. 4.04, p <0.005) and resulted in greater change in morning PEF (31.81 vs. 15.12, p <0.001). Group B (adjusted for baseline) Adding formoterol increased FEV_1 and morning PEF (p <0.001). 100BF vs. 200B treatment improved FEV_1 (p=0.05) and morning PEF (p <0.005).	Group A (adjusted for baseline) *B vs. P group showed reduction in risk for 1st severe exacerbation (RR=0.40, 95% CI 0.27 to 0.59). B vs. P group reduced rate of poorly controlled asthma days (RR=0.52, 95% CI 0.40 to 0.67), rate of exacerbations (RR=0.38, 95% CI 0.25 to 0.57), days with asthma symptoms (p <0.001), days with nocturnal awakening (p <0.001), and number of rescue inhalations (p <0.001). Group B (adjusted for baseline) *200B vs. 100B group had reduced risk of 1st severe exacerbation (RR=0.81, 95% CI 0.65 to 1.01). 200B vs. 100B reduced rate of poorly controlled asthma days (RR=0.87, 95% CI 0.75 to 1.01). Adding F reduced risk of 1st exacerbation (RR=0.57, 95% CI 0.46 to 0.72) and rate of severe exacerbations (RR=0.48, 95% CI 0.69 to 0.59). 100BF was more effective than 200B in reducing risk of severe exacerbation day (RR=0.71, 95% CI 0.52 to 0.96) and rate of severe exacerbations (RR=0.58, 95% CI 0.44 to 0.76).	Number of AE was similar between different treatments.

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Bateman et al. Combination therapy with single inhaler budesonide/formoterol compared with high dose of fluticasone propionate alone in patients with moderate persistent asthma. Am J Respir Med 2003;2(3):275–281. (AstraZeneca)	Multicenter, randomized, double-blind, double-dummy, parallel group (37 centers in 6 countries)	To compare the efficacy of budesonide/formoterol 160/4.5 mcg twice daily with a high dose of the corticosteroid fluticasone propionate 250 mcg twice daily in patients with moderate persistent asthma previously treated with ICSs	344 (344)	Age 17–75 yr, mean = 42 yr Gender 43% male, 57% female Ethnicity Not reported Smoking 6% smokers, 24% exsmokers, 70% never smoked	Moderate persistent asthma Duration of asthma, ≥6 months; mean = 16.3 yr FEV_1, geometric mean = 2.4 L FEV_1 % pred., mean = 78 Morning PEF, mean = 359 Prestudy ICS dose, mean = 594 mcg/day	Arm 1 Budesonide/formoterol (B/F) (n=168; 153 completers) Arm 2 Fluticasone propionate (FP) (n=176; 156 completers)	160/4.5 mcg twice daily 250 mcg twice daily	12 weeks, after 2-week run-in period Terbutaline sulfate or albuterol was used as reliever medication.	*Greater increase in morning PEF occurred with B/F vs. FP (27.4 vs. 7.7 L/min, p <0.001). Difference was evident on 1st day (p <0.001) and continued over last 30 days (p <0.001).	Need for reliever medication was lower with B/F vs. FP (diff 0.18, 95% CI 0.01 to 0.35, p=0.04). Reliever-free days were increased with B/F vs. FP (75.5 vs. 66.4, diff. 9.1, 95%CI 3.8 to 14.3, p <0.001). No difference was found in nighttime awakenings, symptom-free days, and asthma-control days. Risk of mild exacerbation was 32% lower in B/F (RR 0.678, 95% CI 0.465 to 0.988).	Similar AE profiles for occurred with B/F and FP. No treatment-related SAE occurred.
Ind et al. Addition of salmeterol to fluticasone propionate treatment in moderate-to-severe asthma. Respir Med 2003;97(5):555–562. (GlaxoWellcome Research & Development)	Multicenter, randomized, double-dummy, double-blind, parallel group (100 hospitals and primary care centers in 6 countries)	To see whether the benefit of adding salmeterol was superior to that of doubling the dose of fluticasone propionate while also including a control group who continued treatment with low-dose fluticasone propionate	502 (496 ITT analysis)	Age ≥16 yr, mean = 44.8 yr Gender 46% male, 54% female Ethnicity Not reported Smoking 17.5% smokers, 33.7% exsmokers, 48.8% never smoked	Moderate-to-severe asthma Duration: 0.2–68 yr FEV_1, mean = 2.3 L FEV_1 % pred., mean = 74.5 PEF % pred., mean = 74.5 Median ICS daily dose 1,000 mcg budesonide/ beclomethasone dipropionate (BDP) In the past year, 20.8% required hospitalization, 67% required OCS, and 86.5% required other therapy changes.	Arm 1 Salmeterol + fluticasone (S/F) (n=171; 144 completers) Arm 2 Fluticasone (F250) (n=160; n=145 completers). Arm 3 Fluticasone (F500) (n=165; n=143 completers).	Salmeterol 50 mcg twice daily + fluticasone 250 mcg twice daily Fluticasone 250 mcg twice daily Fluticasone 500 mcg twice daily	24 weeks, after 4-week run-in period Salbutamol was used for symptom relief, and oral prednisolone was used in exacerbations.	*Improvement in PEF was greater with S/F (42 L/min) compared with F500 (16.5 L/min) and F250 (16.9 L/min), p <0.001. No difference was found between F250 and F500. S/F reduced diurnal variation in PEF more (–4.9%) vs. F500 (–3.0%) and F250 (–2.2%), both p <0.001.	*66% of S/F, 59% of F250 and 65% of F500 groups had exacerbations (p >0.05). No difference was found in percentage of patients experiencing moderate or severe exacerbations (28% of S/F, 31% of F500, and 25% of F250). Proportion of symptom-free days and nights increased more with S/F (median 21%) compared with F500 (median 1.5%) and F250 (median 0%), both p=0.002.	
Lalloo et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. Chest 2003;123(5): 1480–1487. (AstraZeneca, Lund, Sweden)	Multicenter, randomized, double-blind, parallel group (51 centers in 7 countries)	To evaluate the efficacy and safety of low-dose budesonide/ formoterol (B/F) compared with increased dose of budesonide (B) in adult patients with mild-to-moderate asthma not fully controlled on low doses of ICS alone	467 (430; ITT analysis)	Age 18–78 yr, mean = 41 yr Gender 43% male, 57% female Ethnicity Not reported	Mild-to-moderate asthma Duration: 6 months–53 yr; mean = 11.5 yr FEV_1 % pred., 38–157; mean = 81 FEV_1 % reversibility, 11–98; mean = 22 Dose of inhaled steroid = 200–500 mcg/day; mean = 387 mcg/day	Arm 1 Budesonide + formoterol (B/F) (n=230; 215 completers) Arm 2 Budesonide (B) (n=237; 215 completers)	80 mcg/4.5 mcg twice daily, inhaled 200 mcg twice daily, inhaled	12 weeks after open, 2-week run-in period Inhaled terbutaline or salbutamol was used as reliever medication throughout.	*Greater increase in morning PEF occurred for B/F vs. B treatment (16.5 vs. 7.1, p=0.002) and in evening PEF (13.7 vs. 4.2, p <0.001). FEV_1 increased significantly in both groups, with no difference between groups.	Proportion of asthma-control days increased by 17% in B/F group and 10% in B group (p=0.002). Proportion of symptom-free days increased 16% for B/F group and 10% for B group (p=0.007). 48% of B/F group experienced >1 exacerbation vs. 57% of B group. Time to exacerbation favored B/F (p=0.02). Risk of having mild asthma exacerbation was 26% lower in B/F than B group (p=0.02).	No difference was found between groups in frequency of AE; 5 SAE with occurred with B/F treatment (1 related to treatment) and 2 SAE occurred with B treatment.

Citation (Sponsor)	Study Design	Purpose/Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (If Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Vital Signs/Cardiovascular/Clinical Laboratory Values	Exacerbations/Symptoms	Safety
Bergmann et al. Salmeterol/fluticasone propionate (50/250 microg) combination is superior to double dose fluticasone (500 microg) for the treatment of symptomatic moderate asthma. Swiss Med Wkly 2004; 134(3-4): 50–58. (GlaxoWellcome)	Multicenter, randomized, double-blind study (76 private practices or outpatient clinics at hospitals)	To study the efficacy and tolerability of the salmeterol fluticasone combination (SF) in comparison with doubling the dose of fluticasone (F) in patients with moderate symptomatic asthma	365 (347 ITT analysis)	Age ≥18 yr, mean = 49.3 yr Gender 46.4% male, 53.6% female Ethnicity Not reported Smoking Nonsmokers or exsmokers	Moderate asthma Duration of asthma: 33.5%, 1–5 yr; 66.5%. 5–19 yr Start of ICS: 21.6%, 3–5 yr; 78.4%, >5 yr FVC % pred., mean = 87.7 FEV_1 % pred., mean = 75.1 PEF % pred., 73.3 Morning PEF, mean = 317 Percentage symptom-free days, mean = 16.5 Rescue medications, mean = 2.6 puffs/day	Arm 1 Salmeterol + fluticasone (SF) (n=179; 166 completers) Arm 2 Fluticasone(F) (n=186; 168 completers)	50/250 mcg twice daily 500 mcg twice daily	12 weeks, after 2-week screening period Salbutamol in metered dose inhalers was used as rescue medication.	*SF was superior to F treatment in morning PEF (48 L/min vs. 30 L/min, diff. 19.6, 95% CI 6.8 to 32.4, p=0.0027 at 6 weeks; +52 L/min vs. +36 L/min, diff. 16.6, 95% CI 1.1 to 32.0, p=0.036 at 12 weeks). Difference was adjusted for baseline, age, sex, height, and duration of preceding treatment with ICS. No difference between groups was found in clinic lung function results.	Blood pressure and heart rate remained stable throughout treatment.	SF group vs. F group had an increased percentage of symptom-free days (+40 vs. +29, adj. diff. 12.8, 95% CI 4.5 to 21.0, p=0.0025 at 6 weeks; +49 vs. +38, adj. diff. 12.6, 95% CI 4.0 to 20.7, p=0.004 at 12 weeks). Rescue medication use decreased more in SF group vs. F group (–1.4 vs. –1.0, adj. diff –0.5, 95% CI –0.85 to –0.20, p=0.0015 at 6 weeks; –1.6 vs. –1.0, adj. diff. –0.84, 95% CI –1.13 to –0.37, p <0.001 at 12 weeks.	26.3% AE occurred in SF group vs. 24.2% in F group. One possible drug-related SAE occurred in F group vs. 2 unrelated SAE in SF group.
Jonsson et al. An economic evaluation of combination treatment with budesonide and formoterol in patients with mild-to-moderate persistent asthma. Respir Med 2004;98(11): 1146–1154.	Multicenter, randomized, prospective, double-blind, parallel-group trial (17 countries)	To present the results of an economic analysis of 3 step-up treatments	1,272 for clinical outcomes; 1,233 for economic analysis	No characteristics provided. See O'Byrne et al. for description of sample.	Mild-to-moderate persistent asthma. See O'Bryne et al. for description.	Arm 1 Budesonide (B100) (n=322) Arm 2 Budesonide (B200) (n=312) Arm 3 Budesonide/formoterol (B100/F) (n=323) Arm 4 Budesonide/formoterol (B200/F) (n=315)	100 mcg twice daily 200 mcg twice daily 100/4.5 mcg twice daily 200/4.5 mcg twice daily	1 year, after 4-week run-in			B100/F was more expensive and less effective than B200/F and could not provide best "value for money." B200/F provided more symptom-free days but was associated with higher costs than B200. The incremental cost-effectiveness ratio for this comparison was Sweden Kronor 21 per symptom-free day gained.	

LABA A vs. LABA B in addition to ICS

Citation (Sponsor)	Study Design	Purpose/Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (If Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Post-Intervention/Off-Treatment Followup	Lung Function	Exacerbations/Symptoms	Safety
Masoli et al. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. Thorax 2005;60(9): 730–734.	Meta-analysis of double-blind, randomized trials	To compare the clinical benefit of adding salmeterol in patients not controlled on moderate doses of ICS with increasing the dose of ICS by at least twofold	12 studies with 4,576 subjects	Age ≥12 yr Gender Not reported Ethnicity Not reported	Moderate to severe Symptomatic on moderate doses of ICS (200 mcg/day fluticasone or equivalent) FEV_1 % pred., mean = 64%; range = 40%–85% across studies	Salmeterol + BDP 400 mcg/day vs. BDP 1,000 mcg/day (1 study) Salmeterol + BDP 400 mcg/day vs. BDP 800 mcg/day (3 studies) Salmeterol + fluticasone 200 mcg/day vs. fluticasone 500 mcg/day (6 studies) Salmeterol + fluticasone 200 mcg/day vs. budesonide 800 mcg/day (1 study)		12 weeks (7 studies), 24 weeks (5 studies), or 26 weeks (1 study)	Those who received low-dose ICS/salmeterol vs. high-dose ICS had reduced morning PEF (diff. 23 L/min, 95% CI 10 to 28) and evening PEF (diff. 19 L/min, 95% CI 15 to 23), greater daytime $beta_2$-agonist use (diff. –0.58, 95% CI –0.02 to –0.13), and reduced FEV_1 (diff. 0.12 L, 95% CI 0.09 to 0.15).		*Decreased number of subjects withdrew due to asthma in low-dose ICS/ salmeterol vs. high-dose ICS treatment (2.9% vs. 4.3%; OR 1.58, 95% CI 1.12 to 2.24). *Reduced number of subjects had ≥1 moderate or severe exacerbation in low-dose ICS/ salmeterol vs. high-dose ICS treatment (8.0% vs. 10.7%; OR 1.35, 95%CI 1.10 to 1.66).
Palmqvist et al. Onset of bronchodilation of budesonide/formoterol vs. salmeterol/fluticasone in single inhalers. Pulm Pharmacol Ther 2001;14(1): 29–34.	Randomized, double-blind, placebo-controlled crossover study	To evaluate the onset of action of the combination of budesonide and formoterol in a single inhaler in comparison with the combination of salmeterol and fluticasone	30 (30)	Age 28–73 yr, mean = 49 yr Gender 50% male, 50% female	FEV_1, range 1.48–4.28 L. mean = 2.54 L FEV_1 % pred., range 60.6–98.6. mean = 78.2 Reversibility after 0.1 mg salbutamol, range 5–22%, mean = 12% Reversibility after 0.5 mg salbutamol, range 12–31%, mean = 19% All used inhaled SABAs as needed; 50% used LABAs as needed.	Arm 1 Budesonide/formoterol (BF1) Arm 2 Budesonide/formoterol (BF2) Arm 3 Salmeterol/fluticasone (SF) Arm 4 Placebo (P)	160/4.5 mcg (1 inhalation) 160/4.5 mcg (2 inhalations) 50/250 mcg	4 study days, separated by at least 72 hours SABAs were withheld at least 8 hours, LABAs were withheld at least 72 hours, and LTRAs and anticholinergics were withheld at least 12 hours prior to study drug.	*Both BF groups had faster onset of improvement in FEV_1 compared to SF at 3 minutes after dose (2.74 and 2.75 vs. 2.56, p <0.001) and at 0-5 minute average FEV_1 (2.80 and 2.83 vs. 2.67, p <0.001). No evidence was found of difference between 2 BF doses for any changes in FEV_1 up to 3 hours after inhalation. 47% of SF group showed onset of effect (15%) after inhalation of SF within 60 minutes vs. 73% of BF1 and 77% of BF2 groups.		
Everden et al. Eformoterol Turbohaler compared with salmeterol by dry powder inhaler in asthmatic children not controlled on inhaled corticosteroids. Pediatr Allergy Immunol 2004;15(1): 40–47.	Multicenter, randomized, open, parallel-group comparative study (56 general practice centers in the United Kingdom and 2 in the Republic of Ireland)	To examine the clinical efficacy and safety of eformoterol compared with salmeterol in children receiving regular ICS	156 (155)	Age 6–17 yr, mean = 11.7 yr 52% 6–11 yr, 48% 12–17 yr Gender 57% male, 43% female Height Mean = 148 cm Weight Mean = 46 kg	Moderate persistent asthma Constant dose of ICS ≥4 weeks prior to enrollment; range, 100–1,600 mcg/day, mean = 362 mcg/day Run-in use of SABA: mean = 0.84 inhalations/night; mean = 1.16 inhalations/day at school; mean = 3.95 inhalations/24 hours PEF mean = 314.5 L/min	Arm 1 Eformoterol Turbohaler® (E) (n=80; n=79 in analysis; n=59 completers) Arm 2 Salmeterol Accuhaler® (S) (n=76; n=64 completers)	12 mcg twice daily (9 mcg delivered dose) 50 mcg twice daily	12 weeks, after 7- to 10-day run-in period Patients continued to receive current ICS and SABA throughout study.	Both groups showed improvements over time in clinic PEF at 4, 8, and 12 weeks (p <0.01).	*As-needed $beta_2$-agonist used. Reductions for E vs. S group were 65% vs. 52% at week 12 for daytime use and 66% vs. 49% for 24-hour use. Difference favoring E for daytime SABA use was –0.46 inhalations/day (p=0.08) and –0.70 inhalations/day for 24-hour use (p=0.043). No evidence indicated that age group was associated with change in SABA use. Percentage of patients experiencing severe exacerbation by 12 weeks was 17% in each group. HRQL was improved at all time points (p <0.01) for both groups.	AE was reported by 55% of E group and 59% of S group. Number, nature, and intensity of AEs were the same for both groups. No treatment-related SAE occurred.