Evidence Table 12. Pharmacologic Therapy: Inhaled Corticosteroids—Dosing Strategies

Abbreviations used in table:

AE	adverse event
AQLQ	Asthma Quality of Life Questionnaire
BDP	beclomethasone dipropionate
BF	budesonide/formoterol
$FEF_{25\%-75\%}$	forced expiratory flow between 25% and 75% of vital capacity
FEV_1	forced expiratory volume in 1 sec.
FP-F	fluticasone propionate fixed dose
FP-SD	fluticasone propionate stepdown
FVC	forced vital capacity
HR	hazard ratio
HRQL	health-related quality of life
ICS	inhaled corticosteroid
ITT	intent-to-treat analysis
LABA	long-acting beta-agonist
MiniAQLQ	Mini Asthma Quality of Life Questionnaire
NNT	number needed to treat
OCS	oral corticosteroid
PEF	peak expiratory flow
QoL	quality of life
SABA	short-acting beta-agonist
SAE	serious adverse event
WMD	weighted mean difference

* indicates primary outcome

Evidence Table 12. Pharmacologic Therapy: Inhaled Corticosteroids—Dosing Strategies

Ia. Adjustable Rx With Combo Tx

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	Change in Medication Use	Lung Function	Exacerbations/Symptoms	Other
Leuppi et al. An individualized, adjustable maintenance regimen of budesonide/ formoterol provides effective asthma symptom control at a lower overall dose than fixed dosing. Swiss Med Wkly 2003;133(21–22): 302–309. (AstraZeneca AG, Switzerland)	Multicenter, randomized, open-label, parallel group study (7 outpatient clinics and 25 respiratory practitioners in Switzerland)	To investigate whether asthma control can be maintained with self-guided adjustable maintenance doses of budesonide/ formoterol in a single inhaler in comparison with fixed-dosing regimen	142 (127)	**Age** 12–78 yr, mean = 46 yr **Gender** 49% male, 51% female **Ethnicity** Not reported	NHLBI severity level: 15% mild intermittent, 39% mild persistent, 42% moderate persistent, 5% severe persistent FEV_1 % pred. mean = 79 Relative PEF mean = 91.3	**Arm 1** Budesonide/ formoterol 200/6 mcg adjustable dosing (n=77; 69 analyzed) **Arm 2** Budesonide/ formoterol 200/6 mcg fixed dosing (n=65; 58 analyzed)	with interim step ups to 2 twice/day and if not sufficient, up to 4 tw2 inhalations twice/day. Step down to 1 twice/day or 2 at night ice/day for 14 days 2 inhalations twice/day	12 weeks after 4-week run-in of budesonide/ formoterol (200/6 mcg) twice/day Terbutaline used as rescue medication throughout.	*81% reduced maintenance dose at least once during treatment period; 52% used decreased maintenance dose on > 50% of days and 33% on > 90% of days. Average number of daily inhalations significantly lower (p <0.0001) in adjustable-dosing groups than fixed-dosing group (3.0 vs. 3.9).	Mean FEV_1 increased from 78% to 81% in adjustable-dosing group and from 80% to 83% in fixed-dosing group (p >0.30).	Significant shift to lower symptom severity status in adjustable-dosing group (p=0.004) but not in fixed-dosing group (p=0.11). Frequency of nocturnal awakenings significantly lower (p=0.006) in adjustable-dosing group than fixed-dosing group (0.057 vs. 0.067/night).	3 patients in fixed dosing had SAE that led to withdrawal from study. No asthma-related hospital admissions.
Stallberg et al. Budesonide/ formoterol adjustable maintenance dosing reduces asthma exacerbations versus fixed dosing. Int J Clin Pract 2003;57(8):656–661. (AstraZeneca, Sweden)	Open multicenter, randomized, parallel group (94 primary health care and hospital centers in Sweden)	To examine the potential clinical benefits of a guided adjustable-dosing regimen with budesonide/formoterol in a single inhaler over a 6-month period based on patient assessment of their asthma, compared with fixed-dosing regimen	1,034 (1034)	**Age** 12–83 yr, mean = 44 yr **Gender** 40% male, 60% female **Smoking** 10% current smoker, 22% exsmoker, 68% nonsmoker	FEV_1 postbronchodilation, mean = 3.1L FEV_1 % pred. postbronchodilation, mean = 95.6 Received ICS for ≥6 months with constant dose between 400 and 1,000 mcg/day for 30 days before enrollment. 783% well controlled on ICS + long-acting beta-agonist; 27% uncontrolled on ICS + short-acting beta-agonist.	**Arm 1** Budesonide/formoterol adjustable dosing (n=517; 486 completed) **Arm 2** Budesonide/ formoterol fixed dosing (n=517; 491 completed)	1, 2, or 4 inhalations twice daily according to defined criteria assessed by each patient 2 inhalations twice daily	6 months after 4-week run-in period All patients used terbutaline or salbutamol inhalations as reliever medication throughout the study. Any patient who experienced > 2 episodes of worsening symptoms requiring OCS were withdrawn from the study.			*Compared with fixed-dosing, adjustable-dosing was associated with fewer patients with more than 1 exacerbation (6.2% vs. 9.5%, OR=0.63; 95% CI 0.40–1.00), shorter time to first exacerbation (p=0.05), fewer inhalations/day (2.35 vs. 3.95, 40% reduction, p <0.001), and greater use of reliever medication (10.5% vs. 9.5% of days, p=0.0011). No difference in proportion experiencing exacerbation between 80/4.5 mcg and 160/4.5 mcg of budesonide/ formoterol (p=0.46).	33 SAEs reported (3% of patients on adjustable dosing and 2% on fixed dosing): none related to treatment. 51 study discontinuations due to asthma aggravation (3% each 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 Postintervention/Off-Treatment Followup	Change in Medication Use	Lung Function	Exacerbations/Symptoms	Other
Aalbers et al. Adjustable maintenance dosing with budesonide/ formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. Cur Med Res Opin 2004;20(2): 225–240. (AstraZeneca, Lund, Sweden)	Multicenter, randomized, double-dummy, double/blind/open -extension, parallel group (Outpatient clinics in 93 centers in 6 countries)	To determine whether adjustable dosing with a combination inhaler had greater efficacy compared with FD regimens	658 (654)	**Age** 12–78 yr: mean = 46 yr **Gender** 45% male, 55% female **Ethnicity** Not reported	Symptomatic with mean symptom score = 1.5 Duration 0–73 years, mean = 12 years Mean ICS 735 mcg/day, FEV_1 % pred. mean = 84 Reliever use mean = 1.8 occasions/day 45% combinations of ICS and long-acting beta₂-agonists	**Arm 1** Budesonide/ formoterol AMD (n=219; 217 evaluable) **Arm 2** Budesonide/ formoterol FD (n=215; 214 evaluable) **Arm 3** Salmeterol/ fluticasone FD (n=224; 223 evaluable)	160/4.5 mcg 2 inhalations bid + temporary increase if needed 160/4.5 mcg 2 inhalations bid 50/250 mcg, 1 inhalation bid	4 weeks (2 weeks run-in period) 6-month open extension AMD could increase to 4 inhalations bid for 7–14 days if symptoms worsened.		Difference in FEV_1 favored budesonide/formoterol FD vs. salmeterol/fluticasone FD (p <0.05)	*OR of well-controlled asthma week similar for FD groups (1.29: CI 0.98–1.69): during open extension AMD vs. budesonide/ formoterol FD OR=1.34, CI 1.001–1.78) and vs. salmeterol/fluticasone OR=1.05, CI 0.79–1.39. AMD had fewer exacerbations than other groups (35 vs. 50 and 59, respectively); 40% rate reduction favored AMD vs. salmeterol/fluticasone FD (p=0.018). 45% of patients in AMD gained control of asthma after double-blind phase to reduce maintenance to 1 inhalation bid; 57% in AMD required no step-up in treatment.	31 SAE for 24 patients, 8 with budesonide/formoterol FD, and 11 with AMD, 11 with salmeterol/fluticasone FD; none related to study drugs.
Ind et al. Adjustable and fixed dosing with budesonide/ formoterol via a single inhaler in asthma patients: the ASSURE study. Respir Med 2004;98(5):464–475. (AstraZeneca UK)	Multicenter, randomized, open, parallel group study (365 general practice and hospital centers in the United Kingdon)	To test whether asthma can be effectively controlled by increasing and decreasing the dose of budesonide/ formoterol, delivered twice daily from a single inhaler, to an appropriate level using a patient-driven self-management plan	1,553 (1,539)	**Age** 18–87 yr, mean = 48.3 yr **Gender** 40% male, 60% female **Ethnicity** 98% Caucasian	Uncontrolled on ICS or controlled on ICS and LABA Almost half with moderate-persistent symptoms, 6% with severe-persistent symptoms Duration >1 yr for 97% and > 5 yr for 76% Mean ICS dose = 672 mcg 44% use of SABA during run-in; 40% prestudy LABA PEF mean = 419 L/min	**Arm 1** Adjustable dosing **Arm 2** Fixed dosing	Budesonide/formoterol 80/4.5 or 160/4.5 mcg 1–4 inhalations twice daily depending on asthma symptoms Budesonide/formoterol 80/4.5 or 160/4.5 mcg 2 inhalations twice daily	12 weeks after 4-week run-in period. All patients used terbutaline sulfate 0.5 mg/dose as reliever medication throughout the study.	Of adjustable-dosing group, 79% reduced dose of medication at some point. Overall 28% of patients increased dosage to 8 inhalations/day at least once. Median length of step up was 10 days. Mean number of inhalations/day over trial was lower in adjustable-dosing group than in fixed-dosing group (3.2 vs. 3.8, p <0.05).	Change in mean morning PEF of –2.0 for adjustable dosing and 2.7 for fixed dosing (p <0.05).	Severity symptom levels in the adjustable- and fixed-dosing groups improved for 29% and 28%, respectively, and maintained for 57% in both groups. A greater proportion of patients in both groups were categorized with mild-intermittent symptoms (39% vs. 30%) and fewer were categorized as severe- or moderate-persistent symptoms (29% vs. 38%). *In both groups, 94% of patients did not experience a treatment failure. Patients in both groups showed a higher proportion of asthma-free days and fewer nocturnal awakenings from baseline with no differences between groups. Reliever use in those who successfully stepped down dose was 0.22 less than in fixed-dosing group, p <0.001.	4% of fixed dosing and 3% of adjustable dosing experienced SAEs (asthma aggravation).

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	Change in Medication Use	Lung Function	Exacerbations/Symptoms	Other
FitzGerald et al. The CONCEPT trial: a 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/ budesonide in adults with persistent asthma. Clin Ther 2005;27(4):393–406. (GlaxoSmithKline Research & Development Limited)	Multicenter, randomized, double-blind, double-dummy trial (91 centers in 15 countries)	To compare the efficacy of stable dosing of salmeterol/ fluticasone propionate with adjustable maintenance dosing of formoterol/ budesonide	706 (688; ITT analysis)	**Age** ≥18 yr, mean = 45 yr **Gender** 39% male, 61% female **Weight** Mean = 76 kg	Persistent asthma Asthma duration ≥10 yr, 57% FEV_1, mean = 2.52 L FEV_1 % pred., range 60–90, mean = 81 AM PEF, mean = 359 L/min ICS dose at entry, mean = 512 mcg/day LABA use at entry, 42% Days free of rescue medication, median 14.3% Rescue medication use, median 1.0/day	**Arm 1** Salmeterol/ fluticasone propionate (S/FP) (n=344) **Arm2** Formoterol/ budesonide (F/B) (n=344)	50/250 mcg twice daily 2 inhalations of 6/200 mcg: reduced to 1 inhalation week 4 and stepped up or down based on criteria.	2-week run-in period, 52-week double-blind treatment period, 2-week followup period Salbutamol as needed for rescue medication		AM PEF was higher in S/FP vs. F/B (adjusted mean = 400.1 vs. 390.6 L/min adjusted mean diff. 9.5 L/min, 95% CI 2.7 to 16.3, p=0.006).	*Percentage of symptom-free days was higher with S/FP vs. F/B (median 58.8% vs. 52.1%, p=0.034), equated to an average of 24 additional symptom-free days/year in S/FP vs. F/B. During weeks 5–52, percentage of symptom-free days was higher in S/FP vs. B/F (median 73.8% vs. 64.9%, p=0.03), equal to average of 32 additional symptom-free days/year in S/FP vs. B/F. Adjusted annual mean exacerbation rate was 0.18 for S/FP and 0.33 for F/B (rate ratio 0.53, 95% CI 0.34 to 0.85, p=0.008). Over 52 weeks, mean daily ICS exposure was 81 mcg FP in S/FP and 480 mcg B in F/B.	Drug-related AE for 6.3% of S/FP and 5.9% of F/B. SAE for 2.6% of S/FP and 2.5% of F/B.
O'Byrne et al. Budesonide/ formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005;171(2): 129–136. (AstraZeneca R&D, Lund, Sweden)	Multisite, randomized, double-blind, parallel-group trial (246 centers in 22 countries) stratified randomization by age group in 8:1 ratio	To test hypothesis that in patients already receiving a low daily maintenance dose of budesonide/ formoterol, replacing short-acting beta$_2$-agonist reliever therapy with the as-needed budesonide/ formoterol combination would enable patients to adjust more rapidly their anti-inflammatory therapy at times of greatest need while simultaneously obtaining elective and rapid relief from symptoms	2,760 (2,760 ITT analysis)	**Age** 4–77 yr, mean = 36 yr; 12.3% were 4–11 yr **Gender** 45% male, 55% female **Ethnicity** Not reported	Duration of asthma, 0–69 yr, mean = 36 yr FEV_1 0.62–4.50 L, mean = 2.12 L FEV_1 % pred., 43–108, mean = 73 FEV_1 reversibility, 2–89%, mean = 21 All with history of ≥1 exacerbation in the past year All on constant dose of ICS for ≥3 months, dose 100–120 mcg/day, mean = 612 mcg/day 28% inhaled LABA use at entry Reliever use, 0–9.4 inhalations/day, mean = 1.71/day; 06.6 inhalations/night, mean = 0.72 Symptom-free days, 0–100%, mean = 23% Reliever-free days, 0–100%, mean = 8.4% Asthma control days, 0–90%, mean = 5.6% Night awakenings, 0–100% of nights, mean = 20.9%	**Arm 1** Budesonide/ formoterol + relief (B/F + R) (n=925) **Arm 2** Budesonide/ formoterol + terbutaline (B/F + SABA) (n=909) **Arm 3** Budesonide + terbutaline (B+SABA) (n=926)	80/4.5 mcg twice/day + 80/4.5 mcg as needed 80/4.5 mcg twice/day + 0.4 mg as needed 320 mcg twice/day + 0.4 mg as needed (Children were given half the maintenance dose once daily at night.)	12 months; length of run-in not indicated; measurements at 1, 3, 6, 9, and 12 months of treatment	Mean number of daytime or nighttime inhalations of reliever medication was lower for patients using B/F+R than for other groups (1.03 vs. 0.84 and 0.73 for daytime and 0.43 vs. 0.37 and 0.28 for nighttime, both p <0.001).	B/F+R improved morning and evening PEF and FEV_1 vs. B/F+SABA and B+SABA (all p <0.001). B/F+SABA improved both morning and evening PEF vs. B+SABA (p <0.001).	*Risk of severe exacerbation 45% lower with B/F+R vs. B+SABA (HR 0.55, 95% CI 0.44 to 0.67: p <0.001) and 47% lower vs. B+SABA (HR 0.53, 95% CI 0.43 to 0.65, p <0.001). B/F+R prolonged time to all exacerbations (p <0.001) compared with both alternatives. Relative rate of all types of severe exacerbations was lower by 47% for B/F+R vs. B/F+SABA (HR 0.53, 95% CI 0.44 to 0.65) or B+SABA (HR 0.53, 95% CI 0.44 to 0.64). Rate of severe exacerbations requiring medical intervention reduced by 53% for B/F+R (HR 0.47, 95% CI 0.39 to 0.57) and by 46% vs. B/F+SABA (HR 0.54, 95% CI 0.44 to 0.66). B/F+R had longer time to first mild exacerbation compared to other groups (p <0.001) and rate was 30% lower for B/F+R vs. B/F+SABA (HR 0.70, 95% CI 0.62 to 0.80) and 36% lower vs. B+SABA (HR 0.64, 95% CI 0.57 to 0.73). Nighttime symptoms and awakenings improved with B/F+R compared with others (all p <0.05). Improved control resulted in extra 14 night/year free from awakenings with B/F+R vs. others.	Number with AE was 57% with B+SABA, 52% with B/F+SABA, and 54% with B/F+R. Number with SAE was 5% for B+SABA, 7% for B/F+SABA, and 5% for B/F+R. No clinical differences in electrocardiogram, hematology, clinical chemistry, or urinalysis between groups or over time.

Ib. Adjustable Rx With ICS Alone

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	Change in Medication Use	Lung Function	Exacerbations/Symptoms
Thoonen et al. Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial. Thorax 2003:58(1):30–36. (The Netherlands Organization for Scientific Research and AstraZeneca Pharmaceutica BV) Note: See also Foresi in section IVb. "Step Up—Step Down."	Comparative study with stratified cluster randomization of practices	To determine if guided self-management can provide a safe treatment strategy for asthmatic patients in general practice	19 practices with 214 patients (193 patients in ITT analysis—15 patients did not start and 6 dropped out before 1st followup: 171 completed trial)	**Age** >16 yr, mean = 39.5 yr **Gender** 38% male, 62% female **Ethnicity** Not reported **Smoking** 51% never smoked, 27% exsmokers, 22% smokers	Initial dose of ICS: 14% none, 34% low, 37% intermediate, 15% high 40% with asthma attack in previous 6 months FEV_1 % pred. mean = 85	**Arm 1** Self-management (n=104; 95 ITT; 86 completed) **Arm 2** Usual care (n=110; 98 ITT; 85 completed)	Budesonide 200 mcg/dose with step-up/step-down based on nocturnal waking, use of bronchodilator, and increased dyspnoea Budesonide 200 mcg/dose according to guidelines of Dutch College of Family Physicians	2 years following 6-week run-in period	Mean budesonide usage was 1680 puffs/patient in the self-management group and 1897 puffs/patient in the usual care group. Median dose of 97 mcg/day of SABA in self-management group and 69 mcg/day in usual care group (p=0.711). Significantly higher number of courses of oral prednisolone in self-management than in usual care group (p=015).	FEV_1 had estimated decline rate of 0.048 L/year in the self-management group and 0.026 L/year in the usual care group (p=0.24). No between-group differences in estimated rate of decline in FEV_1 reversibility.	Mean percentage of successfully treated weeks per patient in the self-management group was 78% compared with 72% in the usual care group (p <0.05). Increase in overall asthma quality of life scores of 0.10 points per visit in the usual care group and 0.21 points per visit in the self-management group (p=0.055). Mean number of limited activity days was 1.0 for self-management and 6.0 for usual care. Deleting those above the 98th percentile resulted in a mean of 1.2 for self-management and 3.9 for usual care (p <0.05).
FitzGerald et al. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. Thorax 2004;59(7): 550–556. (AstraZeneca Canada Inc.)	Multisite, randomized, double-blind, placebo-controlled, parallel-group trial (university affiliated teaching hospitals)	To investigate whether doubling the dose of maintenance inhaled budesonide early in an asthma exacerbation prevents worsening and the need for systemic corticosteroid	290 (98; analysis used "all patients treated" approach)	**Age** Mean = 32.2 yr **Gender** 29% male, 72% female **Ethnicity** Not reported **Smoking** 86% nonsmokers	Mean dose of budesonide = 635 mcg FEV_1 mean = 2.8 PEF mean = 422.9 L/min Mean days from recent exacerbation to visit 1=130.6 Stable dose of ICS (<1,200 mcg/day of beclomethasone or equivalent twice daily) for 1 month before visit 1	**Arm 1** Maintenance dose (MD) (n=148; 52 treated) **Arm 2** Double dose (DD) (n=142; 46 treated)	Maintenance inhaler + inhaler with placebo for 2/day use Maintenance inhaler + inhaler with budesonide to double dose of ICS at time of exacerbation	Patients with asthma exacerbation during the study period (6 months) who were stable at the end of the 14-day additional treatment course were followed for a 3-month surveillance period. Terbutaline sulfate inhaler as rescue medication, theophylline, anticholinergics, and nasal steroids allowed throughout.			*40% MD and 41% DD with treatment failure, p=0.94 Mean number of exacerbations 6 of 35 in MD vs. 5 of 34 in DD, p=0.92 Patients with ICS ≤ 400 mcg/day less likely to have treatment failure vs. those receiving ICS dose > 400 mcg/day (28% vs. 50%)

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	Change in Medication Use	Lung Function	Exacerbations/Symptoms
Harrison et al. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. Lancet 2004; 363(9405):271–275. (NHS Executive, UK)	Randomized, placebo-controlled, parallel-group study	To investigate the effects of doubling the dose of inhaled corticosteroids when asthma deteriorates	390 (353 completed study; 207 started study inhaler)	**Age** Mean = 49 yr **Gender** 33% male, 67% female **Ethnicity** Not reported **Smoking** 61% nonsmoker, 36% exsmoker, 3% smoker	Mean ICS = 709 mcg/day; 82% <1,000 mcg/day 36% LABA; 56% OCS, 42% double ICS FEV_1 % pred. mean = 80 PEF mean = 384 L/min	**Arm 1** Active inhaler (n=192; 175 completed; 110 started inhaler) **Arm 2** Placebo inhaler (n=198; 178 completed; 97 started inhaler)	Matched to regular ICS, type of inhaler, and dose Matched to regular type of inhaler	Monitored for up to 12 months after 2-week run-in period. Patients were given a 10-day course of prednisolone (30 mg/day) if control deteriorated. Patients started the study inhaler when peak flow or symptoms started to deteriorate and were withdrawn from the study 28 days after they started the study inhaler.	*ITT analysis: 11% of active and 12% of placebo groups started prednisolone, risk ratio = 0.95, p=0.80. Of those who started the inhaler (per protocol analysis n=207), 17% of active and 23% of placebo group started prednisolone, risk ratio = 0.80, p=0.53.	Mean difference in reduction in mean maximum fall in peak flow of −10 L/min, p=0.07. Doubling the dose of ICS has no effect on time for peak flow or symptom scores to return to baseline.	
Smith et al. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005;352(21): 2163–2173. (Otago Medical Research Foundation; the Dean's Fund of the Dunedin School of Medicine; and the University of Otago, Dunedin, New Zealand)	Randomized, single-blind, placebo-controlled trial	To compare the mcg-based algorithm with adjustment with the use of an algorithm based on guidelines promulgated by the Global Initiative for Asthma	97 (94)	(Reported for recruited sample n=110) **Age** 12–73 yr, mean = 44.8 yr **Gender** 37% male, 63% female reported **Ethnicity** Not reported	Chronic persistent asthma Duration of asthma 1–65 yr, mean = 25.2 yr Receiving ICS for ≥ 6 months with stable dose for ≥ 6 weeks Mean dose of 451 mcg of fluticasone or the equivalent 20% taking long-acting beta$_2$-agonists	**Arm 1** FE_{NO} management (n=48; n=46 entered Phase 2; n=44 completers) **Arm 2** Conventional management (C) (n=49; n=48 entered Phase 2; n=45 completers)	Initial dose of 750 mcg fluticasone adjusted down 1 step at a time at 4-week intervals until FE_{NO} > 15 ppb Initial dose of 750 mcg fluticasone adjusted at 4-week intervals using Global Initiative for Asthma 2002 criteria until loss of control of asthma	Phase I: 9 months; Phase 2: 12 months; 4-week run-in period In Phase 2 upward dose adjustment permitted according to same protocol as in Phase I. Dose steps in Phase I: upward from 750 mcg; downward from 750 mcg to 500 mcg to 250 mcg to 100 mcg placebo	At end of Phase 1, mean daily fluticasone dose was 292 mcg in FE_{NO} group and 567 mcg in C (diff. 270 mcg /day, 95% CI 112 to 430, p=0.003).	No difference between groups at end of Phase 1 and Phase 2 in FEV_1 (p=0.74 and p=0.39), morning PEF (p=0.73 and p=0.94), exhaled nitric oxide (p=0.10 and p=0.29), or sputum eosinophils (p=0.22 and p=0.88).	*Rate of exacerbations during Phase 2 was 0.49/patient/year in FE_{NO} group and 0.90 in C, a mean reduction of 45.6% (95% CI −78.6% to 54.5%) in FE_{NO} group. No difference between groups in exacerbation rates (p=0.27), cumulative total numbers of exacerbations (p=0.27), or time to first exacerbation (p=0.39).

IIa. 1x/day vs. 2x/day: ICS alone

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	Change in Medication Use	Lung Function	Exacerbations/Symptoms	Other
Boulet et al. Comparison of once- with twice-daily dosing of fluticasone propionate in mild and moderate asthma. Can Respir J 2000;7(3): 239–247. (GlaxoWellcome Inc.)	2 separate multicenter, randomized, double-blind, parallel-group studies (Study A: 49 centers in 8 countries; Study B: 32 centers in Canada)	To compare the clinical efficacy of fluticasone propionate administered once-daily with that of twice-daily dosing regimens, and to examine their safety	A: 461 (442: ITT) B: 434 (422: ITT)	**Study A** **Age** ≥12 yr: mean = 37.5 yr **Gender** 46% male, 54% female **Ethnicity** Not reported **Study B** **Age** ≥12 yr: mean = 36.3 yr **Gender** 45% male, 55% female **Ethnicity** Not reported	**Study A** Mild asthma Duration: 4% <1 yr, 27% 1–5 yr, 20% 6–10 yr, 49% >10 yr PEF: 24% <80%, 24% 80–90%, 26% 90–100% ICS mcg/day: 17% prn to 300, 46% ≤400, 30% 401–500, 7% >500 **Study B** Moderate asthma Duration: 38% <1 yr, 60% 1–5 yr, 2% >10 yr PEF: 26% <80%, 26% 80–90%, 24% 90–100%, 24% >100% ICS mcg/day: 20% prn to 300, 21% ≤400, 24% 401–500, 34% >500	**Arm 1** Fluticasone propionate once daily in morning and placebo in evening **Arm 2** Fluticasone propionate twice daily	200 mcg (A) 500 mcg (B) 100 mcg (A) 250 mcg (B)	12 weeks after 2-week run-in Salbutamol provided as relief medication during the study and other asthma medications allowed if route, dose, and frequency remained constant	**Study A:** No difference in salbutamol use during day or night (p > 0.05). **Study B:** No difference in salbutamol use during day (p > 0.05), but greater decrease in nocturnal salbutamol use for twice-daily dosing (p=0.003).	*Study A: Mean morning PEF improved 2.4% with once-daily dosing and 4.3% with twice-daily dosing (p=0.008). **Study B:** Mean morning PEF improved 0.2% with once-daily dosing and 3.7% with twice-daily dosing (p <0.001). **Study A and B:** Difference in increase in FEV_1 not significant. No significant effects on vital signs, urinalysis, hematology or laboratory parameters, and biochemistry in either study.	**Study A:** No difference between groups in symptom scores or number of days scores were < 2. **Study B:** Difference in favor of twice daily dosing in daytime symptom score (p=0.025), nighttime symptom score (p <0.001) and number of days that scores were < 2 (p=0.005). **Study A:** Incidence of exacerbation 13% in once-daily and 5% in twice-daily group. **Study B:** Incidence of exacerbation 12% in once-daily and 10% in twice-daily group.	Incidence of withdrawals higher in once-daily group in both studies: 19 vs. 3 patients in Study A and 7 vs. 5 in Study B.
Jonasson et al. Low-dose inhaled budesonide once or twice daily for 27 months in children with mild asthma. Allergy 2000:55(8): 740–748. (AstraZeneca AS, Skårer, Norway)	Single-center, double-blind, placebo-controlled extension trial Patients had been randomized in balanced blocks 3 months prior	To study the long-term clinical efficacy of low-dose inhaled budesonide once or twice daily in children with mild asthma	122 (89 completed: ITT analysis)	**Age** 7–16 yr, mean = 9.7 yr **Gender** 66% male, 34% female **Ethnicity** Not reported	Mild asthma FEV_1 % pred. mean = 103.7 Reversibility in FEV_1 3.5% Fall in FEV_1 after exercise 12.2% Not previously treated with ICS	**Arm 1** Budesonide once daily in morning + placebo in evening **Arm 2** Budesonide once daily in morning + placebo in evening **Arm 3** Budesonide twice daily **Arm 4** Placebo twice daily	100 mcg once daily 200 mcg once daily 100 mcg twice daily	24 months following 12-month trial (not reported here)		*Significant dose-response effect favoring budesonide 200 mcg daily vs. 100 mcg when comparing changes in FEV_1, $FEF_{25\%}$, and $FEV_{50\%}$; and fall in FEV_1 after exercise test.	Asthma symptoms showed 85% decreased in 200 mcg daily group, 62% decrease in 100 mcg daily group, and 65% decrease in placebo group. Number of mild/severe exacerbations did not differ between groups.	After 3 months, patients treated with budesonide had lower blood eosinophil count (p <0.05) at all but 1 visit (27 months). No difference among the budesonide groups. 10 SAE not asthma-related. Difference in growth rates for those ages 7–11 yr treated with budesonide vs. placebo after 12 months (diff. 1.09–1.49, p <0.006).

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	Change in Medication Use	Lung Function	Exacerbations/Symptoms	Other
Kemp et al. Mometasone furoate administered once daily is as effective as twice-daily administration for treatment of mild-to-moderate persistent asthma. J Allergy Clin Immunol 2000; 106(3):485–492.	Multicenter, randomized, double-blind, placebo-controlled trial (22 centers in the United States)	To compare once-daily and twice-daily dosing with mometasone furoate (MF) administered in the morning by using a dry-powder inhaler (DPI)	306 (263 completed; ITT analysis)	**Age** 12–70 yr, mean = 30.8 yr **Gender** 50% male, 50% female **Ethnicity** 81% Caucasian, 9% Black, 10% other	Mild-to-moderate asthma Duration mean = 16.5 yr FEV_1 % pred. mean = 72 Using SABA $\geq$ 2 weeks No ICS in 3 months	**Arm 1** Morning MF-DPI (n=77; 67 completed) **Arm 2** Morning MF-DPI (n=74; 68 completed) **Arm 3** MF-DPI twice daily (n=79; 72 completed) **Arm 4** Placebo (n=74; 56 completed)	200 mcg, 2 inhalations once/day 400 mcg, 2 inhalations once/day 200 mcg, 2 inhalations twice/day	12 weeks after 7–14 days run-in. Required to use albuterol $\geq$ 3 times/week during run-in. SABA withheld at least 6 hours before any study visit. No other asthma medications allowed during study.	Patients in all 3 MF-DPI groups were able to decrease (p <0.05) albuterol use compared with placebo.	*Increase in FEV_1 for MF-DPI 400 mcg (16.0%) and 200 mcg twice daily (16.1%) significantly different from placebo (5.5%), p <0.01. Improvement in MF-DPI 200 mcg once daily (10.5%) did not differ from placebo. Increase in morning PEF showed improvement (p <0.01) for MF-DPI 400 mcg (13%) and 200 mcg twice/day (17.7%) vs. placebo (6.2%). Improvement in MF-DPI 200 mcg once/day (6.9%) did not differ from placebo.	All MF-DPI groups were superior to placebo (p <0.01) in time to worsening of asthma. Percentage of patients rated by physician as improved was 62% for MF-DPI 200 mcg once/day, 73% for MF-DPI 400 mcg once/day, 80% for MF-DPI 200 mcg twice/day, and 45% for placebo.	Treatment-related AE occurred in 23% of each MF-DPI group and 19% of placebo group. Most were mild to moderate in intensity.
Nayak et al. Once-daily mometasone furoate dry powder inhaler in the treatment of patients with persistent asthma. Ann Allergy Asthma Immunol 2000:84(4): 417–424.	Multicenter, randomized, double-blind, parallel group study (21 centers in the United States)	To compare the efficacy and safety of once-daily administration of mometasone furoate dry powder inhaler (MF DPI) 200 mcg and 400 mcg with placebo in patients with asthma previously maintained only on short-acting inhaled beta-adrenergic receptor agonists	236 (191 completed; ITT analysis)	**Age** 12–72 yr, mean = 33 yr **Gender** 47% male, 53% female **Ethnicity** 86% Caucasian, 9% Black, 5% other **Smoking** 80% never smoked, 20% had not smoked in previous 6 months	Mild-to-moderate persistent asthma Duration 1–48 yr, mean = 16 yr FEV_1 % pred. range 46–95, mean = 72 PEF mean = 374 L/min Mean albuterol use = 4.1 puffs/day	**Arm 1** MF-DPI (n=72; 65 completed) **Arm 2** MF-DPI (n=77; 62 completed) **Arm 3** Placebo	200 mcg once daily in morning 400 mcg once daily in morning	12 weeks after 1–2 week run-in period	Albuterol use decreased significantly for both MF-DPI groups (–1.58 and –1.23 puffs/day) as compared with placebo (–0.27 puffs/day) (p <0.01).	*Significant difference (p <0.01) in increase in FEV_1 for MF-DPI 200 mcg (14.8%) and MF-DPI 400 mcg (14.2%) vs. placebo (2.5%). Significant difference (p <0.05) in increase in FVC for MF-DPI 200 mcg (6.4%) and MF-DPI 400 mcg (11.2%) vs. placebo (0.5%). Significant difference (p <0.025) in increase in $FEF_{25\%-75\%}$ for MF-DPI 200 mcg (31%) and MF-DPI 400 mcg (8.8%) vs. placebo (2.0%).	Kaplan-Meier estimates of time to worsening of asthma showed both MF-DPI groups were better than placebo (p <0.01). Significantly more patients in placebo group (26 patients) experienced asthma worsening than in either the MF-DPI 400 mcg (9 patients) or MF-DPI 200 mcg group (13 patients) (p <0.01). Percentage of patients rated by physician as improved was 64% for MF-DPI 200 mcg and 66% for MF-DPI 400 mcg vs. 21% for placebo (p <0.01).	Treatment-related AE occurred at a similar incidence among the 3 groups.

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	Change in Medication Use	Lung Function	Exacerbations/Symptoms	Other
lfe et al. Comparison of ce- and twice-daily dosing luticasone propionate 200 ograms per day dministered by diskus device atients with asthma ated with or without inhaled ticosteroids. J Allergy Clin munol 2000;105(6 Pt 1): 3–1161. axoWellcome, Inc.)	2 multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group studies (26 clinical centers in the United States)	To compare the efficacy of fluticasone propionate (FP) administered once or twice daily in patients currently treated with bronchodilators only (BD patients) and in patients who required inhaled corticosteroids for maintenance treatment of asthma (ICS patients)	422 (263: ITT analysis)	**Age** 12–78 yr, mean = 35 yr **Gender** 55% male, 45% female **Ethnicity** Not reported **Smoking** 100% nonsmokers	Persistent: 223 (53%) previously treated with bronchodilator therapy to control asthma (BD patients) and 199 (47%) in addition to BD therapy had maintained ICS regimen for at least 3 months FEV_1 % pred. mean = 68 Morning PEF mean = 421 L/min Albuterol use mean = 2.61 puffs/day	**Arm 1** Fluticasone propionate twice daily (n=77 BD and 65 ICS; 64 BD & 35 ICS completed) **Arm 2** Fluticasone propionate once daily (n=73 BD & 65 ICS; 57 BD and 42 ICS completed) **Arm 3** Placebo (n=73 BD and 69 ICS; 38 BD and 26 ICS completed)	100 mcg (FP100bid) 200 mcg (FP200qd)	12 weeks after 2-week screening Albuterol aerosol as needed and regularly administered and theophylline or salmeterol if part of an established fixed dosage regimen was permitted during the study.	BD patients treated with FP100bid reduced albuterol use by 43% and with FP200qd by 36% and placebo increased use by 8% ($p < 0.019$ FP vs. placebo). ICS patients reduced albuterol use by 15% with FP100bid and by 4% with FP200qd vs. placebo increased use by 49% ($p < 0.002$ FP vs. placebo).	*BD patients treated with FP100bid and FP200qd had mean increases of 19% and 14% in FEV_1 vs. 8% placebo ($p < 0.05$). ICS patients treated with FP100bid and FP200qd had mean increases of 12% and 4% in FEV_1 vs. –3% in placebo ($p < 0.023$). Mean change in morning PEF for BD (31 L/min) and ICS (7 L/min) patients was greater after FP100bid vs. placebo ($p < 0.001$).	In BD patients, reduction in asthma symptom scores favored FP100bid (–0.40, $p=0.016$) and FP200qd (–0.37, $p=0.063$) vs. placebo. In ICS patients, reduction was –0.23 in FP100bid and –0.03 in FP200qd vs. increase of +0.14 in placebo ($p < 0.05$).	BD and ICS patients in both FP groups had a greater probability of remaining in the study over time vs. placebo (BD $p < 0.008$; ICS $p < 0.045$) with no difference between FP groups. No SAE in BD patients; 1 SAE related to study drug in ICS patient treated with FP200qd.
onan et al. Comparison of ce-daily to twice-daily atment with mometasone oate dry powder inhaler. n Allergy Asthma Immunol)1;86(1): 36–43. hering-Plough Research titute)	Multicenter, randomized, double-blind, parallel-group study (16 U.S. centers)	To compare twice-daily dosing of mometasone furoate administered by dry powder inhaler (MF-DPI) in patients with mild-to-moderate persistent asthma who were previously being treated with ICS	286 (219 completed: ITT analysis)	**Age** ≥12 yr, mean = 39 yr **Gender** 40% male, 60% female **Ethnicity** 81% Caucasian, 8% Black, 11% other Duration > 6 months, mean = 19 yr FEV_1 % pred. 79	Mild-to-moderate persistent asthma Using daily ICS for at least 30 days: 33% BCD mean = 338 mcg, 30% triamcinolone acetonide mean = 791 mcg, 25% fluticasone propionate mean = 377 mcg, 11% fluticasone propionate mean = 1,179 mcg	**Arm 1** MF-DPI once/daily in AM (n=58) **Arm 2** MF-DPI once-daily in PM (n=54) **Arm 3** MF-DPI once daily in AM (n=58) **Arm 4** MF-DPI twice-daily, AM and PM (n=58) **Arm 5** Placebo (n=58)	200 mcg 200 mcg 400 mcg 200 mcg	12-weeks after a 2-week open-label phase Patients received MF-DPI 200 mcg twice daily during open-label phase. All patients received rescue inhaler (albuterol).	Albuterol use (puffs/day) differed for MF-DPI 200 mcg once daily AM (+0.54), MF-DPI 400 mcg once daily AM (+0.21), and MF-DPI 200 mcg twice daily (–0.15) vs. placebo (+1.53), but not for MF-DPI 200 mcg once daily PM (+0.73) ($p > 0.05$).	*Significant change ($p < 0.01$) in FEV_1 (L) for MF-DPI 200 mcg once daily AM (–0.22), MF-DPI 200 mcg twice daily (–0.03), and MF-DPI 400 mcg once daily (–0.01) vs. placebo (–0.30) but not for MF-DPI 200 mcg once daily PM (0.03) ($p > 0.05$). MF-DPI 200 mcg once daily PM was significantly improved compared with MF-DPI 200 mcg once daily AM ($p < 0.01$). End-point data for both FVC and $FEF_{25\%-75\%}$ showed similar results: MF-DPI 200 mcg once daily PM, 400 mcg once daily AM, and 200 mcg twice daily was significantly improved compared with placebo ($p < 0.03$), but MF-DPI 200 mcg once daily AM was not ($p > 0.05$). All groups differed from placebo for change in PEF ($p < 0.01$) at endpoint.	Kaplan-Meier estimates of time to worsening of asthma showed all MF-DPI groups superior to placebo ($p < 0.01$). Mean scores for AM wheezing and difficulty breathing favored all MF-DPI groups over placebo ($p < 0.01$). Nocturnal awakening was significantly improved ($p < 0.02$) for MF-DPI 200 mcg once daily PM, 400 mcg once daily AM, and 200 mcg twice daily groups compared with placebo; MF-DPI 200 mcg once daily PM was not different from placebo at endpoint. Percentage of patients rated by physician as improved was 41% for MF-DPI 200 mcg once daily AM, 54% for 200 mcg once daily PM, 50% for 400 mcg once daily AM, and 57% for 200 mcg twice daily vs. 28% for placebo.	2 SAE: asthma exacerbation in placebo group and elevated levels of hepatic enzymes at week 12 in MF-DPI 200 mcg once daily PM group for patient with flu-like symptoms who took OTC cold medications.

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	Change in Medication Use	Lung Function	Exacerbations/Symptoms	Other
Postma et al. Treatment of asthma by the inhaled corticosteroid ciclesonide given either in the morning or evening. Eur Respir J 2001;17(6): 1083–1088. (Byk Gulden Pharmaceutical) Note: See also Casale, Hawkins, and Foresi in Section IVb. "Step Up—Step Down."	Multisite, randomized, double-blind, parallel-group design (outpatients)	To determine whether the time point of administration (morning or evening) affects the efficacy of ciclesonide (hypothesized equivalence)	209 (168 per protocol)	Age 18–75 yr, median 38 yr Gender 56% male, 44% female Ethnicity Not reported Smoking 51% never smoked, 45% exsmokers, 4% smokers	Mild-to-moderate asthma 35% pretreated with ICS ICS dose 200–500 mcg in BDP equivalents, median 500 mcg FEV_1 % pred. mean = 76 PEF % pred. mean = 88	Arm 1 Morning + placebo (n=110; 88 per protocol) Arm 2 Evening + placebo (n=99; 80 per protocol)	Both arms: 1 puff of 200 mcg ciclesonide administered by metered-dose inhaler at treatment time and 1 puff of placebo at other time	8 weeks following 1–4 week run-in SABA used to relieve symptoms and same rescue medication used throughout the trial. Cromones and histamine 1 receptor blockers were allowed to treat symptoms of allergic rhinitis.	Daily use of rescue medications changed significantly (p <0.05) for AM (–0.36 puffs) and PM (–0.36) administration with no difference between groups.	*Morning PEF in AM group increased by 8 L/min after 4 weeks and 3 L/min after 8 weeks of treatment (p >0.05) and in PM group by 24 L/min and 30 L/min at 4 and 8 weeks (p <0.005). The difference between AM and PM groups differed at 8 weeks (p <0.05). FEV_1 increased significantly (p <0.05) after 8 weeks in both groups (+0.31). FVC increased (p <0.05) 0.19 in AM group and 0.22 in PM group with no difference between groups after 8 weeks.	Total daily asthma symptoms improved (p <0.001) in both groups (AM –0.38; PM –0.50) with no difference between groups. There was no difference in the percentage of rescue medication-free days (54% for AM and 46% for PM administration).	Four patients in each group experienced lack of efficacy. Investigators rated ciclesonide as effective in 61% of AM group and 71% of PM group. There was no difference in safety aspects between the groups.
Chapman et al. Maintenance of asthma control by once-daily inhaled ciclesonide in adults with persistent asthma. Allergy 2004;60(3):330–337. (ALTANA Pharma AG, Konstanz, Germany)	Multisite, randomized, placebo-controlled, double-blind, parallel-group study (25 centers throughout Canada)	To evaluate the clinical efficacy, tolerability, and safety of ciclesonide in patients with persistent asthma	329 (185 ITT analysis)	Age 18–69 yr, median 41 yr Gender 46.2% male, 53.8% female Ethnicity Not reported Smoking 64% nonsmokers, 36% exsmokers	Persistent asthma FEV_1 mean = 2.66 L FEV_1 % pred. mean = 78 Percent change in FEV_1 with beta₂-agonist, mean = 19.3 Daily ICS dose mean = 754 mcg (BDP equivalent) All treated with stable dose ICS for ≥ 4 weeks	Arm 1 Ciclesonide (C160) (n=107; 71 completers) Arm 2 Ciclesonide (C640) (n=112; 69 completers) Arm 3 Placebo (P) (n=110; 45 completers)	160 mcg once daily in morning (4 puffs) 640 mcg once daily in morning (4 puffs) placebo inhaler once daily in morning (4 puffs)	12 weeks after 2-week baseline period Patients experiencing lack of efficacy were withdrawn from the trial. Salbutamol (100 mcg/puff) provided for as-needed rescue medication		Both doses of C superior to P in maintenance of morning PEF from baseline (p <0.0001). Differences between C groups were not clinically or statistically significant. Both C superior to P in improvement from baseline in spirometry (p <0.05) with no change in FEV_1 or PEF for either C group but decreases for P. No difference between C groups.	44% withdrawal rate: 59% P, 34% C160, 38% C640, mostly due to lack of efficacy. Lack of efficacy was greater for P (63%) than C160 (30%) or C640 (31%) (p <0.0001 for C vs. P) with no difference between C160 and C640.	Changes in serum and urinary cortisol levels were not significant in any of the groups and there was no difference between groups (serum cortisol, p >0.45; urinary cortisol p >0.09). Incidence of AE 'likely related' to study medication was 6% in P, 4% in C160, and 8% in C640.
Masoli et al. Budesonide once versus twice-daily administration: meta-analysis. Respirology 2004;9(4):528–534. (AstraZeneca)	Meta-analysis of randomized trials of at least 4 weeks duration comparing budesonide once versus twice daily 7 trials double-blind and 3 open label	To determine whether once-daily administration of budesonide is as efficacious as twice-daily administration for all major clinical outcome measures and whether budesonide can be recommended as a once-a-day medication in the management of asthma	10 trials with 1,922 children and adults	Age 3 trials with children, mean age = 9 yr, range 5–17 yr; 7 trials with adults, mean age = 40 yr, range 18–70 yr Gender Not reported Ethnicity Not reported	Mild-to-moderate asthma in most studies FEV_1 varied from >60% to >90%	Arm 1 Budesonide once-daily Arm 2 Budesonide twice-daily	Daily dose was 200 mcg (5 trials), 400 mcg (6 trials), and 800 mcg (1 trial). 2 trials included 2 doses.	6 weeks (1 trial), 8 weeks (4 trials), and 12 weeks (5 trials)		No difference between once or twice daily dosing although outcomes favored twice daily: WMD for FEV_1 0.09 (95% CI –0.09 to 0.27) and WMD for morning PEF 0.07 (95% CI –0.04 to 0.17).		No difference between once or twice daily dosing for withdrawal due to asthma although outcomes favored twice daily: OR for withdrawal 1.0 (95% CI 0.65 to 1.52).

IIb. 1x/day vs. 2x/day: with combo

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	Other
Buhl et al. Once-daily budesonide/ formoterol in a single inhaler in adults with moderate persistent asthma. Respir Med 2003;97(4): 323–330. (AstraZeneca, Sweden)	Multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group study (56 centers in 9 countries)	To compare the efficacy of once-daily budesonide/ formoterol with that of once-daily budesonide alone, and twice-daily budesonide/ formoterol. To show that a simpler treatment regimen is effective even in patients with moderate persistent asthma	523 (488; ITT)	**Age** 18–78; mean = 44.3 yr **Gender** 38% male, 62% female **Ethnicity** Not reported **Smoking** 75% nonsmoker, 18% exsmoker, 8% current smoker	Moderate persistent asthma Duration 0–62 yr, mean = 13.2 yr FEV_1 % pred. mean = 77 FEV_1 2.28 L Mean FEV_1 reversibility 21.7% Morning PEF 348 L/min Use of reliever medications mean = 1.1 inhalations/day	**Arm 1** Once-daily budesonide/ formoterol (BF) in evening (n=176; 162 completed) **Arm 2** Twice-daily budesonide/ formoterol (n=176; 161 completed) **Arm 3** Once-daily budesonide in evening (n=171; 157 completed)	160/4.5 mcg, 2 inhalations 160/4.5 mcg, 1 inhalation 400 mcg	12 weeks following 2-week run-in during which patients received budesonide Turbuhaler® (200 mcg) twice daily No concomitant asthma medication except for inhaled short-acting beta$_2$-agonist medication terbutaline sulfate as needed	*Significant change in morning PEF of 27.4 L/min for BF once daily and 22.8 L/min for BF twice daily vs. –0.95 L/min for budesonide once daily (p <0.001). Difference between BF groups not significant. Mean FEV_1 significantly greater in once-daily BF (2.32 L) and twice-daily BF (2.37 L) than in budesonide alone (2.22 L, p <0.001).	No difference between once- and twice-daily BF in asthma in symptom measures. Daily reliever use improved in BF groups vs. budesonide alone (p <0.01). Chance of asthma-control week was 99% higher (OR=1.99) in once-daily BF and 80% higher (OR 1.80) in twice-daily BF group compared with budesonide alone. Median exacerbation-free time of 80 days in once-daily BF and 78 days in twice-daily BF vs. 42 days in budesonide alone (p <0.001).	40% of once-daily BF, 34% of twice-daily BF, and 34% of budesonide alone groups experienced at least 1 AE. 5 SAE, none related to study medications.

III. Decreased Responsiveness to ICS Tx

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	Other
Chalmers et al. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax 2002;57(3):226–230. (Chest Heart & Stroke, Scotland and Glaxo SmithKline)	Randomized, double-blind, placebo-controlled, crossover study	To examine the effect of active cigarette smoking on responses to treatment with ICS in patients with mild asthma	47 (38)	**Age** 35.0 yr **Gender** 55% male, 45% female **Ethnicity** Not reported **Smoking** 45% smokers	Mild asthma; steroid naive pts. FEV_1 % pred. mean = 88 Morning PEF 433 L/min	Fluticasone propionate Placebo	1,000 mcg daily	Three study periods of 3 weeks duration each after 1-week placebo run-in phase	*Significantly greater change in morning PEF following inhaled fluticasone for nonsmokers than smokers (27 L/min vs. –5 L/min, p=0.0006). Nonsmokers had increase in mean morning PEF (27 L/min, p=0.016), mean FEV_1 (0.17 l, p=0.02), and geometric mean PC_{20} (2.6 doubling doses, p=0.0002) and significant decrease in sputum eosinophils (–1.75%, p=0.048) after fluticasone vs. placebo. No significant differences for smokers.	
Gauvreau et al. Increased levels of airway neutrophils reduce the inhibitory effects of inhaled glucocorticosteroids on allergen-induced airway eosinophils. Can Respir J 2002;9(1):26–32. (Canadian Institutes of Health Research)	Randomized, double-blind, placebo-controlled, crossover design	To determine whether allergic responses or the efficacy of steroid treatment could be predicted by baseline levels of inflammatory cells in induced sputum	28 (24)	**Age** $\geq$18 yr, mean = 24.5 yr **Gender** Not reported **Ethnicity** Not reported **Smoking** 100% nonsmokers	Mild atopic asthma FEV_1 % pred. mean = 86 MCh PC_{20} mean = 1.5 mg/mL Allergen-induced late asthmatic response: placebo mean = 23.6% change and glucocorticoid mean = 5.7% change	**Study 1/Study 2** Budesonide or placebo **Study 3** Mometasone furoate or placebo twice daily	200 mcg twice daily 400 mcg twice daily	Study 1–8 days Study 2–7 days Study 3–6 days Treatment periods separated by a 3-week washout period		Baseline sputum neutrophil correlated with % inhibition of allergen-induced sputum eosinophils by glucocorticoids at 7 hr (r = –0.61, p <0.001) and 24 hr (r = –0.73, p <0.0001). No relationship between baseline sputum eosinophils and % inhibition of allergen-induced eosinophilia (p >0.12). Percent inhibition of the LAR by glucocorticoids correlation with % inhibition of sputum eosinophils at 7 hr (r=0.44, p=0.03) and 24 hr (r=0.53, p=0.008). No relationship between baseline sputum eosinophils or neutrophils and % inhibition of EAR or LAR (p >0.05).

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	Other
Green et al. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. Thorax 2002;57 (10): 875–879. (AstraZeneca, Trent Region UK and Glenfield Hospital UK Research Fund)	Comparative	To test the hypothesis that a predominant neutrophilic airway inflammation is present in a subset of patients with milder asthma and that this phenotype is associated with a poor response to inhaled corticosteroids	293	**Age** Mean = 45 yr **Gender** 47% male, 53% female **Ethnicity** Not reported **Smoking** 70% nonsmokers, 22% exsmokers, 8% smokers	49% intermittent asthma (step 1 of British Thoracic Society guidelines), 40% had more persistent symptoms (steps 2 and 3), 12% normal controls with no symptoms of asthma	Full sample consisted of 34 normal controls and 259 adults with symptomatic asthma receiving treatment at steps 1–3 of the British Thoracic Society (BTS) guidelines.	Randomly selected subgroup of 49 out of 92 patients treated with beta$_2$-agonists only met BTS criteria for step up to budesonide 400 mcg twice daily.	2 months	Significantly less improvement in FEV$_1$ as compared with those not treated (−.08 vs. 0.13, p=0.026).	Significantly less improvement in visual analogue symptom scores as compared with those not treated (−5.5 vs. −19.4, p=0.04). Significantly less improvement in PC$_{20}$ as compared with those not treated (0.15 vs. 1.29 doubling doses, p=0.029).	Median sputum eosinophil count lower in atopic subjects receiving ICS (1.1%) than nonatopic subjects receiving ICS (3.3%, p <0.05). 60 patients with sputum neutrophil count outside normal range and normal sputum eosinophil count tended to be older, develop asthma late, be female, and be nonatopic.
Chaudhuri et al. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. Am J Respir Crit Care Med 2003; 168(11): 1308–1311. (National Asthma Campaign, UK)	Randomized, double-blind, placebo-controlled, crossover study	To assess the effect of cigarette smoking on the therapeutic response to oral corticosteroids in chronic stable asthma	59 (50)	**Age** 18–55 yr, mean = 42.3 yr **Gender** 72% male, 28% female **Ethnicity** Not reported **Smoking** 52% never-smokers, 20% exsmokers, 28% smokers	Chronic stable asthma American Thoracic Society score mean = 4.3 FEV$_1$ % pred. mean = 69 ICS mean = 502 mcg/day All had reversibility in FEV$_1$ after nebulized albuterol of 15% or more.	Oral prednisolone Placebo	40 mg daily	Two 14-day periods with 2-week washout phase between	*Change in mean FEV$_1$ (mean 237, p=0.019) and morning PEF (mean 36.8, p=0.006) for never-smokers, but no change for smokers (mean 47, p=0.605 and 6.5, p=0.47). Exsmokers improved in morning PEF (mean 29.1, p=0.04).	Asthma control score significantly reduced in nonsmokers (mean 0.72, p=0.004), but not in other 2 groups (p >0.10).	

IVa. "Step Down"—Dose and Time Dependence

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	Other
Boushey et al. Daily versus as-needed corticosteroids for mild persistent asthma. N Engl J Med 2005;352: 1519–1528. (National Institutes of Health)	Multisite, randomized, double-blind, parallel-group trial (6 centers)	To evaluate the efficacy of intermittent short-course corticosteroid treatment guided by a symptom-based action plan alone or in addition to daily treatment with either inhaled budesonide or oral zafirlukast over a 1-year period	225 (199)	**Age** Mean = 32.9 yr **Gender** 38.7% male, 61.3% female **Ethnicity** 27.1% minority, 15.1% black **Height** Mean = 170 cm **Weight** Mean = 75.3 kg **Body Mass Index** Mean = 26.0	Mild persistent asthma Duration of asthma mean = 19.2 yr FEV_1 mean = 3.2 L FEV_1 % pred. mean = 88.8 Morning PEF 2-week average 466 L/min Asthma QoL score mean = 5.8, range 1–7 Asthma-control score mean = 1.1, range 0–6 Number symptom-free days in past 14 days mean = 5.8 Asthma Symptom Utility Index score mean = 0.8, range 0–1	**Arm 1** Budesonide + oral placebo (B) (n=73; 67 completers) **Arm 2** Zafirlukast + placebo inhaler (Z) (n=76; 62 completers) **Arm 3** Placebo (intermittent treatment: IT) (n=76; 70 completers)	Twice daily inhalation of 200 mcg + oral placebo Twice-daily 20 mg + inhalation of placebo Twice-daily oral and inhaled placebo	52 weeks with 2-week run-in; 10–14 day period of intense combined therapy after both run-in and treatment phases of 0.5 mg prednisone/ kg/day, 800 mcg budesonide twice daily, 20 mg zafirlukast twice daily plus as-needed albuterol (540-720 mcg). All patients received instruction to take budesonide (800 mcg twice daily) for 210 days or prednisone (0.5 mg/kg/day) for 5 days if symptoms worsened.	(adjusted for baseline covariates) *Change in morning PEF increased about 7.8% (32 L/min) in all groups (p=0.90). Increase in average morning PEF from first to second period of intense combined therapy was similar among groups (p=0.61). Change in prebronchodilator FEV_1 increased more in B than in Z or IT (4.0 vs. –1.1 and 0.7, p=0.005), but changes in postbronchodilator did not differ between groups (p=0.29). B vs. Z and IT had greater improvement in percentage of eosinophils in sputum (medians –0.3 vs. 0.0 and 0.2, p=0.007), exhaled nitric oxide levels (medians –14.4 vs. 12.4 and 26.6, p=0.006), and PC_{20} ($\log_2$ of 1.8 vs. 0.3 and 0.1, p <0.001).	No difference between groups in time to first exacerbation (p=0.39). 12-month Kaplan-Meier exacerbations rates for B and IT were 16.1% and 11.3% (diff 4.8%, 95% CI –7% to 16%). Improvements in asthma control score and number of symptom-free days were greater with B than either Z or IT (p <0.001 and p=0.03, respectively); no difference between Z and IT. Greater number of symptom-free days over a 2-week period with B (9.0 days) than Z (8.7 days) or IT (8.8 days) translates to 26 additional symptom-free days/year (95% CI 1.8 to 48.5 days).	
Foresi et al. Step-down compared to fixed-dose treatment with inhaled fluicasone propionate in asthma. Chest 2005;127(1): 117–124. (Glaxo-Smith-Kline Italy)	Randomized, double-blind, parallel group	To compare the efficacy of inhaled fluticasone propionate administered in a dose of 1,000 mcg/day and then reduced to a dose of 200 mcg/day to a fixed dose of fluticasone propionate 200 mcg/day in reducing eosinophilic inflammation and bronchial hyperresponsive-ness to methacho-line in patients with mild-to-moderate asthma. In addition, to assess the duration of the effect of the 2 treatment strategies	35 (35 ITT analysis)	**Age** 18–58 yr, mean = 363.4 yr **Gender** 45.7% male, 54.3% female **Ethnicity** Not reported	Mild (40%) and moderate (60%) asthma Duration of asthma: 37% <5 yr, 37% 5–10 yr, 26% > 10 yr FEV_1, 1.7–4.8 L, mean = 2.9 L FEV_1 % pred., 60–144, mean = 86 PEF, 190–644 L/min, mean = 384 L/min PEF % pred., 45–166, mean = 78.9	**Arm 1** Fluticasone propionate stepdown (FP-SD) N=18; 14 completers **Arm 2** Fluticasone propionate fixed dose (FP-F) (n=17; 14 completers)	500 mcg bid (Phase I) stepped down to 100 mcg bid (Phase 2) followed by placebo (Phase 3). 100 mcg bid (Phase I & 2) followed by placebo (Phase 3).	6 weeks for Phase 1 and 8 weeks for Phase2; 8-week single-blind placebo period; 3-week run-in period Albuterol/salbutamol used on as-needed basis. If exacerbation, patients treated with prednisone, 25 mg/d, for 3 days. If improved, prednisone stopped; if not, prednisone administered for 3 additional days.	No difference between treatments for FVC and FEV_1 at any study period. Morning and evening PEF did not differ between groups at any study period.		PD_{20} increased from 90.9 to 471.5 (Phase 1) to 406.2 (Phase 2) in FP-SD and from 208.9 to 426.6 (Phase 1) to 763.0 (Phase 2). Mean ratio change in geometric mean PD_{20} did not differ between groups at any period. Total cells, macrophages, lymphocytes, and neutrophils in induced sputum did not change during the study. Percentages of patients in whom sputum eosinophilia was normalized after Phase 1 and Phase 2 were 69% and 60% for FP-SD and 50% and 57% for FP-F.

IVb. "Step Up—Step Down"—Dose and Time Dependence

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	Change in Medication Use	Lung Function	Exacerbations/Symptoms	Other
Convery et al. Effect of inhaled fluticasone propionate on airway responsiveness in treatment-naive individuals – a lesser benefit in females. Eur Respir J 2000;15(1):19–24. (GlaxoWellcome Group Research)	Randomized, double-blind, placebo-controlled, parallel-group study stratified by sex and smoking habit	To evaluate the effect on airway responsiveness of inhaled fluticasone propionate	52 (39; ITT)	**Age** 20–50 yr, mean = 33 yr **Gender** 40% male, 60% female **Ethnicity** Not reported **Smoking** 52% nonsmokers, 48% smokers	Normal: had never knowingly received any regular treatment for asthma FEV_1 % pred. mean = 101 FEV_1 mean = 3.61 L	**Arm 1** Fluticasone propionate **Arm 2** Placebo	2,000 mcg daily in morning	6 weeks after 1–2 weeks pretreatment phase: 20-week followup phase		*No significant changes in FEV_1 from baseline occurred throughout study in either group ($p > 0.05$). No changes in PD_{20} in placebo group during treatment, but in the fluticasone propionate group PD_{20} increased steadily with increasing significance ($p < 0.003$). During followup, differences were not significant.	No effect of smoking, age, or FEV_1 on change in PD_{20}. Fluticasone propionate exerted a greater effect in males than in females: 1.2 doublings in geometric mean PD_{20} from baseline in females and additional 2.0 doublings in males ($p < 0.04$).
Foresi et al. Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. Chest 2000;117(2):440–446. (Astra Farmaceutici, Italy)	Multicenter, randomized, double-blind, parallel-group study (14 outpatient clinics)	To compare the effect of prolonged treatment with a low dose of inhaled budesonide in controlling symptoms and maintaining optimal pulmonary function, and to ascertain whether exacerbations could be treated by early intervention with a short-term increase in the daily dose of inhaled budesonide	213 (191 completed study; 209 in intent-to-treat analysis)	**Age** Mean = 38.5 yr **Gender** 47% male, 53% female **Ethnicity** Not reported **Smoking** 70% nonsmokers, 22% exsmokers, 8% smokers	Moderate asthma Duration of asthma: 28% <5 yr, 22% 5–10 yr, 50% >10 yr FEV_1 % pred. mean = 74 PEF % pred. = 75 41% taking salmeterol, 17% theophylline	**Arm 1** High-dose budesonide + placebo (n=67) **Arm 2** Low-dose budesonide + budesonide (n=67) **Arm 3** Low-dose budesonide + placebo (n=75)	400 mcg bid 100 mcg bid + 200 mcg qid 100 mcg bid	6 months following 4-week run-in during which patients inhaled budesonide 800 mcg bid Inhaled beta$_2$-agonists allowed on as-needed basis: treatment with LABA or theophyllines kept constant		PEF higher in HD group vs. LD + budesonide ($p < 0.05$) and vs. LD + placebo ($p < 0.05$) after 6th month.	*No difference between groups in number of days with wheeze, cough, and shortness of breath. Majority of patients recorded no exacerbations: 84% in HD, 82% in LD + budesonide, 68% in LD. Significance between HD and LD ($p < 0.04$) with ITT analysis and $p < 0.015$ for per-protocol analysis. Significance between LD and budesonide vs. LD ($p < 0.025$) with per-protocol analysis.	
Chanez et al. High or standard initial dose of budesonide to control mild-to-moderate asthma? Eur Respir J 2001; 17(5):856–862.	Multicenter, randomized, double-blind and double-dummy, parallel-group study (18 centers in France: block randomization by center)	To determine if a high initial dose of ICS was more efficacious than a standard dose in controlling symptoms and improving lung function. To assess if the daily dose could be decreased rapidly in the high-dose group to a minimum maintenance dose in patients with mild-to-moderate asthma	169 (214 enrolled, 169 randomized, 127 completed study; intent-to-treat analysis)	**Age** 18–68 yr, mean = 38 yr **Gender** 50% male, 50% female **Ethnicity** Not reported	Uncontrolled asthma with daily nocturnal symptoms, wheezing and beta$_2$-agonists required Duration 0–52 yr, mean = 16.5 yr 50% previously used ICS FEV_1 % pred. mean = 74	**Arm 1** High dose (HD) budesonide (n=83: 66 completed) **Arm 2** Standard dose (SD) budesonide (n=86: 71 completed)	Started at 800 mcg bid daily 200 mcg bid daily	4 treatment periods, each of 4 weeks duration. At end of each active period, daily dose was halved in HD group if patient's asthma was controlled.	Proportion qualifying for dose reduction was similar in the 2 groups at each assessment stage. Mean daily dose in HD group tapered to 600 mcg by the end of the study.	*Morning PEF increased by 48 L/min in HD and 46 L/min in SD at 4 weeks and by 6 L/min in HD and 60 L/min in SD at 16 weeks. No difference between groups in FEV_1 at any time point.	*No difference between HD and SD groups in symptom score or number of exacerbations per interval.	

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	Other
Dahl et al. Effect of long-term treatment with inhaled budesonide or theophylline on lung function, airway reactivity and asthma symptoms. Respir Med 2002;96(6):432–438. (Astra Draco, Lund, Sweden)	Randomized, double-blind, double-dummy, parallel-group study (Outpatient clinic)	To investigate whether prolonged treatment with inhaled budesonide influences lung function, bronchial reactivity, and asthma symptoms and whether a dose or time relationship existed for the effects	85 (54 completed treatment phase, 24 completed followup phase; ITT)	**Age** Mean = 46 yr **Gender** 55% male, 45% female **Ethnicity** Not reported **Smoking** 31% smokers	Moderate asthma Mean duration = 7 yr FEV_1 % pred. mean = 69 Reversibility FEV_1 % pred. mean = 14.2 Mean asthma score = 1 on 0–3 scale	**Arm 1** Budesonide + oral placebo **Arm 2** Budesonide + oral placebo **Arm 3** Theophylline + inhaled placebo	800 mcg bd 200 mcg bd 300 mg bd Terbutaline 0.25 mg or salbutamol 0.1 mg inhalers were used as rescue medication.	36 weeks with 12 weeks followup with study medication withheld	* FEV_1 % pred. improved after 1 month (p <0.01) and persisted during treatment period for the budesonide 800 mcg group and increased significantly after 20 weeks for the budesonide 200 mcg group with no change in the theophylline group. FEV_1 % pred. returned to baseline during the first 4 weeks after treatment terminated. PEF unchanged in the 3 groups. PC_{20} decreased after 4 weeks (p <0.01) decreasing by 2 doubling dilutions after 36 weeks (p <0.001) for budesonide 800 mcg, decreased (p <0.005) after 8 weeks for budesonide 200 mcg and remained constant, and did not change with theophylline. During followup, reactivity increased significantly in 2 budesonide groups.	Dose-related decrease in symptom scores after budesonide (p <0.0001) with slight decrease after 4 and 8 weeks of treatment (p <0.01 and p <0.02) for theophylline.	Withdrawal rate due to lack of efficacy during treatment period higher (p <0.01) in the theophylline group (59% vs. 26%). In the followup period, 60% withdrew from budesonide groups vs. 36% in theophylline groups.
Douma et al. Initial improvements in lung function and bronchial hyperresponsiveness are maintained during 5 years of treatment with inhaled beclomethasone dipropionate and terbutaline. Chest 2002;121(1):151–157. (Netherlands Health Research Promotion Program and Glaxo)	Observational: 2.5-year continuation of a previous 2-year evaluation (6 university pulmonary outpatient clinics)	(1) To investigate whether initial improvements would persist on a constant dose of inhaled corticosteroids and (2) to determine if increasing the dose of inhaled corticosteroids would yield benefit in patients who do not respond sufficiently to initial treatment with moderate doses of inhaled corticosteroids	58 (53 completed)	**Age** Mean = 41 yr **Gender** 70% male, 30% female **Ethnicity** Not reported **Smoking** 25% nonsmokers, 40% exsmokers, 34% smokers	Asthma (38%), asthmatic bronchitis (34%), COPD (23%), and 6% undefined symptom diagnosis Treated with terbutaline 500 mcg 4 times/day and BDP 800 mcg/day for 3 years	**Group 1** BDP fixed dose (n=44) **Group 2** (insufficient responders) Increased dose of BDP (n=9)	800 mcg/day 1500 mcg/day	2.5 years (followup evaluation of a 3-year study) Salbutamol 400 mcg used as needed	Mean slope of individual regression lines for FEV_1, PC_{20}, and PEF remained stable over the period. In the BDP 1500 mcg/day group, there was no significant improvement in FEV_1, PC_{20}, and PEF after increasing the dose.	In the BDP 1,500 mcg/day group, there was no significant improvement in symptom scores after increasing the dose.	

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Citation (Sponsor)	Study Design	Purpose/Objective	Study N (Number Evaluated)	Population Characteristics	Asthma Severity at Baseline (If reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Change in Medication Use	Lung Function	Exacerbations/Symptoms	Other
Casale et al. Budesonide turbuhaler delivered once daily improves health-related quality of life and maintains improvements with a stepped-down dose in adults with mild to moderate asthma. Ann Allergy Asthma Immunol 2003; 90(3):323–330. (AstraZeneca LP)	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study (20 centers)	To examine the treatment and maintenance effects of once-daily dosing with budesonide Turbuhaler on patients' HRQL	309 (ITT)	**Age** 18–70: mean = 36.7 yr **Gender** 35% male, 65% female **Ethnicity** 86% Caucasian, 6% Black, 8% other	Mild-to-moderate asthma Duration mean = 18.1 yr FEV$_1$ % pred. mean = 82 Morning PEF 366 L/min Mean AQLQ = 4.8 out of 7 43% previous ICS use	**Arm 1** budesonide (n=103) **Arm 2** budesonide (n=102) **Arm 3** placebo (n=104)	200/200 mcg once daily 400/200 mcg once daily	6-week double-blind phase, 12-week reduction/ maintenance phase after 2-week baseline phase			*HRQL in budesonide 200/200 mcg > than placebo at week 6 (p=0.001) and week 18 (p=0.004); HRQL in budesonide 400/200 mcg > than placebo at week 6 (p <0.001) and at week 18 (p <0.0001). MID>.05 for 46% and 43% at weeks 6 and 18 for 200/200 mcg group and 58% and 55% at weeks 6 and 18 for 400/200 mcg.	
Hawkins et al. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. BMJ 2003;326(7399): 1115–1120. (NHS R&D Programme on Asthma Management)	Multicenter, randomized (stratified by center), double-blind, parallel-group trial (general practices throughout western and central Scotland)	To determine whether the dose of inhaled corticosteroids can be stepped down in patients with chronic stable asthma while maintaining control	259 (259)	**Age** 18–86 yr, mean = 53.9 yr **Gender** 42% male, 58% female **Ethnicity** Not reported **Smoking** 51% nonsmoker, 36% exsmoker, 13% smoker	Chronic, stable asthma ICS of 1430 mcg/day beclomethasone or equivalent 34% LABA Presalbutamol FEV$_1$ % pred. mean = 80.2 St. George's respiratory score mean = 24.8 (100 = maximum impact) EuroQoL mean = 74.9 (100 = best health)	**Arm 1** Stepdown (n=130) **Arm 2** Sham reduction (n=129)	50% of starting dose of ICS Starting dose of ICS	12 months after 1 month run-in period	Significant difference in mean annual dose of ICS: stepdown 390 mg BDP, control 517 mg BDP, p <0.001. No difference in mean annual dose of OCS (prednisolone), stepdown 117 mg, control 109 mg, p=0.25.		*31% of stepdown and 26% of control group had >1 exacerbation , OR 1.29, p=0.35. No difference between groups in St. George's respiratory questionnaire (diff=0.13, p=0.93), short asthma morbidity score (diff=0.16, p=0.54), and EuroQol visual analogue score (diff=2.32, p=0.25).	7 in each group experienced SAE during study, 3 (all in stepdown group) were asthma-related.
Powell & Gibson. Initial starting dose of inhaled corticosteroids in adults with asthma: a systematic review. Thorax 2004;59(12): 1041–1045. (Cooperative Research Centre for Asthma, Australia)	Systematic review of randomized, controlled trials of 2 different doses of the same ICS for a minimum of 4 weeks	To establish the optimal starting dose of ICS for adults with asthma	13 trials; 3,916 participants	**Age** Means ranged from 28 to 51 yr **Gender** Not reported **Ethnicity** Not reported	Mild to moderate in 6 trials, mild in 2 trials, moderate in 2 trials, moderate to severe in 2 trials, level undetermined in 1 trial	Budesonide doses compared in 9 studies, fluticasone in 3, and BDP in 1 study. 7 studies compared high-dose ICS with moderate-dose ICS, 6 compared moderate-dose ICS with low-dose ICS, and 4 studies compared a step-down dose with a constant ICS dose starting with a high dose.	7 studies compared high-dose ICS with moderate-dose ICS, 6 compared moderate-dose ICS with low-dose ICS, and 4 studies compared a step-down dose with a constant ICS dose starting with a high dose.	4 weeks to 36 weeks with majority (n=9) over a 4–12- week period	**High vs. moderate dose ICS:** No difference in rescue medications at night (WMD –0.03, 95% CI – 0.12 to 0.05; 2 trials, n=788). **Moderate vs. low dose ICS:** No difference in change in rescue medications (WMD –0.35, 95% CI –0.99 to 0.29; 3 trials, n=230). **Step down vs. constant dose ICS:** No difference in change in rescue medications at night (WMD –0.04, 95% CI –0.13 to 0.05; 2 trials, n=643).	**High vs. moderate dose ICS:** No significant improvement in morning PEF (WMD 5.72, 95% CI –1.56 to 13.00; 5 trials, n=1,117). **Moderate vs. low dose ICS:** Results for change in morning PEF favor moderate dose (WMD 11.14, 95% CI 1.34 to 20.93; 5 trials, n=411). **Step down vs. constant dose ICS:** No difference in change in morning PEF (WMD 0.83, 95% CI –8.60 to 10.26; 2 trials, n=643).	**High- vs. moderate-dose ICS:** No difference for change in daytime or nighttime symptom scores (WMD 0.02, 95% CI –0.12 to 0.05; 2 trials, n=800). **Moderate- vs. low-dose ICS:** Results for change in nighttime symptom score favor moderate dose (WMD –0.29, 95% CI –0.53 to –0.06; 3 trials, n=285). **Step-down vs. constant dose ICS:** No difference in change in nighttime symptom score (WMD 0.06, 95% CI –0.04 to 0.15; 2 trials, n=645).	

V. ICS dose-response

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	Other
Masoli et al. Dose-response relationship of inhaled budesonide in adult asthma: a meta-analysis. Eur Respir J 2004; 23(4):552–558.	Meta-analysis of randomized, placebo-controlled trials	To examine the dose-response relationship of inhaled budesonide in adolescents and adults with asthma	6 studies, published between 1990 and 2000; 1,435 participants	**Age** 12–70 yr; mean = 41 yr **Gender** Not reported **Ethnicity** Not reported	Mild to moderately severe in most studies FEV_1 % pred. mean = 69	Two or more doses of budesonide delivered by Turbuhaler or metered-dose inhaled + spacer device twice daily.	Ranged from 200–1,600 mcg/day; only 1 study used >800 mcg/day.	At least 4 weeks duration (6 trials: one 4 weeks, two 6 weeks, two 12 weeks, one 16 weeks)	Most of benefit was achieved at dose of 200–500 mcg/day. 80% of benefit obtained with 1,600 mcg/day was achieved at 200–400 mcg/day and 90% at 300–600 mcg/day. Dose of peak effect for FEV_1, morning PEF, evening PEF, and beta-agonists use ranged from 881–1,090 mcg/day. Difference in FEV_1 and PEF at dose of 400 mcg/day as compared with higher doses was not significant.		
Masoli et al. Systematic review of the dose-response relation of inhaled fluticasone propionate. Arch Dis Child 2004; 89(10):902–907.	Systematic review of randomized, double-blind, dose-response studies	To examine the dose-response relation of inhaled fluticasone for both efficacy and adrenal function in children with asthma	5 placebo-controlled studies with 1,150 children and 2 non- placebo-controlled studies with 583 children	**Age** 4–16 yr; mean = 37.5 yr **Gender** Not reported **Ethnicity** Not reported		Fluticasone compared with placebo or 2 doses of fluticasone compared.	100 and 200 mcg/day: 1 trial with 1,000 mcg/day step down to 100 mcg/day; 1 trial with 400 mcg/day.	At least 4 weeks duration (7 trials: one 4 weeks, four 12 weeks, two 52 weeks)	For FEV_1 and PEF response begins to plateau between 100 to 200 mcg/day. In 1 study of children with severe asthma, 400 mcg/day resulted in greater increase in PEF than 200 mcg/day at end of 52 weeks.	For bronchodilator use and night wakening, response begins to plateau between 100 and 200 mcg/day.	No difference in 24-hour urinary cortisol between placebo and 100 and 200 mcg/day doses of fluticasone (one study: 437 children). Urinary cortisol concentrations for 400 vs. 200 mcg/day differed with treatment ratios of 0.86 and 0.81 at weeks 16 and 52 (1 trial; 528 children).
Tomlinson et al. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. Thorax 2005;60 (4):282–287. (Asthma UK; Chief Scientist Office of the Scottish Executive Health Department)	Multicenter, randomized, double-blind, parallel-group trial	To assess the efficacy of inhaled corticosteroid treatment when given for a longer duration than previous studies and at different doses. The hypothesis was that the therapeutic response to inhaled corticosteroids would be reduced in smokers with asthma compared with nonsmokers, despite 12 weeks' duration of inhaled corticosteroid treatment.	95 (89)	**Age** Mean = 44 yr **Gender** 45.3% male, 54.7% female **Ethnicity** Not reported **Smoking** 42% smokers, mean = 25 pack years, 58% nonsmokers	Mild asthma Duration of asthma, median 9 yr for smokers and 18 yr for nonsmokers FEV_1 % pred., mean = 85 Morning PEF, mean = 422 L/min	**Arm 1** Budesonide (Low B) (n=47, 19 smokers and 28 nonsmokers; 44 completers, 16 smokers and 28 nonsmokers) **Arm 2** Budesonide (High B) (n=48, 21 smokers and 27 nonsmokers; 45 completers, 20 smokers and 25 nonsmokers)	400 mcg daily (4 puffs twice daily) 2,000 mcg daily (4 puffs twice daily)	12 weeks after 2 week run-in	*Improvement in morning PEF for nonsmokers vs. smokers in B Low group (+19 vs. –6, adj. p=0.015). No difference in change in morning PEF of nonsmokers vs. smokers in B High group (18 vs. 11, adj. p=0.40). No difference in effect of smoking for the B Low vs. B High (p=0.43). Combining dose groups, there was a difference in morning PEF for nonsmokers vs. smokers (19 vs. 3, adj. p=0.049).	Smokers receiving B Low had more exacerbations than nonsmokers (6 vs. 12, p=0.0067), but no difference in B High for smokers vs. nonsmokers (1 vs. 2, p=0.66).	