Drug Class Review
on
Controller Medications for Asthma

Final Report
Evidence Tables

November 2008

The Agency for Healthcare Research and
Quality has not yet seen or approved this report.

The purpose of this report is to make available information regarding the comparative effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report. Please see timeline on the DERP website for details on the date of its release. Prior versions of the report can be accessed at the DERP website.

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Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1823	Agertoft and Pedersen{Agertoft, 1998 #1823} 1998 Denmark, single center	Study design: Observational- cross sectional Duration: 3 to 6 years (mean 4.5) N=268 NA	Children with persistent asthma and no other chronic disease part of an ongoing RCT

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Agertoft and Pedersen{Agertoft, 1998 #1823} 1998 Denmark, single center	Yes	Systemic steroids for more than 2 weeks a year	NA

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Agertoft and Pedersen{Agertoft, 1998 #1823} 1998 Denmark, single center	Intervention: Drug 1: Control Drug 2: BUD	% female: Drug 1: Control 45 Drug 2: BUD 31 Mean age: Drug 1: Control 9.9 Drug 2: BUD 10.3 White/Black/Other%: Drug 1: Control NR Drug 2: BUD NR	NA

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Agertoft and Pedersen{Agertoft, 1998 #1823} 1998 Denmark, single center	Intervention: Drug 1: Control Drug 2: BUD Number in group (n): Drug 1: 111 Drug 2: 157	BMD (BUD = 0.915 g/cm controls = 0.917 g/cm), BMC (BUD = 1,378 g, controls = 1,367 g), TBC (BUD = 524 g, controls = 519 g), or body composition (lean body weight = 27,600 g [BUD] and 26,923 g [control], % body fat = 20.1% [BUD] and 20.3% [control]).

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Agertoft and Pedersen{Agertoft, 1998 #1823} 1998 Denmark, single center	NA	NA	NA Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1809	Agertoft et al.{Agertoft, 1998 #1809} 1998 Denmark Asthma clinic NR	Study design: Observational Cross sectional annalysis of population enrolled in prospective study for at least 3 yrs Duration: 3-6 years N=268 Enrolled: NR/NR/268 ITT Analysis: Not applicable	: Children with persistent asthma and no other chronic disease; part of an ongoing prospective, long-term controlled study; to be in BUD group for this study, had been taking BUD for at least 3 years Asthma Severity: Mild Moderate Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Agertoft et al.{Agertoft, 1998 #1809} 1998 Denmark Asthma clinic NR	All asthma medication except systemic corticosteroids for > 2 weeks·yr were allowed in the study.	> 14 days treatment with systemic corticosteroids ever (both groups); ICSs for > 2 weeks ever (control group); topical (skin) corticosteroids after the age of 2 yrs ever applied to >25% of the body surface (both groups); metabolic diseases, such as diabetes (both groups); family history PSC; and use of nasal corticosteroids, except for the treatment of seasonal rhinitis < 1month/yr (both groups).	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Agertoft et al.{Agertoft, 1998 #1809} 1998 Denmark Asthma clinic NR	Intervention: Drug 1: BUD Drug 2: No ICS (control) Total daily dose: Drug 1: mean average: 504 mcg Drug 2: N/A Steroid dosing range (Low, medium or high): Drug 1: Can't really determine because some used DPI and some used MDI; also, the age range was 5-16 which is a mix for children and adult dose Delivery device: Drug 1: MDI or DPI Drug 2: N/A Is dosing comparable between treatment groups? Not applicable- why not?: Not comparing ICS to ICS	# in group (n): Drug 1: 157 Drug 2: 111 Mean age (years): Drug 1: 10.3 Drug 2: 9.9 Sex (% female): Drug 1: 31 Drug 2: 45 Optional - Race (% white): Drug 1: NR Drug 2: NR Optional - Disease duration (years): Drug 1: 8.3 Drug 2: 4.5 Optional - Previous ICS use (%): Drug 1Drug 2: 0 (for > 2 wks ever) Optional - Current use of LABA (%): Drug 1: 8 Drug 2: 15 Current use of ICS at baseline (%) Drug 1: 100 Drug 2: 0 Optional - Current methylxanthine (i.e. theophylline) use (%): Drug 1: 2 Optional - Current use of Cromolyn Sodium (%): Drug 2: 20	Number (%) withdrawn: Drug 1: N/A Drug 2: N/A

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Agertoft et al.{Agertoft, 1998 #1809} 1998 Denmark Asthma clinic NR	Intervention: Drug 1: BUD Drug 2: No ICS (control) # in group (n): Drug 1: 157 Drug 2: 111	See adverse events

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Agertoft et al.{Agertoft, 1998 #1809} 1998 Denmark Asthma clinic NR	Hoarseness (%): Drug 1: see below Bruising (%): Drug 1: see below Cataracts (%): Drug 1: see below Additional events and comments: Cataracts (BUD n=155, control n=111): One patient in the BUD group had a PSC (one eye only) that had already been diagnosed by another ophthalmologist 2 yrs prior to initiation of BUD treatment. No other incidents of PSC were found in the two groups; no increased risk of PSC in the BUD group when compared with the control group (p=0.46). Three children were diagnosed with non-PSC opacities: two children in the BUD group showed signs consistent with congenital unilateral cataract and one child in the control group showed signs consistent with congenital bilateral cataract. Twenty-five per cent of the children in both groups reported previous events (physical trauma of the eye) that might influence the occurrence of lens opacities. Bruises: There were no statistically significant differences in the number of bruises between the two groups (BUD=3.3, controls=3.2; P=0.70), area on arm and leg covered by bruises (BUD=10 cm2, controls=10.1 cm2; P=0.97), tendency to bruise as assessed using a Hoarseness: There was no statistically significant difference between	Compliance Compliance with the asthma medication was checked at each visit by asking the child and the family about their compliance. In addition, the frequency of renewal of prescriptions was measured once a year for each child. Finally, the child was given an inhaler at the clinic whenever the inhaler strength was changed. The mean compliance with inhaled BUD was assessed to be 78% (range 42–110%).	Fair Fair

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
350	Aalbers et al.{Aalbers, 2004 #350} 2004 Country and setting: Six countries: Denmark, Finland, Germany, Norway, Sweden and The Netherlands Multicenter: 93 centres AstraZeneca	Study design: RCT Double-blind Double-dummy Duration: 7 months 1 month double-blind, 6 months open N=658 Enrolled: 1044/ 658 / 658 ITT? Yes	Male or female outpatients aged >/= 12 years with asthma for a minimum of 6 months, as defined by the American Thoracic Society and a FEV1 >/= 50% of predicted normal. All patients had used ICS (any brand) for >/= 3 months before and the daily dose was constant in the last month at 500–1200 mg (for BUD, based on metered dose) with or without concomitant long acting b2-agonist or other additional controller therapy. For randomization, patients were required to have: a total asthma symptom score of >/= 1 on at least 4 of the last 7 days of the run-in period; a mean morning PEF during the last 7 days of run-in of 50–85% of post-bronchodilatory PEF (obtained approximately 15 minutes after administration ofinhaled terbutaline [2 x 0.5 mg]); and had to demonstrate the ability to use a PFM and correctly record values in their diary. Morning PEF hadto have been recorded on >/= 8 of the last 10 days of the run-in period. Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Aalbers et al.{Aalbers, 2004 #350} 2004 Country and setting: Six countries: Denmark, Finland, Germany, Norway, Sweden and The Netherlands Multicenter: 93 centres AstraZeneca	short-acting beta 2 agonist for rescue	Respiratory infection affecting asthma within 1 month of study entry, smoking history >/= 10 pack-years, use of systemic corticosteroids within 1 month of study entry and any significant disorder which, in the opinion of the investigator, may have put the patient at risk or influenced the study. The following medications were prohibited during the study: inhaled cromones; LM; any b2-agonist (except study medication); xanthines; any b-blocker medication (including eye drops); and inhaled anticholinergics	Yes- During an open run-in period of 10–14 days, long-acting b2-agonists were not allowed and all patients continued treatment with the same dose of ICS that they had previously been using for the last month before study entry, with as-needed terbutaline sulphate (0.5 mg) for reliever medication or alternativelysalbutamol (if preferred by the patient). The run-in period was used to confirm that patients needed additional controller treatment for their asthma in addition to the ICS allowed during run-in.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Aalbers et al.{Aalbers, 2004 #350} 2004 Country and setting: Six countries: Denmark, Finland, Germany, Norway, Sweden and The Netherlands Multicenter: 93 centres AstraZeneca	Intervention: Drug 1: BUD/FM adjustable dose Drug 2: BUD/FM fixed dose Drug 3: SM/ FP Total daily dose: Drug 1: 320 - 640mcg / 9 - 18mcg (average use 544mcg/15mcg per day) Drug 2: 640 mcg / 18 mcg Drug 3: 100mcg / 500 mcg Steroid dosing range (Low, medium or high): Drug 1: low - medium Drug 2: medium Drug 3: medium Delivery device: Drug 1: Turbuhaler Drug 2: Turbuhaler Drug 3: Diskus Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 219 Drug 2: 215 Drug 3: 224 Mean age (years): Drug 1: 47 Drug 2: 46 Drug 3: 46 Sex (% female): Drug 1: 57 Drug 2: 55 Drug 3: 51 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Optional - Current use of LABA (%): Drug 1: 27/current use of ICS/LABA: 45 Drug 2: 30/45 Drug 3: 2746 : total for either: 73% Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 27 (12%) Drug 2: 31 (14%) Drug 3: 25 (11%) Adverse events caused withdrawal (%): Drug 1: 3 Drug 2: 5 Drug 3: 4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Aalbers et al.{Aalbers, 2004 #350} 2004 Country and setting: Six countries: Denmark, Finland, Germany, Norway, Sweden and The Netherlands Multicenter: 93 centres AstraZeneca	Intervention: Drug 1 Baseline: BUD/FM Adjustable dose Drug 1 Endpoint: BUD/FM Adjustable dose Drug 2 Baseline: BUD/FM Fixed dose Drug 2 Endpint: BUD/FM Fixed dose Drug 3 Baseline: SM/FP Fixed dose Drug 3 Endpoint: SM/FP Fixed dose Number in group (n): Drug 1- baseline: 219 Drug 1- endpoint: 217 Drug 2- baseline: 215 Drug 2-endpoint: 214 Drug 3- baseline: 224 Drug 3- endpoint: 223	Rescue med use during 24 hour period: Drug 1- baseline: mean difference between groups in number of occasions/day during open extension = Drug 1-endpoint: 0 Drug 2-endpoint: +0.30 Drug 3- endpoint: +0.23 P values: p < 0.01 for BUD/FM AD vs BUD/FM FD; p < 0.05 for BUD/FM AD vs FP/SM Asthma exacerbations: D1 end: #35 = 0.024 / month D2 end: #50 = 0.036/ month D3 end: #59 = 0.41/month P: p = 0.018 for BUD/FM AD versus SM/FP; CI -4.8 to 55.9 for BUD/FM AD versus BUD/FM FD Day time symptom control: D1 - end: NR D2 - end: NR D3 - end: NR P: NS Nocturnal awakenings: D1 base: mean difference in % of night time awakenings during open extension = D1 end: -4.7% D2 end: 0 D3 end: NR P: p < 0.05 for BUF/FM AD vs BUD/FM FD) Other: D1 base: odds of achieving WCAW over open extension period (well controlled asthma weeks) = D1 end : 1.335 (compared to Bud/form FD); 1.048 (compared to FP/SM) D2 baseD2 end: 1 (compared to BUD/form AD) D3 baseD3 end: 1 compared to BUD/form AD) P: CI = 1.001 - 1.783, p = 0.049 (for BUD/FM AD vs FD); CI 0.791 - 1.391, NS (BUD/FM AD vs FP/SM) Other:

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Aalbers et al.{Aalbers, 2004 #350} 2004 Country and setting: Six countries: Denmark, Finland, Germany, Norway, Sweden and The Netherlands Multicenter: 93 centres AstraZeneca	Overall adverse events reported (%): Drug 1: 57 Drug 2: 58 Drug 3: 66 Drug 5: NS Serious adverse events (%): Drug 1: 4 Drug 2: 5 Drug 3: 2 Drug 5: NR Oral candidiasis- thrush (%): Drug 1: 1 Drug 2: 2 Drug 3: 3 Drug 5: NR Dysphonia (%): Drug 1: 1 Drug 2: 1 Drug 3: 7 Drug 5: NR Headache (%): Drug 1: 3 Drug 2: 2 Drug 3: 4 Drug 5: NR	Adherence Patients' diary cards in all groups showed high self recorded adherence to their maintenance medication (mean value of > 99% in all groups).	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1044	Allen{Allen, 1998 #1044} 1998 USA, Multicenter (19) Glaxo Wellcome	Study design: RCT Double-blind Duration: 1 year N= 325 Enrolled: 190/160/160	American Thoracic Society criteria for asthma and had normal growth rates as defined by height measurements (one measurement taken 6 to 18 months before the study and one at screening) between the 5th and 95th centiles and growth velocity between the 10th and 97th centiles - boys were aged between 4 and 11 years and the girls were aged between 4 and 9 years

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Allen{Allen, 1998 #1044} 1998 USA, Multicenter (19) Glaxo Wellcome	albuterol syrup and albuterol inhalation aerosol to be used throughout the study as needed for the relief of acute symptoms.	Received systemic, intranasal, or ophthalmic corticosteroids within the month before study entry, or had cataracts, glaucoma, or any other significant concurrent disease or condition. Previous systemic corticosteroid use was limited to a total of 60 days within the 2 years before study entry. Patients on a maintenance dose of inhaled corticosteroids were required to maintain a fixed dosage regimen for at least 3 months before screening.	2-week, single-blind, run-in period to evaluate eligibility to continue to the active treatment period, confirm asthma stability, obtain baseline data, and assess patient compliance

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Allen{Allen, 1998 #1044} 1998 USA, Multicenter (19) Glaxo Wellcome	Intervention: Drug 1: Placebo Drug 2: FP 50 Drug 3: FP 100	% female: 25 Mean age: 8 years White/Black/Other%: NR	57 withdrawals

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Allen{Allen, 1998 #1044}	Intervention:	mean height (± SE)
1998	Placebo	Placebo 6.15 ± 0.17 cm
	FP 50	FP 50 5.94 ± 0.16 cm
USA, Multicenter (19)	FP 100	FP 100 5.73 ± 0.13 cm
		(p = 0.308, overall).
Glaxo Wellcome	Number in group (n):	
	Placebo 87	No differences in height and growth velocity between FP and placebo
	FP 50 85	
	FP 100 96	

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Allen{Allen, 1998 #1044}	Placebo vs.. FP 50 vs.. FP 100 %	Yes	Fair
1998	Any 9 vs.. 14 vs.. 8		Fair
	Cough 4 vs., 3 vs.. 4	Compliance rates ranged between	No
USA, Multicenter (19)	Pharyngitis <1 vs. 4 vs.. <1	90% and	
	Dysphonia 0 vs.. 3 vs.. 0	94% and were similar across	
Glaxo Wellcome	Headache 3 vs.. 2 vs.. 0.	treatment groups	
	Oropharyngeal candidiasis 0 vs.. 3 vs.. <1		

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1207	Ayres et al.{Ayres, 1995 #1207}	Study Design: RCT	Age: 18-70
	Multinational (13) Multicenter (66)	Double-blind Double-dummy	FEV1 expressed as a percent of the predicted value: 80% or less
	NR: 3rd author works for Glaxo	Duration: 6 weeks	Reversability of FEV1: 15% and diurnal variation of at least 15% in 4 of last 7 days
		N=671	Days with asthma symptoms: 1 or more on at least 4 of last 7 days
		Enrolled: 862/nr/671	Previous use of corticosteroids: ICS either 1-2 mg daily of BDP or 0.8-1.6 md of BUD/day : Stable
		ITT Analysis: Yes	Asthma Severity: Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Ayres et al.{Ayres, 1995 #1207} Multinational (13) Multicenter (66)	Salbumatol as needed, pre-trial meds at a constant dose (but stopped inhaled steroids); spacer device allowed.	Pregnant or lactating Current treatment: systemic CS greater than 10 mg/day Smoking - >10 pack years	Yes: 2 week run-in

NR: 3rd author works for Glaxo

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Ayres et al.{Ayres, 1995 #1207} Multinational (13) Multicenter (66) NR: 3rd author works for Glaxo	Intervention: Drug 1: FP Drug 2: FP Drug 3: BUD Total daily dose: Drug 1: 1000 mcg/day Drug 2: 2000 mcg/day Drug 3: 1600 mcg/day Steroid dosing range (Low, medium or high): Drug 1: high Drug 2: high Drug 3: medium Delivery device: Drug 1: MDI Drug 2: MDI Drug 3: MDI Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 225 Drug 2: 225 Drug 3: 221 Mean age (years): Drug 1: 51 (median) Drug 2: 48 (median) Drug 3: 50 (median) Sex (% female): Drug 1: 53 Drug 2: 50 Drug 3: 52 Optional - Race (% white): Drug 1: 91 Drug 2: 91 Drug 3: 93 Current smokers (%): Drug 1: 9 Drug 2: 8 Drug 3: 12 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100	Number (%) withdrawn: Drug 1: NR Drug 2: NR Drug 3: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Ayres et al.{Ayres, 1995 #1207}	Intervention:	Rescue med use day:
	Drug 1 Baseline:	Drug 1- baseline: symptom free days/rescue free days
Multinational (13)	FP 1000	Drug 1 -endpoint: 50% improved/42% improved
Multicenter (66)	Drug 1 Endpoint:	Drug 2 - endpoint: 51%/44%
	FP 1000	Drug 3 - endpoint: 44%/46%
	Drug 2 Baseline:	P value: sx free days 0.048 FP1 vs BUD, 0.101 FP2 vs BUD; rescue free days
NR: 3rd author works for Glaxo	FP 2000	FP1 vs BUD0.592, FP2 vs BUD 0.275
	Drug 2 Endpoint:	
	FP 2000	Symptom control during 24 hour period:
	Drug 3 Baseline:	D1 end: 44% improved
	BUD 1600	D2 end: 51% improved
	Drug 3 Endpoint:	D3 end: 44% improved
	BUD 1600	
		Day time symptom control:
		D1 - base: day time asthma score
		D1 - end: 30% improved
		D2 - end: 27%
		D3 - end: 23%
		P: 0.161 FP 1 vs BUD; 0.029 FP 2 vs BUD
		Night time symptom control:
		D1 - base: night time asthma score
		D1 - end: 21% improved
		D2 - end: 28%
		D3 - end: 23%
		P: 0.058 FP 1mg vs BUD; 0.050 FP 2 vs BUD

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Ayres et al.{Ayres, 1995 #1207} Multinational (13) Multicenter (66) NR: 3rd author works for Glaxo	Overall adverse events reported (%): Drug 1: 61 Drug 2: 49 Drug 3: 51 Oral candidiasis- thrush (%): Drug 1: 3 Drug 2: 4 Drug 3: 5 Cough (%): Drug 1: 3 Drug 2: 6 Drug 3: 5 Sore throat (%): Drug 1: 4 Drug 2: 4 Drug 3: 2 Headache (%): Drug 1: 5 Drug 2: 7 Drug 3: 6 Upper respiratory tract infection (%): Drug 1: 11 Drug 2: 10 Drug 3: 6 Respiratory infection (%): Drug 1: 4 Drug 2: 1 Drug 3: 2 Rhinitis (%): Drug 1: 4 Drug 2: 1 Drug 3: 3 Hoarseness (%): Drug 1: 6 Drug 2: 3 Drug 3: 3	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
5113	Bakhireva et al.{Bakhireva, 2007 #5113} 2007 OTIS Asthma Medications in Pregnancy Study North America, multicenter Aventis Pharmaceutical	Study design: Observational (subgroup analysis of OTIS Asthma Medications in Pregnancy Study) Duration: 16-18 wks N=564 NA	Pregnant women with physician-diagnosed asthma; at least 18 years old; willing to be followed up during the pregnancy and postpartum period; be in their first half of pregnancy (i.e., 20 weeks gestation at the time of enrollment); and have no prenatal diagnostic tests indicating an abnormal pregnancy before enrollment.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bakhireva et al.{Bakhireva, 2007 #5113} 2007 OTIS Asthma Medications in Pregnancy Study North America, multicenter Aventis Pharmaceutical	Yes--Because LTRAs are often taken in combination with other controller and/or rescue medications, 99% of subjects in the LTRA group used short-acting b2-agonists, 40% used oral corticosteroids, and 39% used ICSs sometime in pregnancy. The majority of subjects in the LTRA group who reported concurrent use of oral corticosteroids used them in a burst rather than a continuous fashion.	NR	NA

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bakhireva et al.{Bakhireva, 2007 #5113} 2007 OTIS Asthma Medications in Pregnancy Study North America, multicenter Aventis Pharmaceutical	Intervention: Drug 1: LTRAs Drug 2: SABAs Drug 3: Additional Control group (patients without asthma) Total daily dose: Drug 1: NR Drug 2: NR Drug 3: NA	% female: 100 Maternal age: <25/25-34/35+ % Drug 1: 9.4/56.3/34.4 Drug 2: 16.4/54.1/29.5 Drug 3: 12.1/64.2/23.7 White non-Hispanic%: Drug 1: 86.5 Drug 2: 90.9 Drug 3: 84.7	NA

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bakhireva et al.{Bakhireva, 2007 #5113} 2007 OTIS Asthma Medications in Pregnancy Study North America, multicenter Aventis Pharmaceutical	Intervention: Drug 1: LTRAs Drug 2: SABAs Drug 3: Control (patients without asthma) Number in group (n): Drug 1: 96 Drug 2: 122 Drug 3: 346	Level of asthma control during pregnancy (% LTRAs vs. SABAs): Unscheduled clinic visits: 30.2 vs. 6.6, P < 0.001 Hospital admissions: 16.7 vs. 3.3, P < 0.001 Selected fetal/newborn outcomes (% LTRAs vs. SABAs vs. Control): Preterm delivery (<37 wks): 9.8 vs. 11.8 vs. 7.5, P = 0.398 Major structural anomalies: 5.95 vs. 3.9 vs. 0.3, P = 0.002 Apgar score (1 min) ≤7: 20.3 vs. 15.0 vs. 15.8, P = 0.608 Apgar score (5 min) ≤7: 1.4 vs. 2.5 vs. 3.5, P = 0.613 Birth weight ≤10th percentile: 6.1 vs. 3.9 vs. 4.9, P = 0.794 Birth height ≤10th percentile: 1.2 vs. 2.0 vs. 3.8, P = 0.413 Birth OFC ≤10th percentile: 11.6 vs. 8.3 vs. 9.5, P = 0.801 Ponderal index < 2.2: 12.2 vs. 7.8 vs. 13.7, P = 0.292 Mean (SD) birth length (cm): 51.1 (2.3) vs. 51.5 (2.7) vs. 51.5 (2.7), P = 0.616 Mean (SD) OFC (cm): 34.6 (1.4) vs. 34.6 (1.2) vs. 34.7 (1.4), P = 0.815 Mean (SD) birth weight (g): 3447 (450) vs. 3544 (446) vs. 3529 (482), P = 0.341 Adjusted mean birth weight (SE): 3384 (72) vs. 3533 (68) vs. 3529 (54), P = 0.063 Adjusted (above + asthma control) mean birth weight (SE): 3449 (96) vs. 3576 (99) vs. NA, P = 0.094 Selected maternal complications (LTRAs vs. SABAs vs. control): Pregnancy loss (%): 6.7 vs. 5.6 vs. 3.4, P = 0.338

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bakhireva et al.{Bakhireva, 2007 #5113} 2007 OTIS Asthma Medications in Pregnancy Study North America, multicenter Aventis Pharmaceutical	NA	In this study, 96 women took LTRAs (72, montelukast; 22, zafirlukast; and 2, both) sometime during pregnancy. The majority of subjects had a first trimester exposure (89.6%), and 50% of women used LTRAs throughout the pregnancy. More than 85% of subjects took the recommended adult doses: 10 mg daily for montelukast and 20 mg twice a day for zafirlukast.	Poor Poor (sample size too small to detect differences in the perinatal outcomes of interest; potential for selection bias) No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
890	Baraniuk et al.{Baraniuk, 1999 #890} 1999 USA Pulmonary/allergy medicine clinics (50) Glaxo Wellcome	Study design: RCT Double-blind Triple-dummy Duration: 12 weeks N=680 Enrolled: NR ITT Analysis: Yes	Age: greater than 12 FEV1 expressed as a percent of the predicted value: 40 to 85% Reversability of FEV1: more than 15% Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Baraniuk et al.{Baraniuk, 1999 #890} 1999 USA Pulmonary/allergy medicine clinics (50) Glaxo Wellcome	NR	Pregnant or lactating Concommitant diseases: significant concomitant illness; or concurrent use of any other prescription or over-the-countermedication that might affect the course of asthma or interact with sympathomimetic amines. Current treatment: methotrexate, gold, cyclosporine,or azathioprine for control of asthma within 30 days prior to the study; use of inhaled cromolyn or inhaled nedocromil within 4 weeks prior to the study; use of oral or injectable corticosteroids within 4 weeks prior to the study	Yes: 2 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Baraniuk et al.{Baraniuk, 1999 #890} 1999 USA Pulmonary/allergy medicine clinics (50) Glaxo Wellcome	Intervention: Drug 1: FP + SM Drug 2: FP Drug 3: TAA Total daily dose: Drug 1: 196+84 Drug 2: 440 Drug 3: 1200 Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: med Drug 3: med Is dosing comparable between treatment groups? Cannot determi	# in group (n): Drug 1: 231 Drug 2: 223 Drug 3: 226 Mean age (years): Drug 1: 41 Drug 2: 40 Drug 3: 39 Sex (% female): Drug 1: 59 Drug 2: 61 Drug 3: 65 Optional - Race (% white): Drug 1: 87 Drug 2: 83 Drug 3: 89 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 16 (7%) Drug 2: 13 (6%) Drug 3: 21 (9%) Optional - Withdrew due to lack of efficacy (%): Drug 1: <1 Drug 2: <1 Drug 3: 4 Adverse events caused withdrawal (%): Drug 1: 4 Drug 2: 1 Drug 3: 2 Optional - Other reasons for withdrawal (%): Drug 1: 2 Drug 2: 4 Drug 3: 4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Baraniuk et al.{Baraniuk, 1999 #890} 1999 USA Pulmonary/allergy medicine clinics (50) Glaxo Wellcome	Intervention: Drug 1 Endpoint: FP + SM Drug 2 Endpoint: FP Drug 3 Endpoint: TAA	Rescue med use during 24 hour period:(SEM) Drug 1- baseline: puffs/d 4.6 Drug 1-endpoint: -2.9 (0.2) Drug 2-baseline: 4.9 Drug 2-endpoint: -2.4 (0.2) Drug 3 - baseline: 4.7 Drug 3- endpoint: -1.8 (0.2) Rescue med use day: (SEM) Drug 1- baseline: Rescue free 10.9 Drug 1 -endpoint: 45.0 (2.9) Drug 2 - baseline: 12.5 Drug 2 - endpoint: 28.9 (2.7) Drug 3 - baseline: 11.6 Drug 3 - endpoint: 27.4 (2.5) Symptom control during 24 hour period: (SEM) D1 base: Overall symptom score 0.98 D1 end: -0.44 (0.05) D2 base: 1.09 D2 end: -0.46 (0.05) D3 base: 1.04 D3 end: -0.31 (0.5) Nocturnal awakenings: (SEM) D1 base: 0.47 D1 end: -0.31 (0.04) D2 base: 0.47 D2 end: -0.32 (0.04) D3 base: 0.41 D3 end: -0.18 (0.03) Other: D1 base: % symptom free days (SEM) D1 end : 29.2 (2.9) D2 end: 22.6 (2.6) D3 end: 11.9 (2.1)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Baraniuk et al.{Baraniuk, 1999 #890} 1999 USA Pulmonary/allergy medicine clinics (50) Glaxo Wellcome	Overall adverse events reported (%): Drug 1: Drug-related 14 Drug 2: 13 Drug 3: 8 Oral candidiasis- thrush (%): Drug 1: 2 Drug 2: 2 Drug 3: 1 Dysphonia (%): Drug 1: 3 Drug 2: 4 Drug 3: <1 Sore throat (%): Drug 1: 3 Drug 2: <1 Drug 3: 2	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1267	Barnes et al.{Barnes NC, 1993 #1267} Multinational (7) Multicenter (18 outpatient clinics) NR: One author affiliated with GSK	Study design: RCT Double-blind Duration: 6 weeks N=154 Enrolled: 172/154/154 (172 enrolled for run-in; 154 randomized at end of run-in) ITT Analysis: No another type of analysis was used (define): to be included in the analysis, patients were required to have provided data for at least 7 days during the run-in and at least 11 days in any treatment assessment period.	Age: >/= 18 yrs Reversability of FEV1: >/= 15% following inhalation of a beta-2 agaonist during run-in or within 3 months before study start Days with asthma symptoms: on at least 4 of last 7 days of run-in period Other: Patients were entered into treatment period if demonstrated at least two of the following: mean morning PEFR </= 70% of predicted during last 7 days of run-in period; >/= 15% reversibility in FEV1 following inhalation of a B2-agonist during run-in or within 3 months before start of study; >/= 20% diurnal variation in PEFR on at least 4 of last 7 days of run-in; asthma symptoms on at least 4 of last 7 days of run-in. Asthma Severity: Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Barnes et al.{Barnes NC, 1993 #1267} Multinational (7) Multicenter (18 outpatient clinics) NR: One author affiliated with GSK	Inhaled salbutamol as required; other asthma medications at constant doses were allowed to continue	Pregnant or lactating Prior treatment: systemic corticosteroids within 1 month of study or on >4 occasions during 6 months before run-in period; treatment with other investigational drugs within 4 weeks of study Concommitant diseases: likely to complicate evaluation of study drug : Hypersensitivity to ICSs; changes in asthma medication (except inhaled beta2 agonists) during run-in period	Yes: 2 week run-in period, patients discontinued use of their usual inhaled bronchodilator and took salbutamol as required

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Barnes et al.{Barnes NC, 1993 #1267} Multinational (7) Multicenter (18 outpatient clinics) NR: One author affiliated with GSK	Intervention: Drug 1: FP Drug 2: BDP Total daily dose: Drug 1: 1000 mcg/day Drug 2: 2000 mcg/day Steroid dosing range (Low, medium or high): Drug 1: High Drug 2: High Delivery device: Drug 1: MDI Drug 2: MDI Is dosing comparable between treatment gro	# in group (n): Drug 1: 82 Drug 2: 72 Mean age (years): Drug 1: 50 Drug 2: 52 Sex (% female): Drug 1: 46% Drug 2: 43% Optional - Race (% white): Drug 1: 95% Drug 2: 99% Current smokers (%): Drug 1: 17% Drug 2: 24% Optional - Disease duration (years): Drug 1: >10 yrs: 59% Drug 2: 53% Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Optional - Current methylxanthine (i.e. theophylline) use (%): Drug 1: 46% Drug 2: 43% Other: Drug 1: Duration >1 yr: 100%	Number (%) withdrawn: Drug 1: 13 (15.9%) Drug 2: 5 (6.9%) Optional - Withdrew due to asthma exacerbations (%): Drug 1: 7.3% Drug 2: 2.8% Adverse events caused withdrawal (%): Drug 1: 2.4% Drug 2: 4.2% Optional - Other reasons for withdrawal (%): Drug 1: noncompliance: 6.1%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Barnes et al.{Barnes NC, 1993 #1267} Multinational (7) Multicenter (18 outpatient clinics) NR: One author affiliated with GSK	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: BDP Drug 2 Endpoint: BDP Number in group (n): Drug 1- baseline: 82 Drug 1- endpoint: NR Drug 2- baseline: 72 Drug 2-endpoint: NR	Rescue med use day: Drug 1- baseline: mean number of times used: 13 Drug 1 -endpoint: 10 Drug 2 - baseline: 14 Drug 2 - endpoint: 11 P value: 0.866 Rescue med use at night: Drug 1- baseline: mean number of times used: 6 Drug 1 - endpoint: 5 Drug 2 - baseline: 8 Drug 2 - endpoint: 6 P value: 0.875 Day time symptom control: D1 - base: symptom-free days (mean %): 38% D1 - end: 52% D2 - base: 28% D2 - end: 37% P: 0.212 Night time symptom control: D1 - base: symptom-free nights (mean%): 46% D1 - end: 59% D2 - base: 38% D2 - end: 50% P: 0.854 Other: D1 base: Days=0 (days with median symptom score=0): 38% D1 end : 58% D2 base: 28% D2 end: 38% D3 baseD3 endP: not calculated Other: D1 base: Nights=0 (nights with median symptoms score=0): 49% D1 end : 61% D2 base: 35%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Barnes et al.{Barnes NC, 1993 #1267}	Overall adverse events reported (%): Drug 1: 52% Drug 2: 51% P > 0.15 Serious adverse events (%): Drug 1: 3.7% Drug 2: 0 Oral candidiasis- thrush (%): Drug 1: 6% Drug 2: 4% Cough (%): Drug 1: 2% Drug 2: 3% Sore throat (%): Drug 1: 5% Drug 2: 6% Headache (%): Drug 1: 4% Drug 2: 1% Upper respiratory tract infection (%): Drug 1: 6% Drug 2: 3% Rhinitis (%): Drug 1: 7% Drug 2: 3% Other (%): Drug 1: Severe AE: 10% Drug 2: 7% No significant changes in weight, pulse rate, or systolic or diastolic blood pressure were detected in the total population.	NR Just provide #'s for patients withdrawn by investigator for noncompliance with no explanation: 5 (6.1%) FP patients; 0 BDP patients	Fair Fair No
Multinational (7) Multicenter (18 outpatient clinics) NR: One author affiliated with GSK			

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
289	Bateman and Bateman {#49} 2004 and 2007 GOAL Study (Gaining Optimal Asthma Control) Multinational (44 countries) Multicenter (326 centers) general practice and hospital clinics GlaxoSmithKline	Study design: RCT Double-blind Duration: One year N=3416 Enrolled: 5068/3421/3416 ITT? NR	Age: 12-80 Reversability of FEV1: 15% or greater Duration of condition: at least 6 months; During run-in, must not have at least 2 well-controlled weeks. Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bateman and Bateman {#49} 2004 and 2007 GOAL Study (Gaining Optimal Asthma Control) Multinational (44 countries) Multicenter (326 centers) general practice and hospital clinics GlaxoSmithKline	NR	Current treatment: long-acting inhaled or oral ß2-agonists within the previous 2 weeks Smoking - current or former: more than 10 pack years	Yes- 4 weeks, continued usual dose (if any) of ICS; if met run-in criteria, they were randomized, stratified by prior ICS dose (for the 6 months prior to study)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bateman and Bateman {#49}	Intervention:	# in group (n):	Number (%) withdrawn:
	Drug 1: S1 (stratum 1, no prior ICS) SFC	Drug 1: 548	Drug 1: all SFC-
2004 and 2007	Drug 2: S1 FP	Drug 2: 550	Drug 2: all FP- 289 (16.9%)
	Drug 3: S2 (prior ICS, <500 BDP	Drug 3: 585	
GOAL Study (Gaining Optimal Asthma	equivalent) SFC	Drug 4: 578	Optional - Withdrew due to asthma
Control)	Drug 4: S2 FP	Drug 5: 576	exacerbations (%):
	Drug 5: S3 (>=500, <1000 prior ICS) SFC	Overall: 579	Drug 1: 0.4
Multinational (44 countries)	Overall: S3 FP		Drug 2: 0.35
Multicenter (326 centers) general		Mean age (years):	
practice and hospital clinics	Total daily dose:	Drug 1: 36.1	Adverse events caused withdrawal (%):
	Drug 1: 50/100 to 50/500	Drug 2: 36.4	Drug 1: 2.2
GlaxoSmithKline	Drug 2: 100 to 500	Drug 3: 40.4	Drug 2: 2.1
	Drug 3: 50/100 to 50/500	Drug 4: 40.3	
	Drug 4: 100 to 500	Drug 5: 57	Optional - Lost to follow-up (%):
	Drug 5: 50/250 to 50/500	Overall: 59	Drug 1: 3.1
	Overall: 250 to 500		Drug 2: 3.4
		Sex (% female):	
	Steroid dosing range (Low, medium or	Drug 1: 57	Optional - Protocol violation (%):
	high):	Drug 2: 57	Drug 1: 1.7
	Drug 1: low-med	Drug 3: 58	Drug 2: 2.8
	Drug 2: low-med	Drug 4: 60	
	Drug 3: low-med	Drug 5: 57	Optional - Consent withdrawn (%):
	Drug 4: low-med	Overall: 59	Drug 1: 3.0
	Drug 5: med		Drug 2: 2.9
	Overall: med	Current smokers (%):	
		Drug 1: 9	Optional - Other reasons for
	Is dosing comparable between treatment	Drug 2: 10	withdrawal (%):
	groups? NA	Drug 3: 6	Drug 1: 3.6
		Drug 4: 7	Drug 2: 3.3
		Drug 5: 7	
		Overall: 8	
		Optional - Previous ICS use (%):	
		Drug 1: 0	
		Drug 2: 0	
		Drug 3: 100 (500 or less)	
		Drug 4: 100 (500 or less)	
		Drug 5: 100 (500-1000)	
		Overall: 100 (500-1000)	

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bateman and Bateman {#49}	Intervention:	AQLQ - overall:
	Drug 1 Baseline: S1 SFC	D1 base: 1.5 /1.6
2004 and 2007	Drug 1 Endpoint: S1 FP	D1 end: 1.3 / 1.4
	Drug 2 Baseline: S2 SFC	D2 base: 1.3 / 1.3
GOAL Study (Gaining Optimal Asthma	Drug 2 Endpoint: S2 FP	D2 end: 1.0 / 1.2
Control)	Drug 3 Baseline: S3 SFC	D3 base: 1.1 / 1.2
	Drug 3 Endpoint: S3 FP	D3 end: 0.8 / 1.0
Multinational (44 countries)		P: NR, but "statistically significant difference in favor of SM/FP in strata 2 and 3"
Multicenter (326 centers) general	Number in group (n):	
practice and hospital clinics	Drug 1- baseline: 282	Other Relevant Health Outcome Results:
	Drug 1- endpoint: 275	At one year- Total control across all strata: SFC 690 (41%) versus FP 468 (28%);
GlaxoSmithKline	Drug 2- baseline: 339	Total control across all strata after dose escalation: SFC 520 (31%) versus FP 326
	Drug 2-endpoint: 331	(19%), p<0.001; Well controlled at 1 year: SFC 1,204 (71%) versus FP 988 (59%);
	Drug 3- baseline: 346	well-controlled after dose-escalation 1071 (63%) vs 846 (50%), p<0.001
	Drug 3- endpoint: 345	

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bateman and Bateman {#49} 2004 and 2007 GOAL Study (Gaining Optimal Asthma Control) Multinational (44 countries) Multicenter (326 centers) general practice and hospital clinics GlaxoSmithKline	Serious adverse events (%): Drug 1: 4 Drug 2: 3 Oral candidiasis- thrush (%): Drug 1: 3 Drug 2: 3 Headache (%): Drug 1: 5 Drug 2: 7 Upper respiratory tract infection (%): Drug 1: 13 Drug 2: 13 Hoarseness (%): Drug 1: 3 Drug 2: 2 Other (%): Drug 1: asthma 8 Drug 2: 12 Other (%): Drug 1: influenza 5 Drug 2: 4 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: In the subset of patients in which cortisol data were available at baseline and at Week 52 (n = 194), the geometric mean of the cortisol/creatinine ratio (nmol/mmol) at these time points was 3.74 versus 3.04 for SM/FP (n = 102) and 3.92 versus 2.85 for FP (n = 92). No statistical differences between treatments at Week 52 were observed (p = 0.318; 95% CI, 0.92, 1.31). For patients who received the highest dose of corticosteroid (500 µg twice a day), the geometric means were 3.76 versus 2.90 for SM/FP (n = 82) and 3.82 versus 2.73 for FP (n = 84). Despite these decreases (see Figure E4 in the online supplement), the majority of patients (92%) had normal or high values at Week 52. Seven of 102 patients on SM/	Compliance during the blinded phases was 89% for both treatment groups	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
718	Bateman et al.{Bateman ED, 2001 #718} 2001 Multinational (10), multicenter (69) Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=497 724 eligible (entered run-in); 497 randomized to treatment ITT? No…..	Age: 12 or older FEV1 expressed as a percent of the predicted value: >50% of predicted normal Previous use of corticosteroids: using ICS (BDP, BUD, FLUN 400-500/day, or FP 200-250/day) for at least 4 weeks before the run-in Other: smoking history of < 10 pack years; must demonstrate room for improvement during run-in (defined as a mean morning PEF over the last 7 days of the run-in of >50% and <85% of the PEF measured after inhalation of salbutamol); must be symptomatic during run-in (cumulative total symptom score of >=8 for the last 7 days of the run-in; taking <=800mcg/d of salbutamol. Asthma severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bateman et al.{Bateman ED, 2001 #718} 2001 Multinational (10), multicenter (69) Glaxo Wellcome		Prior treatment with: LABA or oral B-agonist within 2 weeks of the run-in; oral, depot or parenteral corticosteroids or combination therapy (containing a B2-agonist and/or ICS) Concommitant diseases: lower respirator tract infection within 4 weeks of run-in; acute asthma exacerbation w/in 12 weeks of study entry Smoking - current or former: smoking history of >= 10 pack years Other: changed their asthma medication within 4 weeks of run-in	Yes- 2 weeks; had to meet above inclusion criteria during run-in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bateman et al.{Bateman ED, 2001 #718} 2001 Multinational (10), multicenter (69) Glaxo Wellcome	Intervention: Drug 1: SM/FP Drug 2: SM/FP Drug 3: FP Total daily dose: Drug 1: 100/200 Drug 2: 100/200 Drug 3: 200 Steroid dosing range: Drug 1: low Drug 2: low Drug 3: low Delivery device: Drug 1: HFA MDI Drug 2: Diskus Drug 3: MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 165 Drug 2: 167 Drug 3: 165 Mean age (years): Drug 1: 40.7 Drug 2: 38.6 Drug 3: 39.5 Sex (% female): Drug 1: 56 Drug 2: 53 Drug 3: 59 Current smokers (%): Drug 1: 13 Drug 2: 9 Drug 3: 11 Optional - Disease duration (years): Drug 1: 6% 0 to <1 year; 30% 1 to <5 year; 18% 5 to <10 yr; 46% >=10 yr Drug 2: 7% 0 to <1 year; 21% 1 to <5 year; 20% 5 to <10 yr; 52% >=10 yr Drug 3: 7% 0 to <1 year; 22% 1 to <5 year; 20% 5 to <10 yr; 51% >=10 yr Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Other:	Number (%) withdrawn: Drug 1: 20 Drug 2: 22 Drug 3: 25 Optional - Withdrew due to lack of efficacy (%): Drug 1: 1 Drug 2: 2 Drug 3: 0 Adverse events caused withdrawal (%): Drug 1: 7 Drug 2: 8 Drug 3: 11 Optional - Lost to follow-up (%): Drug 1: 1 Drug 2: 3 Drug 3: 2 Optional - Protocol violation (%): Drug 1: 4 Drug 2: 2 Drug 3: 3

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bateman et al.{Bateman ED, 2001 #718} 2001 Multinational (10), multicenter (69) Glaxo Wellcome	Intervention: Drug 1 Baseline: SALM/FP HFA MDI Drug 2 Baseline: SALM/FP Diskus Drug 3 Baseline: FP	Rescue med use day: Drug 1- baseline: median salbutamol-free days (%) weeks 1-12: 73 Drug 2 - baseline: 75 tDrug 3 - baseline: 58 P value: 0.003 (SALM/FP HFA MDI vs. FP) Rescue med use at night: Drug 1- baseline: median salbutamol-free nights (%) weeks 1-12: 90 Drug 1 - endpointDrug 2 - baseline: 93 Drug 3- baseline: 80 P value: 0.033 (SALM/FP HFA MDI vs. FP) Day time symptom control: D1 - base: median symptom-free days (%) weeks 1-12: 55 D2 - base: 52 D3 - base: 25 D3 - endP: 0.001 (SALM/FP HFA MDI vs. FP) Night time symptom control: D1 - base: median symptom-free nights (%) weeks 1-12: 71 D2 - base: 78 D3 - base: 53 D3 - endP: 0.063 (SALM/FP HFA MDI vs. FP) Other Relevant Health Outcome Results: NOTE: only valid comparison made for our purposes is SALM/FP HFA MDI vs. FP. In comparison with the FP MDI group, the SALM/FP MDI group reported significantly more symptom-free days (weeks 1-12: 55 vs. 25%; 95% CI: 719, 72; P=0.001) (Fig. 2), and more symptom-free nights (71 vs. 53%; 95% CI: 714, 0; P=0.063) (Table 5). Significantly more salbutamol-free days and nights were reported in the SALM/FP MDI group than in the FP MDI group for all except one as

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bateman et al.{Bateman ED, 2001 #718} 2001 Multinational (10), multicenter (69) Glaxo Wellcome	Overall adverse events reported (%): Drug 1: 50 Drug 2: 57 Drug 3: 55 Serious adverse events (%): Drug 1: 2 Drug 2: 2 Drug 3: 2 Oral candidiasis- thrush (%): Drug 1: <1 Drug 2: 2 Drug 3: <1 Sore throat (%): Drug 1: 3 Drug 2: 2 Drug 3: 4 Headache (%): Drug 1: 8 Drug 2: 8 Drug 3: 6 Upper respiratory tract infection (%): Drug 1: 12 Drug 2: 17 Drug 3: 13 Respiratory infection (%): Drug 1: 4 Drug 2: 4 Drug 3: 5 Rhinitis (%): Drug 1: <1 Drug 2: 5 Drug 3: 3 Other (%): Drug 1: sinusitis: 2 Drug 2: 4 Drug 3: 3	NR they report withdrawal in 2, 1, and 0 patients respectively for non-compliance, but do not report compliance for the study population.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
369	Bateman et al.{Bateman, 2003 #369} 2003 Multinational (6) Multicenter (37) AstraZeneca	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=344 Enrolled: NR/NR/373 ITT? Yes	Age: 18 or greater; duration of at least 6 months FEV1 expressed as a percent of the predicted value: FEV1 60-90% of predicted Reversability of FEV1: 12% improvement from baseline after SABA Previous use of corticosteroids: 200-1000ug/ day of any ICS at constant daily dose for at least 30 days Asthma Severity: Moderate Other: persistant

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bateman et al.{Bateman, 2003 #369} 2003 Multinational (6) Multicenter (37) AstraZeneca	albuterol or terbutaline	Pregnant or lactating: women of childbearing potential not using adequate contraception Current treatment: sytemic corticosteroids Smoking - current or former: greater than 10 pack years	Yes- 2 weeks of tx with low dose ICS (BUD)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bateman et al.{Bateman, 2003 #369} 2003 Multinational (6) Multicenter (37) AstraZeneca	Intervention: Drug 1: BUD/FM Drug 2: FP Total daily dose: Drug 1: 320/9 Drug 2: 500 Delivery device: Drug 1: Turbuhaler Drug 2: Diskus Is dosing comparable between treatment groups? Not applicable	# in group (n): Drug 1: 168 Drug 2: 176 Mean age (years): Drug 1: 42.6 Drug 2: 41.8 Sex (% female): Drug 1: 58.3 Drug 2: 55.7 Current smokers (%): Drug 1: 5.4 Drug 2: 6.8 Optional - Disease duration (years): Drug 1: 16.3 Drug 2: 16.3 Current use of ICS at baseline (%): Drug 1: 100 (mean dose 591µg) Drug 2: 100 (597µg) Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 15 (8.9) Drug 2: 20 (11.4) Optional - Withdrew due to asthma exacerbations (%): Drug 1: 3 (1.8) Drug 2: 8 (4.5) Adverse events caused withdrawal (%): Drug 1: 5 (3.0) "non-asthma related" Drug 2: 5 (2.8) "non-asthma related" Optional - Other reasons for withdrawal (%): Drug 1: 7 (4.2) "other reasons" Drug 2: 7 (4.0) "other reasons"

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bateman et al.{Bateman, 2003 #369} 2003 Multinational (6) Multicenter (37) AstraZeneca	Intervention: Drug 1 Baseline: Bud/FM Drug 1 Endpoint: Bud/FM Drug 2 Baseline: FP Drug 2 Endpint: FP Number in group (n): Drug 1- baseline: 168 Drug 1- endpoint: 168 Drug 2- baseline: 176 Drug 2-endpoint: 176	Rescue med use during 24 hour period: Drug 1- baseline: NR Drug 1-endpoint: Reduction in reliever med use (inh/day) 0.31 Drug 2-baseline: NR Drug 2-endpoint: Reduction in reliever med use (inh/day) 0.13 P values: difference 0.18, p=0.04 Asthma exacerbations: D1 base: patients experiencing 1 or more - severe/mild D1 end: 8% / 50 (29.8%) D2 end: 11% / 74 (42.0%) Symptom control during 24 hour period: D1 base: NR D1 end: sx-free days (%) 60.4 D2 base: NR D2 end: 55.5 D3 endP: diff 4.9 NS Night time symptom control: D1 - base: NR D1 - end: night time awakenings due to asthma (%) 7.9 D2 - base: NR D2 - end: 9.6 D3 - endP: difference 1.7 NS Other: D1 baseD1 end : Symptom free days 60.4 D2 end: 55.5% D3 endP: NS Other: D1 baseD1 end : Reliever free days 75.5% D2 end: 66.4% D3 endP: p<0.001 Other: D1 baseD1 end : Asthma control days 57.8% D2 end: 52.4%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bateman et al.{Bateman, 2003 #369} 2003 Multinational (6) Multicenter (37) AstraZeneca	Serious adverse events (%): Drug 1: 2/168 (1.2%) Drug 2: 3/176 (1.7%) none considered asthma related Drug 5: NR Respiratory infection (%): Drug 1: 17.9 Drug 2: 18.8 Drug 5: NR Other: Drug 1: Bronchitis 7.7 Drug 2: 2.8 Drug 5: NR Other: Drug 1: Viral infection 6.0 Drug 2: 2.8 Drug 5: NR	Adherence Self reported adherence >98% in both groups.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1987	Bateman et al.{Bateman, 2006 #1987} 2006 Multinational Multicenter GlaxoSmithKline	Study design: RCT Double-blind Duration: 12 weeks N=484 Enrolled: 855/641/484 ITT? Yes	FEV 1 expressed as a percent of the predicted value: prebronchdilator FEV1 of 60-80% predicted; age 12 to 80 years with at least 6 month history of asthma and less than 10 pack-year smoking history and treated with only inhaled short-acting b2-agonists for the past 6 months; combined daytime and nighttime symptom scores of at least 2 on 4 or more of the last 7 days of the run-in, no exacerbations in the run-in, and demonstrated reversibility in lung function. Asthma Severity: Controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bateman et al.{Bateman, 2006 #1987} 2006 Multinational Multicenter GlaxoSmithKline		Smoking - current or former: >10 pack yr history Other: NR	Yes- 2 week run-in, then 12 week open label FSC 250/ 100 plus prn albuterol, then 12 week randomized comparison phase

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bateman et al.{Bateman, 2006 #1987} 2006 Multinational Multicenter GlaxoSmithKline	Intervention: Drug 1: FSC Drug 2: FP Total daily dose: Drug 1: 200/100 Drug 2: 500 Delivery device: Drug 1: NR Drug 2: NR Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 246 Drug 2: 238 Mean age (years): Drug 1: 40.3 Drug 2: 40.7 Sex (% female): Drug 1: 61 Drug 2: 58 Current smokers (%): Drug 1: NR Drug 2: NR Current use of ICS at baseline (%): Drug 1: 100 - per protocol Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 6 (2.4) Drug 2: 4 (1.7) Adverse events caused withdrawal (%): Drug 1: 0 Drug 2: 0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bateman et al.{Bateman, 2006 #1987} 2006 Multinational Multicenter GlaxoSmithKline	Intervention: Endpoint: FSC Endpoint: FP Number in group (n): Drug 1- endpoint: 246 Drug 2- endpoint: 238 P = 0.042	Rescue med use day: Drug 1 -endpoint: 0.02 (0.02) Drug 2 - endpoint: 0.09 (0.02) P value: P = 0.016 Rescue med use at night: Drug 1 - endpoint: 0.03 (0.02) Drug 2 - endpoint: 0.07 (0.02) P value: P =).065 Day time symptom control: D1 - base: daytime symptom score D1 - end: 0.03 (0.02) D2 - end: 0.09 (0.02) D3 - endP: P = 0.348 Night time symptom control: D1 - base: night time symptom score D1 - end: 0.05 (0.01) D2 - end: 0.06 (0.01) D3 - endP: P = 0.348 Other: D1 base: 100% symptom free days/nights D1 end : 57%/74% D2 end: 46%/60% D3 endP: P = 0.004 and 0.001 Other: D1 base: 100% rescue-free days/nights D1 end : 62%/71% D2 end: 54%/62% D3 endP: P = 0.021 and 0.019

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bateman et al.{Bateman, 2006 #1987}	Overall adverse events reported (%):	NR	Fair
2006	Drug 1: 23		Fair
	Drug 2: 26		No
Multinational			
Multicenter	Oral candidiasis- thrush (%):		
	Drug 1: 2		
GlaxoSmithKline	Drug 2: 2		

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
89	Becker et al.{Becker, 2006 #89} 2006 Multinational (30 medical centers worldwide: Asia, Africa, Europe, North America, South America) Multicenter (30) Merck	Study design: RCT Double-blind Double-dummy Duration: 56wk N = 360 Number screened: 575 screened/360 randomized ITT Analysis: No another type of analysis was used (define): "near ITT": patients with at least 2 height measurements s/p randomization	Age: Tanner 1 FEV 1 expressed as a percent of the predicted value: >=75% Days with asthma symptoms: mild, persistent asthma at step 2 of the GINA guidelines Duration of condition: >=6mo Other: height and weight between 5th and 95th percentile, bone age based on radiography of wrist within 2 years of chronological age Asthma Severity: Mild

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Becker et al.{Becker, 2006 #89} 2006 Multinational (30 medical centers worldwide: Asia, Africa, Europe, North America, South America) Multicenter (30) Merck	short acting beta agonists prn, one OCS rescue during run-in, and up to 4 OCS rescue treatments during treatment period (with no more than one treatment in a 30-day period)	Concommitant diseases: severe chronic sinus disease, nasal polyposis, pulmonary disease other than asthma, upper or lower respiratory tract infection Current treatment: antilueukotrienes within 1 month of screening visit; nasal, ocular, and inhaled CS from 4wk to 2wk; OCS within 4 months; more than 2 courses of ICS (no course exceeding 14 days) for asthma within 12mo; astemizole within 3mo; theophylline, nedocromil, cromolyn, long-acting beta agonists, and antimuscarinics within 4wk; and previous use of methylphenidate, thyroxine, HGH, anabolic corticosteroids, calcitonin, estrogens, progestins, bisphosphonates, anticonvulsants, and phosphate-binding antacids	Yes: 16wk placebo run-in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Becker et al.{Becker, 2006 #89} 2006 Multinational (30 medical centers worldwide: Asia, Africa, Europe, North America, South America) Multicenter (30) Merck	Intervention: Drug 1: ML Drug 2: BDP Drug 3: placebo Total daily dose: Drug 1: 5mg Drug 2: 400mcg Drug 3: NA Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: medium Drug 3: NA Delivery device: Drug 1: tablet Drug 2: MDI (CFC) Drug 3: tablet, MDI Is dosing comparable between treatment groups? NA: not comparing ICS with each other	# in group (n): Drug 1: 120 Drug 2: 119 Drug 3: 121 Mean age (years): Drug 1: 7.50 Drug 2: 7.57 Drug 3: 7.68 Sex (% female): Drug 1: 39.2 Drug 2: 32.8 Drug 3: 34.7 Optional - Race (% white): Drug 1: 17.5 Drug 2: 20.2 Drug 3: 19.0 Optional - Disease duration (years): Drug 1: 4.09 Drug 2: 4.10 Drug 3: 4.07 Optional - % of rescue free days: Drug 1: 80.92 Drug 2: 79.65 Drug 3: 79.46 Optional - Current use of Cromolyn Sodium (%): Drug 1: OCS use in previous year 2.60 Drug 2: 2.91 Drug 3: 2.55 Other:	Number (%) withdrawn: Drug 1: 9.2 Drug 2: 9.2 Drug 3: 10.7 Overall: 9.7 Optional - Withdrew due to lack of efficacy (%): Overall: 0.3 Adverse events caused withdrawal (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Overall: 0 Optional - Lost to follow-up (%): Overall: 2.2 Optional - Protocol violation (%): Overall: 1.1 Optional - Consent withdrawn (%): Overall: 3.6 Optional - Other reasons for withdrawal (%): Overall: moved 2.2, site termination 0.3

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Becker et al.{Becker, 2006 #89} 2006 Multinational (30 medical centers worldwide: Asia, Africa, Europe, North America, South America) Multicenter (30) Merck	Intervention: Drug 1 Baseline: ML Drug 1 Endpoint: ML Drug 2 Baseline: BDP Drug 2 Endpint: BDP Drug 3 Baseline: placebo Drug 3 Endpoint: placebo Number in group (n): Drug 1- baseline: 120 Drug 1- endpoint: 108 Drug 2- baseline: 119 Drug 2-endpoint: 109 Drug 3- baseline: 121 Drug 3- endpoint: 108	Rescue med use day: Drug 1- baseline: % of days rescue med use, median (+-SD of median) 19.08 (27.22) Drug 1 -endpoint: median (95%CI) 10.55 (7.86, 13.33) Drug 2 - baseline: 20.35 (28.05) Drug 2 - endpoint: 6.65 (4.18, 9.92) Drug 3 - baseline: 20.54 (31.76) Drug 3 - endpoint: 14.58 (9.85, 19.30) P value: <0.05 between both treatment groups vs placebo; p=0.17 for ML vs BDP Courses of steroids: D1 base: % of patients D1 end: 25.0 D2 baseD2 end: 23.5 D3 baseD3 end: 34.7 P: NS Other: D1 base: linear growth rate (cm/year): 5.96 D1 end : 5.67 D2 base: 5.74 D2 end: 4.86 D3 base: 5.72 D3 end: 5.64 P: Mean differences (95%CI): ML vs placebo 0.03 (-0.26, 0.31); BDP vs placebo -0.78 (-1.06, -0.49) p<0.001; ML vs BDP 0.81 (0.53, 1.09) p<0.001 Other: D1 base: more than one course of OCS, % patients D1 end : 5.8 D2 baseD2 end: 5.9 D3 baseD3 end: 15.7 P: p=0.02 for both treatment groups vs placebo Other: D1 base: markers of bone turnover: osteocalcin 89.09, mean; N-telopeptide-creatinine, mean 431.31 D1 end : treatment to baseline ratios (95%CI) 0.98(0.92,1.05); 0.95 (0.81, 1.10) D2 base: 90.87; 477.55

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Becker et al.{Becker, 2006 #89} 2006 Multinational (30 medical centers worldwide: Asia, Africa, Europe, North America, South America) Multicenter (30) Merck	Serious adverse events (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Severe adverse events (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Growth: Drug 1: see above Drug 2: see above Drug 3: see above Sore throat (%): Drug 1: pharyngitis 13.3 Drug 2: NR Drug 3: NR Upper respiratory tract infection (%): Drug 1: NR Drug 2: 17.6 Drug 3: 19.0 Other (%): Drug 1: asthma exacerbation 36.7 Drug 2: 42.9 Drug 3: 50.4 Mean difference between ML and placebo % (95%CI) -13.7% (-25.7, 1.2) Other (%): Drug 1: nasopharyngitis 23.3 Drug 2: 23.5 Drug 3: 24.0	Adherence adherence calculated from patient disposition figure: ML 109/120 (90.8%) completed study, BDP 108/119 (90.8), placebo 108/121 (89.3)	not true ITT, incomplete reporting Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
364	Bergmann et al.{Bergmann, 2004 #364} 2004 Germany Multicenter -private practice and hospital clinics Glaxo Wellcome	Study design: RCT Double-blind Duration: 12 weeks N=365 399 screened ITT? No	Age: 18 to 70 years who had their asthma diagnosed at least 6 months before the screening visit. Diagnosis was made according to the German asthma guidelines, asthma of moderate severity (ie, asthmatic symptoms less than once per day, but not more frequently than twice per week, during the daytime, or asthmatic symptoms at least twice per month, but less than once per week, at night time, a FEV1 between 50% and 80% of predicted, and an increase in FEV1 after 200 µg of inhaled salbutamol of at least 15% from baseline). Further entry criteria were: the patient was a non- or ex-smoker, and asthma had been treated with inhaled corticosteroids BDP or BUD, 800 to 1000 ìg per day, or fluticasone, 500 ìg per day) for atleast 3 months prior to the study. During the screening phase, patients recorded asthma symptoms and peak flow measurements in the diary cards (see below), while continuing their usual asthma medication. After two weeks, they returned for the second study visit to determine whether they had been symptomatic and were eligible for receiving study medication. At least one Asthma Severity: Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bergmann et al.{Bergmann, 2004 #364} 2004 Germany Multicenter -private practice and hospital clinics Glaxo Wellcome	Treatment with theophylline, cholinergic drugs, or leukotrienes was permitted provided the dose was not changed during the trial.	Other: Patients who had received previous therapy with inhaled long-acting beta agonists, oral beta-agonists, oral or parenteral corticosteroids during the preceding 4 weeks. Further exclusion criteria were: change of asthma medication, treatment with other study medication, respiratory tract infection or hospital stay due to respiratory problems during the preceding 4 weeks; inability of the patient to correctly administer study drugs; known allergy to components of the study medication; severe concomitant illness or other chronic respiratory disease (such as cystic fibrosis or interstitial fibrosis); and in women, inadequate contraception, pregnancy, or lactation.During screening phase, patients were not admitted to the treatment phase if entries into the diaries were incomplete and not considered reliable by the study physician, or if they had experienced a respiratory tract infection during the screening period.	Yes- During the screening phase, patients recorded asthma symptoms and peak flow measurements in the diary cards (see below), while continuing their usualasthma medication. After two weeks, they returned for the second study visit to determine whether they had been symptomatic and were eligible for receiving study medication. At least one of the following criteria had to be metfor inclusion into the treatment period: use of rescue medicationon >7 of 14 days, OR total asthma symptom score >10 points (the sum of scores from 14 days and nights). Patients were not admitted to the treatment phase if entries into the diaries were incomplete and not consideredreliable by the study physician, or if they had experienced a respiratory tract infection during the screening period.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bergmann et al.{Bergmann, 2004 #364} 2004 Germany Multicenter -private practice and hospital clinics Glaxo Wellcome	Intervention: Drug 1: SAL/FP Drug 2: FP Total daily dose: Drug 1: 250mcg FP/50mcg SAL Drug 2: 500mcg FP Steroid dosing range: Drug 1: low Drug 2: medium Delivery device: Drug 1: Diskus Drug 2: Diskus Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 170 Drug 2: 177 Mean age (years): Drug 1: 50 Drug 2: 49 Sex (% female): Drug 1: 51 Drug 2: 57 Current smokers (%): Drug 1: 0 Drug 2: 0 Optional - Disease duration: Drug 1: 1 to 5 years before entry = 30.6 5 to 19 years before entry = 24.1 Drug 2: 1 to 5 years before entry = 36.25 to 19 years before entry = 14.7 Optional - Rescue medication use (puffs per day): Drug 1: 2.4 Drug 2: 2.7 Optional - % of rescue free days: Drug 1: % of symptom-free days = 27 Drug 2: 25 Optional - Rescue medication use (puffs per day): Drug 1: 2.4 Drug 2: 2.7 Optional - % of rescue free days:	Number (%) withdrawn: Drug 1: 13 (7) Drug 2:18 (10) Optional - Other reasons for withdrawal (%): Drug 1: withdrawn = 7; medication not used = 0.5 Drug 2: withdrawn = 9; medication not used = 0.5

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bergmann et al.{Bergmann, 2004 #364} 2004 Germany Multicenter -private practice and hospital clinics Glaxo Wellcome	Intervention: Drug 1: SAL/FP Drug 2: FP # in group (n): Drug 1: 170 Drug 2: 177	Rescue med use during 24 hour period: Drug 1-endpoint: -1.6 (1.9) Drug 2-endpoint: -1 (2.2) P = 0.0001 Asthma exacerbations: D1 end: #1 D2 end: #4 Symptom control during 24 hour period: D1 end: symptom free days (%) = 49 (38) D2 end: 38 (40) P = 0.0038 AQLQ - overall: D1 baseD1 end: no numbers reported: SAL/FP all greater after 12 weeks compared to FP D2 end: no numbers reported: SAL/FP all greater after 12 weeks compared to FP P = NR Asthma Control Score: D1 end: Asthma symptom score = -1.5 (1.4) D2 end: -1 (1.5) P = 0.0005

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bergmann et al.{Bergmann, 2004 #364} 2004 Germany Multicenter -private practice and hospital clinics Glaxo Wellcome	NR	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
999	Berkowitz, et al {Berkowitz, 1998 #999} US Multicenter; 17 asthma/allergy centers Schering Corporation	Study design: RCT Double-blind Double-dummy Duration: 8 weeks N=339 Enrolled: NR ITT Analysis: Yes	FEV1 expressed as a percent of the predicted value: 50-90 Reversability of FEV1: 15% s/p short-acting beta-agonist Previous use of corticosteroids: requirement for and use of ICS during 1 month prior to study; conditions stabilized with the most commonly used daily doses of an ICS (ie, BDP 336 mg/d, TA 800 mg/day, or FLUN 1,000 to 2,000 mg/d) for at least 30 days prior to study enrollment. Duration of condition: >= 2yr : history of asthma at least 2 years prior to study Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Berkowitz, et al {Berkowitz, 1998 #999} US Multicenter; 17 asthma/allergy centers Schering Corporation		Concommitant diseases: any lung condition other than asthma, clinically significant disease (cardiac, renal, hepatic, neurologic, GI, endocrine, metabolic, psychiatric) that could interfere with the conduct or evaluation of the study; respiratory tract infection within 30 days prior to study; abnormal results from a physical examination or ECG that would interfere with patient safety, history of assisted ventilation or admission to an ICU or frequent emergency department visits or hospitalization for severe asthma exacerbation, or presence of a known hypersensitivity to beta2-agonist or corticosteroids. Smoking - within last 12mo	Other than study or rescue medications (ie, inhaled albuterol), patients were restricted from the use of cromolyn or nedocromil,systemic antibiotics, and any investigative drugs for 30 days priorto enrollment. Use of theophylline qd was prohibited for 48 to72 h prior to enrollment, theophylline bid for 24 to 48 h,short-acting theophylline for 12 to 24 h, SM xinafoatewithin 48 h, aspirin and other nonsteroidal anti-inflammatorydrugs and b-blockers within 24 h, and inhaled bronchodilatorswithin 8 h.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Berkowitz, et al {Berkowitz, 1998 #999} US Multicenter; 17 asthma/allergy centers Schering Corporation	Intervention: Drug 1: BDP Drug 2: TA Drug 3: placebo Drug 4: OVERALL Total daily dose: Drug 1: 336mcg Drug 2: 800mcg Drug 3: NA Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Drug 3: NA Delivery device: Drug 1: MDI s/ spacer Drug 2: MDI c/ built-in tube extender Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: unless otherwise stated, for this whole section, it is the defined efficacy population 98 Drug 2: 94 Drug 3: 82 Mean age (years): Drug 1: 36.1 Drug 2: 40.3 Drug 3: 38.3 Sex (% female): Drug 1: 62.2 Drug 2: 63.8 Drug 3: 661 Optional - Race (% white): Drug 1: 86.7 Drug 2: 87.2 Drug 3: 95.1 Optional - Disease duration (years): Drug 1: 20.4 Drug 2: 19.8 Drug 3: 19.6 Other: Drug 1: baseline FEV1(L) 2.45 Drug 2: 2.41 Drug 3: 2.45	Number (%) withdrawn: Drug 1: 16/114 (14) Drug 2: 17/111 (15.3) Drug 3: 32/114 (28.1) Optional - Withdrew due to asthma exacerbations (%): Drug 1: "treatment failure" 7 (6.1) Drug 2: 9 (8.1) Drug 3: 30 (26.3) Adverse events caused withdrawal (%): Drug 1: 11/112 (9.8) Drug 2: 9/108 (8.3) Drug 3: 18/110 (16.3) Drug 4: 38/330 (11.5)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Berkowitz, et al {Berkowitz, 1998 #999} US Multicenter; 17 asthma/allergy centers Schering Corporation	Intervention: Drug 1 Baseline: BDP Drug 1 Endpoint: BDP Drug 2 Baseline: TA Drug 2 Endpoint: TA Drug 3 Baseline: Placebo Drug 3 Endpoint: Placebo P-values (Define comparison): BDP & TA vs placebo Number in group (n): Drug 1- baseline: 114 Drug 1- endpoint: ITT(114), efficacy(98) Drug 2- baseline: 111 Drug 2-endpoint: ITT(111), efficacy (94) Drug 3- baseline: 114 Drug 3- endpoint: ITT(114), efficacy(82)	Rescue med use during 24 hour period: Drug 1- baseline: (mean, calculated weekly) Drug 1-endpoint: 3.24-3.45 Drug 2-endpoint: 3.24-3.7 Drug 3- endpoint: 3.82-4.25 P values: only BDP vs placebo during certain weeks, <0.05 Other: D1 base: Asthma Symptom Score per above P: =0.001 Other Relevant Health Outcome Results: No difference in symptom reduction between active treatments; both were significantly better than placebo (P < 0.01)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Berkowitz, et al {Berkowitz, 1998 #999}	Overall adverse events reported (%): Drug 1: includes due to study drug 50 Drug 2: 57.4 Drug 3: 55.5 P = 0.663	Compliance >95% for each treatment group.	Fair Fair No
US Multicenter; 17 asthma/allergy centers			
Schering Corporation	Serious adverse events (%): Drug 1: 0 Drug 2: 0.9 Drug 3: 0		
	Oral candidiasis- thrush (%): Drug 1: 1.8 Drug 2: 0 Drug 3: 0		
	Dysphonia (%): Drug 1: 1.8 Drug 2: 1.9 Drug 3: 0		
	Cough (%): Drug 1: 3.6 Drug 2: 2.8 Drug 3: 2.7		
	Sore throat (%): Drug 1: dry throat 0 Drug 2: 0.9 Drug 3: 0		
	Death (%): Drug 1: 0 Drug 2: 0 Drug 3: 0		
	Other (%): Drug 1: make distinction between adverse events overall and those due to study drug- study drug 22.3 Drug 2: 20.4 Drug 3: 25.5		
	Other (%): Drug 1: pharyngitis 2.7 Drug 2: 0.9 Drug 3: 2.7		
	Other (%):		

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
871	Bernstein et al.{Bernstein D, 1999 #871} 1999 United States Multicenter (20) Schering-Plough Corporation	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=365 Enrolled: NR/NR/365 ITT Analysis: Yes	: history of asthma for at least 6 months; using an ICS daily for at least 30 days; 2 weeks prior to screening, on a stable regimen of FLUN, TAA, BDP, or FP. All patients were non-smokers or had discontinued smoking more than 6 months prior to screening. Certain medications that might interfere with the action of ICS (e.g. corticosteroids byother routes, bronchodilators, cromolyn sodium, antihistaminesand decongestants) were restricted prior to thescreening visit; reversibility of airway disease, increase in absolute FEV1 of >=12%; FEV1 values >= 60% <=90% of predicted normal values; all patients had clinically acceptable values for complete blood count, blood chemistry profile, urinalysis, standard 12-lead ECGs and vital signs, and all were free of other clinically significant disease. Patients screened at five sites were required to have a baseline unstimulated plasma cortisol level >=5 and a level >= 18 30 min after stimulation with cosyntropin. Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bernstein et al.{Bernstein D, 1999 #871} 1999 United States Multicenter (20) Schering-Plough Corporation	NR	pre-menarche, pregnancy, or lactation; immunotherapy, unless on a stable maintenance; treatment with oral glucocorticoids for > 14 days in the 6 months before screening, methotrexate, cyclosporin, or gold within 3 months, or systemic steroids or another investigational drug in the month before screening; dependence upon daily use of nebulized B-agonists; the need for ventilator support in previous 5 years; hospitalization for asthma in the previous 3 months; requirement of > 12 puffs day of albuterol on 2 consecutive days between the screening and (viral or bacterial) in the 2 weeks; oropharyngeal candidiasis; women of child-bearing age required to use birth control	Yes: 2 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bernstein et al.{Bernstein D, 1999 #871} 1999 United States Multicenter (20) Schering-Plough Corporation	Intervention: Drug 1: MF Drug 2: MF Drug 3: MF Drug 4: BDP Drug 5: Placebo Total daily dose: Drug 1: 200 Drug 2: 400 Drug 3: 800 Drug 4: 336 Drug 5: NA Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: medium Drug 3: high Drug 4: medium Delivery device: Drug 1: DPI Drug 2: DPI Drug 3: DPI Drug 4: MDI Drug 5: DPI/MDI Is dosing comparable between treatment groups? NA: Yes for medium vs medium; no for other comparisons	# in group (n): Drug 1: 76 Drug 2: 70 Drug 3: 74 Drug 4: 71 Drug 5: 74 Mean age (years): Drug 1: 38 Drug 2: 36 Drug 3: 37 Drug 4: 37 Drug 5: 37 Sex (% female): Drug 1: 41 Drug 2: 42 Drug 3: 47 Drug 4: 47 Drug 5: 45 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Drug 4: 0 Drug 5: 0 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Drug 4: 100 Drug 5: 100	Number (%) withdrawn: Overall: 24% Adverse events caused withdrawal (%): Drug 1: 5% Drug 2: 3% Drug 3: 4% Drug 4: 8% Drug 5: 11%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bernstein et al.{Bernstein D, 1999 #871} 1999 United States Multicenter (20) Schering-Plough Corporation	Intervention: Drug 1 Baseline: MF 200/MF 400 Drug 1 Endpoint: MF 200/MF 400 Drug 2 Baseline: MF 800/BDP Drug 2 Endpoint: MF 800/BDP Drug 3 Baseline: Placebo Drug 3 Endpoint: Placebo	Rescue med use during 24 hour period: Drug 1- baseline: Albuterol use per day (%), change from baseline Drug 1-endpoint: 22%*/-21.4%* Drug 2-endpoint: -2.3%*/-21.4%* Drug 3- endpoint: 25.3% P values: *p < 0.01 vs placebo; NR for MF 400 vs BDP Nocturnal awakenings: D1 base: number of nocturnal awakenings, change from baseline: D1 end: -0.02*/-0.08* D2 baseD2 end: -0.12*/0.00* D3 baseD3 end: 0.31 P: p<0.01 vs placebo; NR for MF vs BDP Other: D1 base: Asthma symptom scores for wheezing, change from baseline: D1 end : -0.15*/-0.22* D2 end: -0.25*/-0.25* D3 end: 0.30 P: p<0.01 vs placebo; NR MF vs BDP Other: D1 base: Asthma symptom scores for difficulty breathing, change from baseline: D1 end : -0.15*/-0.31* D2 end: -0.25*/-0.29* D3 baseD3 end: 0.39 P: p<0.01 vs placebo; NR MF vs BDP Other: D1 base: Asthma symptom scores for cough, change from baseline: D1 end : -0.03*/-0.05* D2 end: -0.04*/-0.13* D3 end: 0.36 P: p<0.01 vs placebo; NR MF vs BDP Other Relevant Health Outcome Results: Both active treatment groups significantly improved asthma symptom scores, albuterol use, nocturnal awakenings (P < 0.05), but there were no significant differe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bernstein et al.{Bernstein D, 1999 #871} 1999 United States Multicenter (20) Schering-Plough Corporation	Overall adverse events reported (%): Drug 1: 18 Drug 2: 26 Drug 3: 28 Drug 4: 21/22 Oral candidiasis- thrush (%): Drug 1: 4 Drug 2: 6 Drug 3: 15 Drug 4: 3/1 Dysphonia (%): Drug 1: 1 Drug 2: 1 Drug 3: 3 Drug 4: 1/1 Cough (%): Drug 1: 1 Drug 2: 0 Drug 3: 0 Drug 4: 0/3 Headache (%): Drug 1: 3 Drug 2: 4 Drug 3: 4 Drug 4: 4/5 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: The response to cosyntropin stimulation was analysed as the difference between post-stimulation and pre-stimulation plasma cortisol concentrations for 98 patients from five treatment centres, representing 18 or 20 patients from each treatment group. Mean pre-stimulation values for plasma cortisol were >5, mean post-stimulation values were > 18, and mean changes from prestimulation to post-stimulation values were > 7 mcg. These results indicated no evidence of HPA-axis suppression in any treatment group.	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
32	Bisguaard et al.{Bisguaard, 2006 #32} 2006 Multinational (12 countries), Multicenter (41 centers) AstraZeneca R&D	Study design: RCT Double-blind Duration: 12 months N=341 388 enrolled, 341 randomized ITT? Yes	Reversability of FEV1: > = 12% c/in 15min s/p terbutaline 1mg/ inh Previous use of corticosteroids: constant dose in the range of 200-500mcg/d for >=3 months before study entry Duration of condition: >= 6m; >= 1 clinically important asthma exacerbation in the 12m preceding study entry; eight or more inhalations of terbutaline in the last 10 days of run-in and up to seven inhalations on any 1 day. Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bisguaard et al.{Bisguaard, 2006 #32} 2006 Multinational (12 countries), Multicenter (41 centers) AstraZeneca R&D	terbutaline rescue, depending on treatment group as expressed below	Other: asthma exacerbation or necessitated change in ICS dose during run-in period	Yes- length of run-in is not described, although it is at least 10 days. during the run-in, patients used their previous ICS dose and utilized terbutaline as needed.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bisguaard et al.{Bisguaard, 2006 #32} 2006 Multinational (12 countries), Multicenter (41 centers) AstraZeneca R&D	Intervention: Drug 1: BUD Drug 2: BUD/FM fixed and terbutaline 0.4mg prn Drug 3: BUD/FM (SMART-Symbicort maintenance and relief therapy) Total daily dose: Drug 1: 320mcg Drug 2: 80mcg Drug 3: 80mcg plus additional 80mcg prn Steroid dosing range: Drug 1: low Drug 2: very low Drug 3: very low to high Delivery device: Drug 1: Turbuhaler Drug 2: Turbuhaler Drug 3: Turbuhaler Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 106 Drug 2: 117 Drug 3: 118 Mean age (years): Drug 1: 8 Drug 2: 8 Drug 3: 8 Sex (% female): Drug 1: 34 Drug 2: 30 Drug 3: 28 Optional - Race (% white): Drug 1: 85 Drug 2: 86 Drug 3: 85 Optional - Disease duration (years): Drug 1: 3 Drug 2: 3 Drug 3: 3 Optional - Rescue medication use (puffs per day): Drug 1: 1.6 Drug 2: 1.6 Drug 3: 1.7 Optional - % of rescue free days: Drug 1: 17 Drug 2: 17 Drug 3: 15 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100	Number (%) withdrawn: Drug 1: 14 (13) Drug 2: 10 (9) Drug 3: 9 (8) Adverse events caused withdrawal (%): Drug 1: 1 Drug 2: 1 Drug 3: 2 Optional - Lost to follow-up (%): Drug 1: 3 Drug 2: 2 Drug 3: 1 Optional - Other reasons for withdrawal (%): Drug 1: 10 Drug 2: 6 Drug 3: 5

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bisguaard et al.{Bisguaard, 2006 #32} 2006 Multinational (12 countries), Multicenter (41 centers) AstraZeneca R&D	Intervention: Drug 1 Baseline: BUD Drug 1 Endpoint: BUD Drug 2 Baseline: BUD/FM fixed and terbutaline 0.4mg prn Drug 2 Endpoint: BUD/FM fixed and terbutaline 0.4mg prn Drug 3 Baseline: BUD/FM (SMART-Symbicort maintenance and relief therapy) Drug 3 Endpoint: BUD/FM (SMART-Symbicort maintenance and relief therapy) P-values (Define comparison): unless otherwise stated, endpoint only: SMART vs BUD; SMART vs BUD/FM; BUD/FM vs BUD Number in group (n): Drug 1- baseline: 106 Drug 1- endpoint: 106 Drug 2- baseline: 117 Drug 2-endpoint: 117 Drug 3- baseline: 118 Drug 3- endpoint: 118	Rescue med use during 24 hour period: Drug 1- baseline: as needed, # puffs 1.6 Drug 1-endpoint: 0.74 Drug 2-baseline: 1.6 Drug 2-endpoint: 0.76 Drug 3 - baseline: 1.7 Drug 3- endpoint: 0.58 P values: 0.1; 0.038; 0.72 Asthma exacerbations: D1 end: 28 (26%) D2 end: 44 38%) D3 end: 17 (14%) P: 0.22; <0.001; 0.12 Asthma exacerbations requiring medical attention: D1 end: 21 (20%) D2 end: 36 (31%) D3 end: 10 (8%) P: <0.001 <0.001; 0.12 Symptom control during 24 hour period: D1 base: symptom-free days, % 28.9 D1 end: 56.2 D2 base: 36.4 D2 end: 68.0 D3 base: 35.3 D3 end: 63.4 P: 0.28; 0.31; 0.041 Day time symptom control: D1 - base: as needed, # puffs D1 - end: 0.59 D2 - end: 0.59 D3 - end: 0.49 P: 0.16; 0.066; 0.71 Night time symptom control: D1 - base: as needed, # puffs

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bisguaard et al.{Bisguaard, 2006 #32} 2006 Multinational (12 countries), Multicenter (41 centers) AstraZeneca R&D	Overall adverse events reported (%): Drug 1: 4.7 Drug 2: 13.6 Drug 3: 1.7 Serious adverse events (%): Drug 1: serious, related to asthma exacerbation 2 Drug 2: 6 Drug 3: 0 Respiratory infection (%): Drug 1: PNA 0 Drug 2: 2 Drug 3: 0 Other (%): Drug 1: fracture 0 Drug 2: 3 Drug 3: 1 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: patients receiving the SMART regimen grew significantly more than patients in the fixed-dose BUD group. There was an adjusted mean difference in growth of 1 cm between patients receiving SMART vs those receiving fixed-dose budesonide (95% confidence interval, 0.3 to 1.7; p = 0.0054) and a similar difference of 0.9 cm was seen between the fixed-dose combination and fixeddose BUD groups (95% confidence interval, 0.2 to 1.6; p = 0.0099). The number of patients with abnormal (< 400nmol/L) pre–ACTH- and post–ACTH-stimulated plasma cortisol levels were similarly low in all groups (2 of 51 patients vs 1 of 55 patients vs 3 of 41 patients in the SMART, fixed-dose combination, and fixeddose BUD groups, respectively). Additional adverse events and comments: class-related adverse effects, such as tremor, dysphonia, and tachyc	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
398	Bjermer et al.{Bjermer, 2003 #398} 2003 Multinational - Eastern Europe (37 countries) Multicenter - 148 sites Merck	Study design: RCT Double-blind Double-dummy Duration: 48 weeks N=1490 Enrolled: 2144, NR, 1490 ITT Analysis: Yes	: Patients were aged 15-72 years and had a history of chronic asthma for one year or longer, a baseline FEV1 of 50-90% predicted, and an improvement of 12% or more in FEV1 or in morning PEF after using a b-agonist. Other inclusion criteria included regular use of an ICS (equivalent to BDP 200-1000 mg per day) for at least eight weeks before the run-in period, an average use of b-agonist of one puff or more per day, and a pre-specified minimum biweekly daytime symptom score. Asthma Severity: Mild Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bjermer et al.{Bjermer, 2003 #398} 2003 Multinational - Eastern Europe (37 countries) Multicenter - 148 sites Merck		Other: We excluded patients who received oral corticosteroids in the preceding month; chromones, leukotriene receptor antagonists, long acting inhaled or oral b- agonists, or inhaled anticholinergics during the preceding two weeks; and patients who received theophylline or antihistamines during the week preceding the first visit.	Yes: four week run-in period when patients received non-blinded inhaled dry powder fluticasone 100 mcg twice daily. During the last two weeks of this period, single blind placebo SM (metered dose inhaler) and placebo ML were added.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bjermer et al.{Bjermer, 2003 #398} 2003 Multinational - Eastern Europe (37 countries) Multicenter - 148 sites Merck	Intervention: Drug 1: ML / FP Drug 2: SM / FP Total daily dose: Drug 1: 10mg / 200mcg Drug 2: 100mcg / 200mcg Steroid dosing range (Low, medium or high): Drug 1: NA/ low Drug 2: NA / low Delivery device: Drug 1: tablet / DPI Drug 2: MDI/ DPI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 747 Drug 2: 743 Mean age (years): Drug 1: 41.2 Drug 2: 41 Sex (% female): Drug 1: 54.6 Drug 2: 55.2 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 125 (16.7) Drug 2: 110 (14.8) Overall: 235 (15.8) Adverse events caused withdrawal (%): Drug 1: 5.1 Drug 2: 5 Overall: 5

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bjermer et al.{Bjermer, 2003 #398} 2003 Multinational - Eastern Europe (37 countries) Multicenter - 148 sites Merck	Intervention: Drug 1 Baseline: ML/ FP Drug 1 Endpoint: ML/ FP Drug 2 Baseline: SM/ FP Drug 2 Endpoint: SM/FP Number in group (n): Drug 1- baseline: 747 Drug 1- endpoint: 747 Drug 2- baseline: 743 Drug 2- endpoint: 743	Asthma exacerbations: D1 end: at least one asthma exacerbation (each patient counted once in each category) = 150 (20.1%) D2 end: 142 (19.1%) P: Risk Ratio 1.05 (95% CI = 0.86 to 1.29) Courses of steroids: D1 end: use of oral, IM, IV, or rectal corticosteroids = 118 D2 end: 107 P: Risk Ratio 1.10 (95% CI = 0.86 to 1.40) Nocturnal awakenings: D1 base: mean days/week: 2.6 (2.4) D1 end: mean change from baseline = -1.68 D2 base: 2.6 (2.4) D2 end: -1.74 P: NS between groups; p </= 0.001 for both groups versus baseline AQLQ - overall: D1 base: mean: 4.7 (1.0) D1 end: mean change from baseline = 0.71 D2 base: 4.7 (1.0) D2 end: 0.76 P: NS between groups; p </= 0.001 for both groups versus baseline Emergency room visits: D1 end: 21 D2 end: 21 P: Risk Ratio 0.99 (95% CI = 0.55 to 1.81) Hospitalizations: D1 end: 5 D2 end: 7 P: Risk Ratio 0.71 (95% CI = 0.21 to 2.22) Urgent care use: D1 end: 82 D2 end: 80 P: Risk Ratio 1.02 (95% CI = 0.76 to 1.36)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bjermer et al.{Bjermer, 2003 #398} 2003 Multinational - Eastern Europe (37 countries) Multicenter - 148 sites Merck	Overall adverse events reported (%): Drug 1: 530 (71%) Drug 2: 538 (72.4%) Serious adverse events (%): Drug 1: 4.6% Drug 2: 7.4% Drug 5: 0.022 Other (%): Drug 1: drug related adverse events = 6.3% Drug 2: 10% Drug 5: 0.01 Additional adverse events and comments: One patient in the SM/FP group died 15 days after the start of treatment with a severe asthma attack that was reported by the investigator as possibly related to study treatment. Laboratory adverse experiences were reported by 83 (11.4%) and 85 (11.7%) patients in the ML-FP and SM-FP groups, respectively. One patient reported serious laboratory adverse experiences (neutropenia; and increased lymphocytes, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) in the SM-fluticasone group, and none in the ML-FP group.	NR	Good Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
804	Bleecker et al.{Bleecker, 2000 #804} 2000 Multinational Multicenter (41 sites) Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 12wk N = 451 Number screened: 592/451/451 ITT Analysis: Yes	: 12 years of age and older with a diagnosis of persistent asthma for at least 6 months; a predose FEV1 of 50% to 80% of predicted normal and an increase in FEV1 of 12% or greater from baseline after inhalation of 180 µg of albuterol; used albuterol on a scheduled or as-needed basis during the 4 weeks immediately before. Asthma Severity: Mild Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bleecker et al.{Bleecker, 2000 #804} 2000 Multinational Multicenter (41 sites) Glaxo Wellcome	Antihistamines, decongestants, and intranasal medications for the treatment of allergic rhinitis were allowed and rescue albueterol	Other: ML, zafirlukast, or zileuton within 2 weeks, and ICS or systemic corticosteroids were not allowed within 2 months; history of life-threatening asthma or who had received more than 3 bursts of oral or parenteral corticosteroids within 1 year; use of tobacco products within the previous year or a smoking history of greater than 10 pack-years, a respiratory infection within 2 weeks of screening, current evidence of significant respiratory disorders other than asthma, or other significant uncontrolled disease states; concurrent use of medications, which might affect the course of asthma (eg, SM, theophylline) or interact with zafirlukast (eg, terfenadine, warfarin).	Yes: 8-14 day run-in during which all patients used rescue albuterol to relieve asthma symptoms

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bleecker et al.{Bleecker, 2000 #804} 2000 Multinational Multicenter (41 sites) Glaxo Wellcome	Intervention: Drug 1: Zafirklast Drug 2: FP Total daily dose: Drug 1: 40 mg Drug 2: 176 mcg Steroid dosing range (Low, medium or high): Drug 2: Low Delivery device: Drug 1: capsule Drug 2: MDI Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 220 Drug 2: 231 Mean age (years): Drug 1: 31 Drug 2: 31 Sex (% female): Drug 1: 51 Drug 2: 48 Current smokers (%): Drug 1: 0 Drug 2: 0 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 50(23) Drug 2: 31 (13) Adverse events caused withdrawal (%): Drug 1: 5 Drug 2: 3

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bleecker et al.{Bleecker, 2000 #804} 2000 Multinational Multicenter (41 sites) Glaxo Wellcome	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: Zafirlukast Drug 2 Endpint: Zafirlukast FP vs. Zafirlukast Number in group (n): Drug 1- baseline: 231 Drug 1- endpoint: 231 Drug 2- baseline: 220 Drug 2- endpoint: 220	Rescue med use during 24 hour period: Drug 1- baseline: 4.55 Drug 1-endpoint: -2.39 (0.19) Drug 2-baseline: 4.8 Drug 2-endpoint: -1.45 (0.19) P < 0.001 Rescue med use day: Drug 1- baseline: Rescue free days % 7.2 Drug 1 -endpoint: 40.4 Drug 2 - baseline: 7.4 Drug 2 - endpoint: 24.2 P < 0.001 Asthma exacerbations: D1 baseD1 end: 4% D2 baseD2 end: 6% P=0.191 Symptom control during 24 hour period: D1 base: Symptom free days % 7.4 D1 end: +28.5 (2.6) D2 base: 5.1 D2 end: +15.6 (2.3) P < 0.001 Nocturnal awakenings: D1 base: Nights with no awakenings % 67.0 D1 end: +21.2 (2.3) D2 base: 66.5 D2 end: +8.0 (2.1) P = NR Other: D1 base: Nighttime awakenings (no): 0.44 D1 end : -0.28 (0.04) D2 base: 0.49 (0.05) D2 end: -0.15 (0.04) D3 baseD3 endP: P<0.001

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bleecker et al.{Bleecker, 2000 #804} 2000 Multinational Multicenter (41 sites) Glaxo Wellcome	Overall adverse events reported (%): Drug 1: TAEs 10 Drug 2: 10 Headache (%): Drug 1: 3 Drug 2: 1 Hoarseness (%): Drug 1: 2 Drug 2: 0 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: nr	Compliance Patient reported compliance with MDI and oral capsules was approximately 92% in both FP and zafirlukast groups	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
5112	Bleecker et al.{Bleecker, 2007 #5112} 2007 Multinational Multicenter (41 sites) Glaxo Wellcome	Study design:Secondary analysis of two RCTs Duration: Study 1: 6 months and study 2 : 7 months N = Study 1: 2250 and study 2: 405 Enrolled: NR/NR/2655 ITT analysis: NR	Study 1: individuals aged 12 years or more with a diagnosis of asthma (as defi ned by the American Thoracic Society)25 for at least 6 months and who were taking inhaled corticosteroids (≥500 µg per day) for the month before enrolment: forced expiratory volume in 1 s (FEV1) of at least 50% predicted normal with at least 12% reversibility after 1 mg terbutaline and one or more asthma exacerbations in the previous 1–12 months Study 2; aged at least 12 years with a diagnosis of asthma for 6 or more months who had been maintained on a moderate daily dose of inhaled corticosteroid or an inhaled corticosteroid plus longacting β2-agonist combination for at least 12 weeks before screening (1225 participants were randomised). Bronchodilator reversibility was not an entry requirement.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bleecker et al.{Bleecker, 2007 #5112} 2007 Multinational Multicenter (41 sites) Glaxo Wellcome	Study 1: Terbutaline as needed Study 2; albuterol as needed	Study 1: more than ten as-needed inhalations in any day of run-in or who had an asthma exacerbation during that time Study 2; NR	Study 1: 2 week run in Study 2; 2 week run in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bleecker et al.{Bleecker, 2007 #5112} 2007 Multinational Multicenter (41 sites) Glaxo Wellcome	Study 1: Intervention: Drug 1: Bud/FM maintainence and reliever Drug 2: Bud/FM maintainence (terbutaline reliever) Drug 3: FP/SM maintainence (terbutaline reliever) Total daily dose: Drug 1: 320/9 + reliever use Drug 2: 640/18 Drug 3: 500/100 Steroid dosing range (Low, medium or high): Drug 2: Low to high Delivery device: Drug 1: dry powder inhaler Drug 2: dry powder inhaler Drug 3: dry powder inhaler Study 2; Intervention: Drug 1: Bud/FM adjustable dose Drug 2: Bud/FM maintainence fixed dose Drug 3: FP/SM maintainence Total daily dose: Drug 1: 320/9 to 1380/36, adjusted depending on control Drug 2: 640/18 Drug 3: 500/100 Steroid dosing range (Low, medium or high): Drug 2: Low to high	Study 1: # in group (n): Drug 1: Gly/Gly 833 Drug 2: Gly/Arg 1029 Drug 3: Arg/Arg 363 Mean age (years): Drug 1: Gly/Gly 38.8 Drug 2: Gly/Arg 37.3 Drug 3: Arg/Arg 37.2 Sex (% female): Drug 1: Gly/Gly 60 Drug 2: Gly/Arg 58 Drug 3: Arg/Arg 59 Study 2; # in group (n): Drug 1: Gly/Gly 169 Drug 2: Gly/Arg 169 Drug 3: Arg/Arg 67 Mean age (years): Drug 1: Gly/Gly 39.8 Drug 2: Gly/Arg 39.4 Drug 3: Arg/Arg 40.9 Sex (% female): Drug 1: Gly/Gly 61 Drug 2: Gly/Arg 55 Drug 3: Arg/Arg 63	Study 1: NR Study 2; NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bleecker et al.{Bleecker, 2007 #5112} 2007 Multinational Multicenter (41 sites) Glaxo Wellcome	Study 1: # in group (n): Drug 1: Gly/Gly 833 Drug 2: Gly/Arg 1029 Drug 3: Arg/Arg 363 Study 2; # in group (n): Drug 1: Gly/Gly 169 Drug 2: Gly/Arg 169 Drug 3: Arg/Arg 67	Study 1: Severe exacerbations Gly/Gly Drug 1: 33 Drug 2: 59 Drug 3: 61 Gly/Arg Drug 1: 35 Drug 2: 37 Drug 3: 80 Arg/Arg Drug 1: 8 Drug 2: 17 Drug 3: 13 Exacerbations per participant per 6 months Gly/Gly Drug 1: 0.13 Drug 2: 0.23 Drug 3: 0.26 Gly/Arg Drug 1: 0.12 Drug 2: 0.12 Drug 3: 0.24 Arg/Arg Drug 1: 0.08 Drug 2: 0.14 Drug 3: 0.13 Participants with 1 or more hospital or ER Gly/Gly Drug 1: 3% Drug 2: 5% Drug 3: 7% Gly/Arg Drug 1: 5% Drug 2: 3% Drug 3: 7% Arg/Arg Drug 1: 3% Drug 2: 5% Drug 3: 5% Study 2; Severe exacerbations Gly/Gly 15 Gly/Arg 18 Arg/Arg 10 Exacerbations per participant per 6 months Gly/Gly 0.09 Gly/Arg 0.10 Arg/Arg 0.14

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bleecker et al.{Bleecker, 2007 #5112}	Study 1:	Study 1:	Fair, but some concerns w/ analysis (no sample size calculation presented; post-hoc analysis)
2007	NR	NR	
Multinational	Study 2;	Study 2;	NA
Multicenter (41 sites)	NR	NR	No
Glaxo Wellcome			

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1216	Boe et al.{Boe, 1994 #1216} 1994 Norway Multicenter NR	Study design: RCT Double-blind Duration: 12 weeks N=134 Enrolled: NR/NR/134 ITT Analysis: Unable to determine	: Subjects aged 18 yrs or more with a clinical diagnosis of asthma; receiving 0.4–2.0 mg of BDP or BUD at least 4 weeks prior; some evidence of lack of good asthma control; to fulfill at least two of the following criteria: 1) FEV1 <80% of predicted [8] at pretrial or first trial visit; 2) mean morning PEF during the last 7 days of run-in period <80% of predicted [8]; 3) diurnal variation in PEF of at least ±20% on a minimum of four of the last seven days of the run-in period; 4) asthma symptoms during a minimum of four 24 h periods in the last 7 days of the run-in period Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Boe et al.{Boe, 1994 #1216} 1994 Norway Multicenter NR		oral corticosteroids during the last 4 weeks preceding the study	Yes: 2 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Boe et al.{Boe, 1994 #1216} 1994 Norway Multicenter NR	Intervention: Drug 1: FP Drug 2: BDP Total daily dose: Drug 1: 1.6 Drug 2: 2.0 Steroid dosing range (Low, medium or high): Drug 1: High Drug 2: High Delivery device: Drug 1: Rotodisk-Diskhaler Drug 2: Rotodisk-Diskhaler Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 71 Drug 2: 63 Mean age (years): Drug 1: 51 Drug 2: 51 Sex (% female): Drug 1: 45 Drug 2: 35 Current smokers (%): Drug 1: 38 Drug 2: 30 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100	Number (%) withdrawn: Drug 1: 9 (13) Drug 2: 3 (5) Adverse events caused withdrawal (%): Drug 1: 8 Drug 2: 2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Boe et al.{Boe, 1994 #1216}	Intervention:	Rescue med use day:
1994	Drug 1 Baseline: FP	Drug 1- baseline: mean daily puffs (SEM): 2.75 (0.24)
	Drug 1 Endpoint: FP	Drug 1 -endpoint: 2.24 (0.24)
Norway	Drug 2 Baseline: BDP	Drug 2 - baseline: 2.92 (0.24)
Multicenter	Drug 2 Endpoint: BDP	Drug 2 - endpoint: 2.35 (0.25)
		P value: NS
NR	Number in group (n):	
	Drug 1- baseline: 71	Rescue med use at night:
	Drug 1- endpoint: 71	Drug 1- baseline: 0.77 (0.12)
	Drug 2- baseline: 63	Drug 1 - endpoint: 0.73 (0.14)
	Drug 2- endpoint: 63	Drug 2 - baseline: 0.76 (0.11)
		Drug 2 - endpoint: 0.51 (0.09)
		P value: NS
		Day time symptom control:
		D1 - base: mean symptom score (SEM) on 0-5 scale: 1.7 (0.11)
		D1 - end: 1.35 (0.13)
		D2 - base: 1.94 (0.11)
		D2 - end: 1.6 (0.12)
		P: NS
		Night time symptom control:
		D1 - base: mean symptom score (SEM) on 0-4 scale: 0.77 (0.08)
		D1 - end: 0.62 (0.08)
		D2 - base: 0.85 (0.08)
		D2 - end: 0.65 (0.08)
		P: NS

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Boe et al.{Boe, 1994 #1216} 1994 Norway Multicenter NR	Oral candidiasis- thrush (%): Drug 1: Candidiasis 31 Drug 2: 30 Sore throat (%): Drug 1: 28 Drug 2: 14 Upper respiratory tract infection (%): Drug 1: 27 Drug 2: 38 Respiratory infection (%): Drug 1: 14 Drug 2: 10 Hoarseness (%): Drug 1: 14 Drug 2: 5 Other (%): Drug 1: GI disorders 13 Drug 2: 19 Other (%): Drug 1: Muscoskeletal disorders 13 Drug 2: 25 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: mean change from baseline values for serum cortisol and plasma ACTH in each treatment group at three different visits for the total population. Analysis of covariance with serum cortisol and ACTH as dependent variables (in two separate analyses), and treatment, stratum, centre, and the baseline reading as covariates showed no significant effect of stratum or centre. In the analysis of serum cortisol, controlled for the baseline value and found significant differences between FP and BDP (p<0.001) at 4 and 12 weeks, but no significant difference at the follow-up visit (14 weeks). The corresponding analysis of ACTH showed a significant difference betw	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
869	Bouros et al.{Bouros, 1999 #869} 1999 Greece Multicenter (11) Novartis	Study design: RCT open-label Duration: 3 months N=134 Enrolled: NR, NR, 159 enrolled, then 134 randomized. ITT Analysis: No another type of analysis was used (define): Only those who complete the entire treatment period	: >/=18 yrs old, were enrolled in the study. Patients were subsequently randomized to study treatment, if they fulfilled the following inclusion criteria: a symptom score (day and night) of two or greater on at least 4 of the 7 days during the second week of the run-in period, FEV1 before administration of an inhaled agonist 40 - 85% of the predicted normal for the patient, and a reversibility test with 200 mg salbutamol demonstrating an increase in FEV1 of at least 15% from baseline value. Finally, patients were required to have been using inhaled BDP aerosol for a least 1 month prior to enrollment, and at a constant daily dose of 500 mg. Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bouros et al.{Bouros, 1999 #869} 1999 Greece Multicenter (11) Novartis	salbutamol as needed for resuce	Other: evidence of other clinically significant diseases, pregnant or lactating women,patients on b-blocker therapy or with hypersensitivity to sympathomimetic amines, those who were considered unable to comply with the study protocol and patients who had received a short course with an oral corticosteroid inthe 6 weeks prior to enrolment, or more than three oral corticosteroid short courses during the year prior to enrollment.	Yes: A run-in period of 2 weeks facilitated the establishment of eligibility for subsequent randomization and served as the baseline for the analyses. At the initial screening (visit 1), b2-agonists and other anti-asthma medication were removed (except BDP). Patients were provided with salbutamol pMDI 100 mcg/puff to be used for rescue purposes on an "as needed" basis. A spacer device was provided for use with the inhaled steroid only. At visit 2, randomized patients were requested to discontinue use of their own BDP pMDI, and BDP pMDI 250 mcg/puff and FM pMDI 12mcg/puff was provided to all.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bouros et al.{Bouros, 1999 #869} 1999 Greece Multicenter (11) Novartis	Intervention: Drug 1: BDP/Form Drug 2: BDP Total daily dose: Drug 1: 500mcg + 24mcg FM Drug 2: 1000mcg Steroid dosing range (Low, medium or high): Drug 1: high Drug 2: high Delivery device: Drug 1: pMDI (spacer with ICS) Drug 2: pMDI (spacer with ICS) Is dosing comparable between treatment groups? NA: ICS versus ICS + LABA	# in group (n): Drug 1: 69 Drug 2: 65 Mean age (years): Drug 1: NR Drug 2: NR Overall: 43 Sex (% female): Drug 1: NR Drug 2: NR Overall: 65 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100	Number (%) withdrawn: Drug 1: 4 (6%) Drug 2: 6 (9%) Adverse events caused withdrawal (%): Drug 1: NR Drug 2: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bouros et al.{Bouros, 1999 #869} 1999 Greece Multicenter (11) Novartis	Intervention: Drug 1: BDP/Form Drug 2: BDP # in group (n): Drug 1: 69 Drug 2: 65	Rescue med use day: Data NR P < 0.001 Rescue med use at night: Data NR P =0.003 Day time symptom control: Data NR P = 0.001 Night time symptom control: Data NR P < 0.001 Other: D1 base: premature discontinuation = D1 end : 4 D2 end: 6 P: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bouros et al.{Bouros, 1999 #869} 1999 Greece Multicenter (11) Novartis	None reported	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4781 Combo	Bosquet et al.{Bosquet, 2007 #4781} 2007 Multinational Multicenter AstraZeneca	Study design: RCT Double-blind Duration: 6 months N=2309 Enrolled: nr/nr/3346 enrolled 2309 randomized ITT Analysis: Yes	Outpatients aged 12 years or more, with persistent asthma, who had been treated with ICS alone (800–1600 mcg/day) or ICS (400–1000 mcg/day) in combination with LABA for at least 3 months prior to study entry, were eligible for inclusion. All eligible patients had a pre-bronchodilator FEV1 X50% of predicted normal value, with X12% reversibility following 1.0 mg terbutaline, and hadexperienced one or more clinically important asthma exacerbations (as judged by the clinician) in the previous 12 months (but none in the month before enrolment). To be eligible for randomization at the end of run-in, patients had to have used as-needed terbutaline on X5 of the previous 7 days, with no more than eight inhalations in any single day. Asthma severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bosquet et al.{Bosquet, 2007 #4781} 2007 Multinational Multicenter AstraZeneca	None reported	Other? (Please list all): recent respiratory infection, use of systemic corticosteroids within 30 days of study entry, use of any b blocking agent (including eye drops) and a smokinghistory of at least 10 pack-years.	Yes- elucidate....: 2 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bosquet et al.{Bosquet, 2007 #4781} 2007 Multinational Multicenter AstraZeneca	Intervention: Drug 1: BUD/FM Drug 2: SM/FP Total daily dose: Drug 1: 320/9 Drug 2: 100/1000 Steroid dosing range (Low, medium or high): Drug 1: Med but rescue med is same Drug 2: High Delivery device: Drug 1: Turbuhaler Drug 2: Diskus Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 1154 Drug 2: 1155 Mean age (years): Drug 1: 40 Drug 2: 39 Sex (% female): Drug 1: 62 Drug 2: 62 Current smokers (%): Drug 1: 4 Drug 2: 5 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 98 (8.5%) Drug 2: 115 (10%) Adverse events caused withdrawal (%): Drug 1: 1% Drug 2: 1.7%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bosquet et al.{Bosquet, 2007 #4781} 2007 Multinational Multicenter AstraZeneca	Intervention: Drug 1 Baseline: BUD/FM Drug 1 Endpoint: BUD/FM Drug 2 Baseline: SM/FP Drug 2 Endpint: SM/FP Number in group (n): Drug 1- baseline: 1144 Drug 1- endpoint: 1144 Drug 2- baseline: 1145 Drug 2- endpoint: 1145	Rescue med use during 24 hour period: Drug 1- baseline: 2.23 Drug 1-endpoint: 0.95 Drug 2-baseline: 2.29 Drug 2-endpoint: 1.01 –0.04 (–0.12 to 0.04); P = 0.36 Asthma exacerbations: Severe, Rate, events/100 patients/year D1 end: 25 D2 end: 31 21 (95% CI1 to 37); P = 0.039 Symptom control during 24 hour period: D1 base: Total symtom score 1.87 D1 end: 0.98 D2 base: 1.89 D2 end: 0.98 P = 0.92 Day time symptom control: D1 - base: Symptom free days 10.7 D1 - end: 47.2 D2 - base: 11.2 D2 - end: 48.1 P = 0.73 Nocturnal awakenings: D1 base: 32.1% D1 end: 12% D2 base: 32.2% D2 end: 13.3% –1.30 (–2.8 to 0.3); P = 0.11 Hospitalizations: Rate, events/100 patients/year D1 end: 9 D2 end: 13 31 (1 to 51); P = 0.046 Other: D1 base: ACQ-5 1.84 D1 end : 1.08 D2 base: 1.89 D2 end: 1.12 P= 0.59 Other: D1 base: Rescue free days, %: 10.3 D1 end : 58.2 D2 base: 9.3 D2 end: 58.4 -0.80 (-3.6 to 1.9); P = 0.56

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bosquet et al.{Bosquet, 2007 #4781} 2007 Multinational Multicenter AstraZeneca	Overall adverse events reported (%): Drug 1: 39 Drug 2: 40 Serious adverse events (%): Drug 1: 3 Drug 2: 3	Adherence - 98% for both according to diary cards	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
732	Bousquet et al.{Bousquet, 2000 #732} 2000 Multinational (17 countries) Multicenter (57 centers) Schering-Plough Research Institute	Study design: RCT Single-blind evaluator-blind Duration: 12 weeks N=730 Enrolled: NR/NR/730 ITT Analysis: Yes	Age: >/= 12 yrs FEV1 expressed as a percent of the predicted value: 60%-90% of predicted normal value after all restricted medications had been withheld for specified intervals. Reversability of FEV1: reversibility of airway disease by an increase in FEV1 of >/=12.0% over the pre-bronchodilator value, with an absolute volume increase of at least 200mL, within 30 min after two inhalations of salbutamol Previous use of corticosteroids: had been using an inhaled glucocorticoid daily for at least 30 days Duration of condition: at least 6 months Other: Prior to screening and through to baseline, patients must have been maintained on a stable regimen of inhaled corticosteroid, including FLUN, TAA, BDP, BUD or FP Asthma Severity: Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bousquet et al.{Bousquet, 2000 #732} 2000 Multinational (17 countries) Multicenter (57 centers) Schering-Plough Research Institute	Short acting inhaled or nebulized beta-agonists (withheld 6 hours before any study visit); theophylline permitted if stable dose prior to screening visit	Pregnant or lactating : treatment with oral corticosteroids for >14 days in the six months prior to screening Concommitant diseases: clinical evidence of significant pulmonary disease other than asthma, a history of glaucoma and/or posterior subcapsular cataracts Current treatment with: treatment with methotrexate, cyclosporine or gold within 3 months, or systemic steroids or another investigational drug in the month prior to screening, daily use of more than 1 mg of nebulized b2-adrenergic agonists (either MDI or inhaled powder, depending on the preference of the study site), use of any long-acting b2-adrenergic agonist less than 2 weeks prior to screening : requiring allergenspecific immunotherapy, unless on a stable maintenance schedule, the need for ventilator support in the past five yrs, hospitalization for asthma in the last three months, use of >12puffs/day-1 of salbutamol on any two consecutive daysbetween screening and baseline visits, treatment for asthma in an emergency room or admission to a hospital for management of airway obstruction, on two or more occasions in th	Yes: run-in period (length NR) during which patients received treatment with their normally prescribed inhaled corticosteroid. At the baseline visit, patients eligible for participation in the study discontinued use of their previous inhaled corticosteroid and were randomly assigned to one of four treatment arms.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bousquet et al.{Bousquet, 2000 #732} 2000 Multinational (17 countries) Multicenter (57 centers) Schering-Plough Research Institute	Intervention: Drug 1: MOM Drug 2: MOM Drug 3: MOM Drug 4: BUD Total daily dose: Drug 1: 200 mcg Drug 2: 400 mcg Drug 3: 800 mcg Drug 4: 800 mcg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: medium Drug 3: high Drug 4: medium Delivery device: Drug 1: DPI Drug 2: DPI Drug 3: DPI Drug 4: DPI Is dosing comparable between treatment groups? Not applicable- not comparable for all arms: low, medium and high dose arms for MOM; medium dose for BUD	# in group (n): Drug 1: 185 Drug 2: 176 Drug 3: 188 Drug 4: 181 Mean age (years): Drug 1: 39 Drug 2: 42 Drug 3: 41 Drug 4: 42 Sex (% female): Drug 1: 57 Drug 2: 54 Drug 3: 60 Drug 4: 57 Optional - Race (% white): Drug 1: 77 Drug 2: 75 Drug 3: 75 Drug 4: 77 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Drug 4: 0 Optional - Disease duration (years): Drug 1: 16 (1-57) Drug 2: 17 (1-64) Drug 3: 15 (1-46) Drug 4: 15 (1-59) Optional - Rescue medication use (puffs per day): Drug 1: 256 mcg/day	Number (%) withdrawn: Drug 1: 15% Drug 2: 10% Drug 3: 18% Drug 4: 14% Overall: 101 (14%) Optional - Withdrew due to lack of efficacy (%): Drug 1: 5% Drug 2: 3% Drug 3: 6% Drug 4: 3% Overall: 33 (5%) Adverse events caused withdrawal (%): Drug 1: 3% Drug 2: <1% Drug 3: 2% Drug 4: 4% Overall: 17 (2%)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bousquet et al.{Bousquet, 2000 #732} 2000 Multinational (17 countries) Multicenter (57 centers) Schering-Plough Research Institute	Intervention: Drug 1 Baseline: MOM 200/400 Drug 1 Endpoint: MOM 200/400 Drug 2 Baseline: MOM 800 Drug 2 Endpoint: MOM 800 Drug 3 Baseline: BUD Drug 3 Endpoint: BUD Number in group (n): Drug 1- baseline: 185/176 Drug 1- endpoint: 185/176 Drug 2- baseline: 188 Drug 2- endpoint: 188 Drug 3- baseline: 181 Drug 3- endpoint: 181	Rescue med use during 24 hour period: Drug 1- baseline: mcg/day: 256/282 Drug 1-endpoint: -45.86/-90.66* Drug 2-baseline: 259 Drug 2-endpoint: -72.13 Drug 3 - baseline: 252 Drug 3- endpoint: -33.90 P values: *<0.05 MF 400 vs. BUD (medium vs medium) Other: D1 base: pt self-report mean score: wheezing am (mean): 0.31/0.47 D1 end : -0.07/-0.17 D2 base: 0.43 D2 end: -0.27 D3 base: 0.35 D3 end: -0.10 P: <0.05 MF 800 vs. BUD (high vs med); NR for med vs med (presumed NS) Other: D1 base: pt self-report mean score: difficulty breating am (mean): 0.46/0.59 D1 end : -0.10/-0.20 D2 base: 0.53 D2 end: -0.24 D3 base: 0.50 D3 end: -0.14 P Other: D1 base: pt self-report mean score: cough am (mean): 0.35/0.45 D1 end : -0.10/-0.16 D2 base: 0.41 D2 end: -0.19 D3 base: 0.30 D3 end: -0.19 P: NR Other Relevant Health Outcome Results: Nocturnal awakenings baseline (n): 0.36/0.33/0.41/0.30

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bousquet et al.{Bousquet, 2000 #732}	Dysphonia (%):	Compliance	Fair
2000	Drug 1: 4.3		Fair
	Drug 2: 2.8		No
Multinational (17 countries)	Drug 3: 4.8		
Multicenter (57 centers)	Drug 4: 2.2		
Schering-Plough Research Institute	Additional adverse events and comments: All treatments were well tolerated, and no unusual or unexpected adverse events were reported. Most events were mild to moderate in severity and none were life threatening. The most common adverse events, reported by >/=10% of patients in any treatment group, included headache, pharyngitis, viral infection, and rhinitis. The incidence of adverse events judged by investigators to be related to treatment was similar for all treatment groups (17-20%). The most common treatment-related adverse events were headache (4-8%), pharyngitis (4-5%), and dysphonia (2-5%). Oral candidiasis was uncommon in this study, reported by only 16 patients overall, and had a similar incidence among the treatment groups (n=4, 6, 4, and 3 in the MF DPI 100, 200, 400, mg BID and BUD Turbuhaler1 400 mg b.i.d groups, respectively). Oral candidiasis was predominantly mild to moderate in		

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
208	Bousquet et al.{Bousquet, 2005 #208} 2005 IMPACT: IMProving Asthma Control Trial Multinational NR	Study design: Observational Database analysis Duration: 52 weeks N=1490 in IMPACT; 893 with AR in this analysis Enrolled: NR ITT Analysis: Not applicable: post hoc analysis	: Aged 15–72 years with chronic asthma for at least 1 year, a baseline FEV1 of 50–90% predicted and an improvement of 12% or more in FEV1 or in morning peak expiratory flow (PEF). Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bousquet et al.{Bousquet, 2005 #208} 2005 IMPACT: IMProving Asthma Control Trial Multinational NR		Other: see IMPACT	Yes: During the first 4-week run-in period, patients received opened inhaled fluticasone 100 mg twice daily. A single placebo of SM or ML was added during the two last weeks of this period.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bousquet et al.{Bousquet, 2005 #208} 2005 IMPACT: IMProving Asthma Control Trial Multinational NR	Intervention: Drug 1: FP plus SM Drug 2: FP plus ML Drug 3: Asthma plus Allergic rhinitis Drug 4: asthma (no AR) Total daily dose: Drug 1: 200mcg plus 100mcg SM Drug 2: 200mcg plus 10mg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Is dosing comparable between treatment groups? NA: long acting beta agoinst versus leukotriene inh.	# in group (n): Drug 1: NR Drug 2: NR Drug 3: 893 Drug 4: 597 Mean age (years): Drug 1: NR Drug 2: NR Drug 3: 39 Drug 4: 44 Sex (% female): Drug 1: NR Drug 2: NR Drug 3: 56 Drug 4: 54 Optional - Race (% white): Drug 1: NR Drug 2: NR Drug 3: 76 Drug 4: 80 Current use of ICS at baseline (%): Drug 1: NR Drug 2: NR Drug 3: 100 Drug 4: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 3: NA Drug 4: NA

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bousquet et al.{Bousquet, 2005 #208} 2005 IMPACT: IMProving Asthma Control Trial Multinational NR	Intervention: Drug 1 Baseline: FP plus SAL for those with asthma + AR Drug 1 Endpoint: FP plus ML for those with asthma + AR Drug 2 Baseline: 95% CI Drug 2 Endpoint: Asthma + AR Drug 3 Baseline: Asthma (no AR) Number in group (n): Drug 1- baseline: NR Drug 1- endpoint: NR - total of 893 Drug 2-endpoint: 893 Drug 3- baseline: 597	Asthma exacerbations: D1 base: Odds ratios for all: 1.006 D1 end: 1 D2 base: CI = 0.73-1.39 D2 end: 21.3% D3 base: 17.3% P: p= 0.046 Courses of steroids: D2 end: 16.6 D3 base: 12.9 P: ns Emergency room visits: D1 base: 1.04 D1 end: 1 D2 base: CI = 0.51-2.11 D2 end: 3.6% D3 base: 1.7% P: p= 0.029 Hospitalizations: D1 base: 2.11 D1 end: 1 D2 base: CI = 0.52-8.5 D2 end: 1 D3 base: 0.5 P: p= NS Other: D1 base: unsheduled visits = 1.01 D1 end : 1 D2 base: CI = 0.67-1.52 D2 end: 11.8 D3 base: 9.6 D3 endP: ns Other: D1 base: specialist visit = 1.4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bousquet et al.{Bousquet, 2005 #208} 2005 IMPACT: IMProving Asthma Control Trial Multinational NR	NR	NR	Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
2384	Boyd G{Boyd, 1995 #2384} 1995 UK Out-patient centers (15) Allen & Hanburys Ltd	Study design: RCT open-label parallel-group study Duration: 26 weeks N=181 ITT Analysis: ?	: at least 18 yrs, with a requirement for at least 1,500 µg daily of inhaled BDP (or equivalent), under consideration for maintenance oral corticosteroid therapy, as judged by their physician, a documented history of at least 15% improvement from baseline in lung function following inhaled salbutamol, and of acute exacerbations of asthma on at least two occasions in the preceding 18 months.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Boyd G{Boyd, 1995 #2384} 1995 UK Out-patient centers (15) Allen & Hanburys Ltd		a concurrent uncontrolled systemic disease, had received treatment for an acute respiratory infection in the last 2 weeks, or were unable to demonstrate at least 40% of their predicted forced expiratory volume in one second (FEV1) at baseline	None

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Boyd G{Boyd, 1995 #2384} 1995 UK Out-patient centers (15) Allen & Hanburys Ltd	Intervention: Drug 1: FM Drug 2: SM Total daily dose: Drug 1: 24µg Drug 2: 100µg Steroid dosing range: Delivery device: Drug 1: Aerolizer Drug 2: Diskus Is dosing comparable between treatment groups?	# in group (n): Drug 1: 256 Drug 2: 260 Mean age (years): Drug 1: 36 ± 16 Drug 2: 36 ± 17 Sex (% female): Drug 1: 62% Drug 2: 52%	Number (%) withdrawn: Drug 1: 14.5 Drug 2: 11.3 Adverse events caused withdrawal (%): Drug 1: 5.7 Drug 2: 3.4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Boyd G{Boyd, 1995 #2384} 1995 UK Out-patient centers (15) Allen & Hanburys Ltd	Intervention: Drug 1: ICS Drug 2: ICS + SM Number in group (n): Drug 1: 256 Drug 2: 260	Symptoms: ICS + SM > ICS + placebo for nighttime symptoms, trend for daytime [Daytime symptom scores, mean (SD): baseline: 0.94 (0.23) vs 0.94 (0.22); during treatment: 0.74 (0.45) vs 0.82 (0.39); change from baseline: -0.21 (0.41) vs -0.12 (0.32), P=0.24; Nighttime symptom scores, mean (SD): baseline: 0.91 (0.28) vs 0.73 (0.44); treatment: 0.45 (0.50) vs 0.58 (0.50); change from baseline: -0.45 (0.49) vs -0.15 (0.48); P=0.002 Proportion of symptom-free days, mean (SD): baseline: 0.08 (0.17) vs 0.07 (0.19); treatment: 0.30 (0.36) vs 0.20 (0.31); change from baseline: 0.22 (0.30) vs 0.13 (0.22); P=0.07; Proportion of symptom-free nights, mean (SD): baseline: 0.20 (0.25) vs 0.29 (0.33); treatment: 0.53 (0.38) vs 0.42 (0.38); change from baseline: 0.33 (0.32) vs 0.13 (0.26), P=0.001] Exacerbations: No difference [# of patients requiring short course of oral steroids: 19 vs 15, P=0.19] Rescue med use: ICS + SM > ICS + placebo [Puffs/24 hours, mean (SD): baseline: 11.3 (6.0) vs 9.7 (4.0); treatment: 6.3 (6.2) vs 7.2 (4.9); change from baseline: -5.1 (4.7) vs -2.5 (4.0), P=0.002]

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Boyd G{Boyd, 1995 #2384} 1995 UK Out-patient centers (15) Allen & Hanburys Ltd	Overall adverse events reported (n): minor Drug 1: 53 Drug 2: 44 Respiratory disorders (%): Drug 1: 73% Drug 2: 73% Headache (%): Drug 1: 27% Drug 2: 31%	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
560	Brabson et al.{Brabson, 2002 #560} 2002 US Multicenter (44) Glaxo Wellcome Inc., RTP, NC	Study design: RCT Double-blind Double-dummy Duration: 6wk N = 440 Number screened: 563/440/440 ITT Analysis: Yes	At least 12 years of age who had asthma were eligible if they had been receiving low-dose ICS (excluding FP and FLUN) for at least 8 weeks and had an FEV1 between 60% to 85% of the predicted values at screening and before randomization. To remain in the study, each patient must have met the following predefined continuation (efficacy) criteria: no more than a 20% decrease in baseline FEV1 and, in each visit week, no more than 3 days during which >12 puffs of rescue albuterol was used, no more than 4 days during which the peak flow was decreased by >/=20% of baseline, and no more than 3 nights with awakenings due to asthma. Patients not meeting these continuation criteria were withdrawn from the study. Patients who experienced an asthma exacerbation (defined as any worsening of asthma symptoms that required a change in the patient's current therapy) that was treated with medication other than albuterol aerosol or nebulized short-acting bronchodilators were also withdrawn from the study. In addition, a patient could be withdrawn from the study at the investigator's discre Asthma Severity: Other: relatively stable persistent

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Brabson et al.{Brabson, 2002 #560} 2002 US Multicenter (44) Glaxo Wellcome Inc., RTP, NC	Albuterol	Other: Patients were excluded if they had used more than an average of 4 puffs of albuterol per day or experienced more than 1 night time awakening due to asthma during the 7 days before randomization. In addition, patients were excluded if they had received any oral or parenteral corticosteroid within 6 weeks, more than 1 burst of oral corticosteroids within 6 months, inhaled FP or FLUN within 4 weeks, or LM within 1 week before screening.	Yes: At enrollment, patients were taking a fixed daily dose of inhaled BDP (168 to 336 mcg) TA (400 to 800 mcg). Eligible patients continued treatment with their ICS during an 8-day run-in period, during which they rated asthma symptoms and recorded the frequency and number of puffs of albuterol used, as well as morning and evening peak expiratory flow each day to establish baseline respiratory status. After the run-in period, all patients who met the study criteria discontinued their previous ICS.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Brabson et al.{Brabson, 2002 #560} 2002 US Multicenter (44) Glaxo Wellcome Inc., RTP, NC	Intervention: Drug 1: zafirlukast Drug 2: FP Total daily dose: Drug 1: 40 mg Drug 2: 176 mcg Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: low Delivery device: Drug 1: tablet Drug 2: MDI Is dosing comparable between treatment groups? NA: ICS vs LTRA	# in group (n): Drug 1: 216 Drug 2: 224 Mean age (years): Drug 1: 35 Drug 2: 36 Sex (% female): Drug 1: 65 Drug 2: 60 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 45 (21) Drug 2: 17 (8) Overall: 62 (14) Optional - Withdrew due to lack of efficacy (%): Drug 1: 13 Drug 2: 2 Adverse events caused withdrawal (%): Drug 1: 2 Drug 2: <1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Brabson et al.{Brabson, 2002 #560} 2002 US Multicenter (44) Glaxo Wellcome Inc., RTP, NC	Intervention: Drug 1 Baseline: zafirlukast Drug 1 Endpoint: zafirlukast Drug 2 Baseline: FP Drug 2 Endpoint: FP Number in group (n): Drug 1- baseline: 216 Drug 1- endpoint: 216 Drug 2- baseline: 224 Drug 2-endpoint: 224	Rescue med use day: Drug 1- baseline: 1.8 (1.5) Drug 1 -endpoint: 0.1 (1.8) Drug 2 - baseline: 2.0 (1.5) Drug 2 - endpoint: -0.6 (1.5) -0.7 (-1.0 to -0.4), P<0.001 Day time symptom control: D1 - base: Symptom free days (%): 34 (+/-36) D1 - end: 8 (36) D2 - base: 30 (33) D2 - end: 22 (39) 14 (7 to 21), P<0.001 Nocturnal awakenings: D1 base: Nights with uninterrupted sleep (%): 96 (7) D1 end: -5 (21) D2 base: 95 (7) D2 end: 0 (16) 5 (2 to 9), P=0.006 Other: D1 base: Asthma symptom score: 0.57 (0.58) D1 end : -0.01 (0.64) D2 base: 0.55 (0.48) D2 end: -0.16 (0.53) D3 baseD3 endP: -0.17 (-0.28 to -0.06), P=0.001 Other: D1 base: Rescue-free days (%): 39 (39) D1 end : 10 (39) D2 base: 33 (37) D2 end: 23 (36) D3 baseD3 endP: 13 (6 to 20), P=0.002 Other Relevant Health Outcome Results: Only 2 patients (1%) treated with FP experienced an asthma exacerbation during the study, compared with 12 patients (6%) treated with zafirlukast (P=0.005). The majority (9 of 12) of exacerbations occurring in zafirlukast-treated patients required

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Brabson et al.{Brabson, 2002 #560} 2002 US Multicenter (44) Glaxo Wellcome Inc., RTP, NC	Overall adverse events reported (%): Drug 1: Treatment related AE: 4 Drug 2: 7 P=0.14 Serious adverse events (%): Drug 1: 0 Drug 2: 0 Headache (%): Drug 1: 2 Drug 2: 2 Other (%): Drug 1: nausea: 0 Drug 2: 1	Compliance For both groups, patient-reported compliance with the metered-dose inhalers and with the capsules was >/=88%.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1036	Bronsky et al.{Bronsky, 1998 #1036} 1998 USA Multicenter Schering Corporation	Study design: RCT Double-blind Double-dummy Duration: 8 weeks N=329 Enrolled: NR/NR/329 ITT Analysis: No another type of analysis was used (define): It's not ITT nor is it straightforwardly a completer's analysis. 329 were ranodmized, baseline characteristics given for 286; 248 completed study. The authors defined an ITT population and an "efficacy population" but do not do their analysis on the ITT population. The efficacy population included all patients randomized who had at least one dose of study drug and, "in general, were compliant with the protocol in terms of receipt of study treatment, avoidance of disallowed concomitant medications, and availability of efficacy measurements at baseline and follow-up."	Age: 18-65 Previous use of corticosteroids : a documented history of asthma beginning at least 2 years prior to enrollment; an FEV1 on day 1 between 50% and 90% of predicted value following an 8-hour beta2-agonist withholding period; airway reversibility within the last 12 months or on day 1, as shown by an increase in FEV1 >/=15% within 20 minutes of adminitration of albuterol; asthma that warranted treatment with ICS and for at least 30 days prior to enrollment, had to have been maintained on recommended doses of an ICS Asthma Severity: Mild Moderate Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Bronsky et al.{Bronsky, 1998 #1036} 1998 USA Multicenter Schering Corporation	Albuterol	Smoking - chronic lung disease other than asthma; recurrent hospital admissions for severe asthma exacerbations or any other clinically significant disease that could interfere with the conduct of the study; presence of a respiratory infection within preceding 30 days; known hypersensitivity to any study medication; abnormal physical exam or ECG	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Bronsky et al.{Bronsky, 1998 #1036} 1998 USA Multicenter Schering Corporation	Intervention: Drug 1: BDP Drug 2: TAA Drug 3: placebo Total daily dose: Drug 1: 336 mcg Drug 2: 800 mcg Drug 3: N/A Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Drug 3: N/A Delivery device: Drug 1: MDI w/o spacer Drug 2: MD Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 102 (110 randomized) Drug 2: 97 (107 randomized) Drug 3: 97 (112 randomized) Mean age (years): Drug 1: 37.4 Drug 2: 38.6 Drug 3: 36.2 Sex (% female): Drug 1: 54.9 Drug 2: 49.5 Drug 3: 54.0 Optional - Race (% white): Drug 1: 91.2 Drug 2: 88.7 Drug 3: 89.7 Optional - Disease duration (years): Drug 1: 20.5 Drug 2: 21.0 Drug 3: 20.2 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 0	Number (%) withdrawn: Drug 1: 16 (14.5%) Drug 2: 18 (16.8%) Drug 3: 47 (42.0%) Optional - Withdrew due to lack of efficacy (%): Drug 1: 0.9% Drug 2: 0.9% Drug 3: 17.0% Adverse events caused withdrawal (%): Drug 1: 2.7% Drug 2: 8.4% Drug 3: 17.9% Optional - Other reasons for withdrawal (%): Drug 1: 12 (10.9%) Drug 2: 8 (7.5%) Drug 3: 8 (9.2%)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Bronsky et al.{Bronsky, 1998 #1036} 1998 USA Multicenter Schering Corporation	Intervention: Drug 1 Baseline: BDP Drug 1 Endpoint: BDP Drug 2 Baseline: TAA Drug 2 Endpint: TAA Drug 3 Baseline: placebo Drug 3 Endpoint: placebo Number in group (n): Drug 1- baseline: 102 (110 randomized) Drug 1- endpoint: 102 Drug 2- baseline: 97 (107 randomized) Drug 2-endpoint: 97 Drug 3- baseline: 87 (112 randomized) Drug 3- endpoint: 87	Total symptom severity score: P=0.028, BDP vs. TA; P<0.001, BDP vs. placebo; P=0.001, TA vs. placebo Night time symptom control: D1 - base: Nighttime awakenings P: Not significantly different between the treatment groups; P NR Other: D1 base: Total asthma symptom score, mean: 3.18 (2.99) D1 end : mean change: -1.37 (2.89) D2 base: 2.71 (2.63) D2 end: -0.58 (2.86) D3 base: 2.77 (2.84) D3 end: 0.83 (2.97) P: P=0.028 BDP vs. TA; P<0.001 TA or BDP vs. placebo Other Relevant Health Outcome Results: Albuterol use reported for baseline and week 8; no statistically significant differences between the groups (mean avg # puffs/d at week 8, 2.86 vs 3.61; p=0.094); symptom score from 0(none) to 3(severe) for 4 symptoms (wheezing, cough, chest tightness, shortness of breath)--symptom severit score was the sum of the 4 scores.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Bronsky et al.{Bronsky, 1998 #1036} 1998 USA Multicenter Schering Corporation	Overall adverse events reported (%): Drug 1: # of patients with all AEs (%): 48.2 Drug 2: 50.9 Drug 3: 59.8 P=0.786 BDP vs. TA; P=0.005 BDP vs. placebo; P=0.225 TA vs. placebo Serious adverse events (%): Drug 1: 0.9 Drug 2: 0.0 Drug 3: 0.9 Oral candidiasis- thrush (%): Drug 1: 0.0 Drug 2: 0.9 Drug 3: 0.0 Dysphonia (%): Drug 1: 0.9 Drug 2: 1.9 Drug 3: 0.0 Cough: Drug 1: 0.9 Drug 2: 0.9 Drug 3: 1.8 Upper respiratory tract infection (%): Drug 1: 2.7 Drug 2: 10.4 Drug 3: NR P=0.027, BDP vs. TA Death (%): Drug 1: 0.0 Drug 2: 0.0 Drug 3: 0.0 Other (%): Drug 1: aggravated asthma: 0 Drug 2: 5.7 Drug 3: 24.1	Compliance Two percent or less of patients in each treatment group were noncompliant. However, this does not include patients who were withdrawn due to noncompliance.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
462	Buhl et al.{Buhl, 2003 #462} 2003 Multinational (9: Argentina, Belgium, Czech Repub, Germany, Mexico, Russia, Spain, Netherlands) Multicenter (56) AstraZeneca	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=523 Enrolled: NR/NR/549 enrolled in run-in/523 randomized ITT? Yes	At least 18 years with asthma (minimum duration 6 months; been using any ICS (irrespective of the specific drug) at a constant daily dose of 400-1000 mg for at least 30 days before entry and still had sub-optimal asthma control; baseline FEV1 of 60-90% of predicted normal and a reversibility from baseline FEV1 of at least 12% at 15 min after inhalation of a short-acting b2-agonist. Asthma Severity: Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Buhl et al.{Buhl, 2003 #462} 2003 Multinational (9: Argentina, Belgium, Czech Repub, Germany, Mexico, Russia, Spain, Netherlands) Multicenter (56) AstraZeneca	Terbuteline	Other: 4weeks before the run-in period, they required treatment with systemic corticosteroids or had a respiratory tract infection; any severe cardiovascular disorders, use of b-blocker therapy or a history of heavy smoking (>=10 pack-years).	Yes- 2-week run-in during which they received BUDTurbuhalers(200 mg) twice daily

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Buhl et al.{Buhl, 2003 #462} 2003 Multinational (9: Argentina, Belgium, Czech Repub, Germany, Mexico, Russia, Spain, Netherlands) Multicenter (56) AstraZeneca	Intervention: Drug 1: BUD/FM QD Drug 2: BUD/FM BID Drug 3: BUD QD Total daily dose: Drug 1: 320/9 (once daily) Drug 2: 320/9 (divided into twice per day) Drug 3: 400 Delivery device: Drug 1: Turbuhaler Drug 2: Turbuhaler Drug 3: Turbuhaler Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 176 Drug 2: 176 Drug 3: 171 Mean age (years): Drug 1: 42.7 Drug 2: 44.8 Drug 3: 45.5 Sex (% female): Drug 1: 62 Drug 2: 64 Drug 3: 60 Optional - Disease duration (years): Drug 1: 12.7 Drug 2: 12.3 Drug 3: 14.5 Optional - Rescue medication use (puffs per day): Drug 1: 1.1 Drug 2: 1.1 Drug 3: 1.2 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 14 (8) Drug 2: 15 (9) Drug 3: 14 (8) Optional - Withdrew due to asthma exacerbations (%): Drug 1: astha deterioration 3 Drug 2: 2 Drug 3: 3 Optional - Other reasons for withdrawal (%): Drug 1: 5 Drug 2: 6 Drug 3: 5

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Buhl et al.{Buhl, 2003 #462} 2003 Multinational (9: Argentina, Belgium, Czech Repub, Germany, Mexico, Russia, Spain, Netherlands) Multicenter (56) AstraZeneca	Intervention: Drug 1 Baseline: BUD/FM qd Drug 1 Endpoint: BUD/FM qd Drug 2 Baseline: BUD/FM BID Drug 2 Endpoint: BUD/FM BID Drug 3 Baseline: BUD QD Drug 3 Endpoint: BUD QD P-values (Define comparison): BUD/FM qd vs. BUD and BUD/FM bid vs BUD Number in group (n): Drug 1- baseline: 176 Drug 1- endpoint: 176 Drug 2- baseline: 176 Drug 2- endpoint: 176 Drug 3- baseline: 171 Drug 3- endpoint: 171	Rescue med use during 24 hour period: Drug 1- baseline: mean Change in inhalations/day Drug 1-endpoint: -0.37 Drug 2-endpoint: -0.45 Drug 3- endpoint: -0.10 P values: P < 0.01 and P< 0.001 Rescue med use day: Drug 1- baseline: mean Reliever use free days (%) Drug 1 -endpoint: 68.6% Drug 2 - endpoint: 70.7 Drug 3 - endpoint: 59.7% P value: P < 0.01 and P< 0.001 Asthma exacerbations: D1 base: % Mild/Severe (and see below) D1 end: 42/8% D2 end: 45/9% D3 end: NR/11% P: NS between groups Symptom control during 24 hour period: D1 base: Asthma control days D1 end: 55.2% D2 end: 53.5% D3 end: 47.6% P: P < 0.05 and P< 0.05 Day time symptom control: D1 - base: Total asthma symptom score (0-6) D1 - end: 0.76 D2 - end: 0.78 D3 - end: 0.9 P: P < 0. 05 and NS Night time symptom control: D1 - base: Nights w/awakenings (%) D1 - end: 9.9 D2 - end: 12.1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Buhl et al.{Buhl, 2003 #462} 2003 Multinational (9: Argentina, Belgium, Czech Repub, Germany, Mexico, Russia, Spain, Netherlands) Multicenter (56) AstraZeneca	Cough (%): Drug 1: Bronchitis 5.1 Drug 2: 2.3 Drug 3: 5.7 Sore throat (%): Drug 1: Pharyngitis 4.0 Drug 2: 1.8 Drug 3: 1.7 Respiratory infection (%): Drug 1: 6.8 Drug 2: 8.2 Drug 3: 8.5 Rhinitis (%): Drug 1: 3.4 Drug 2: 4.1 Drug 3: 3.4 Other (%): Drug 1: Viral infection 3.4 Drug 2: 3.5 Drug 3: 4.0	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
671 3032 414 5106	Busse et al. Finn et al. Lanier et al. 2001, 2003, 2005 + unpublished data (FDA) Multinational Multicenter Novartis Pharmaceuticals Corp. and Genetech Inc.	Study design: RCT 28 wks (16 wks stable ICS dose + 12 wks tapering ICS) Duration: Optional 24 wk DB extension N = 525 Extension N=460	: 12-75; required daily ICS; asthma duration > 1 yr; positive immediate responses on SPT to at least 1 common allergen; txt with 420-840 mcg/day BDP or equivalent ICS for > 3 months Moderate-severe allergic asthma

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Busse et al. Finn et al. Lanier et al. 2001, 2003, 2005 + unpublished data (FDA) Multinational Multicenter Novartis Pharmaceuticals Corp. and Genetech Inc.	Rescue albuterol as needed (max, 8 puffs/day); stables doses of immunotherapy & other nonasthma medication continued at maintenance dose	Prior exposure or sensitivity to OM; acute upper respiratory tract infection within 1 month; < 3 months of stable immunotherapy; elevated IgE levels for reasons other than atopy; regular treatment with β-adrenergic antagonists	Yes- 4-6 weeks to determine stable BDP dose for symptom control

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Busse et al. Finn et al. Lanier et al. 2001, 2003, 2005 + unpublished data (FDA) Multinational Multicenter Novartis Pharmaceuticals Corp. and Genetech Inc.	Drug 1: OM 0.016 mg/kg IgE IU/mL per 4 weeks (150 mg or 300 mg every 4 wks or 225 mg, 300 mg or 375 mg every 2 wks) SQ n=268 Drug 2: Placebo NA n=257	Age: Drug 1: OM 39.3 Drug 2: Placebo 39.0 Sex (% female): Drug 1: OM 61.2 Drug 2: Placebo 56.8 Race (%white): Drug 1: OM 88.8 Drug 2: Placebo 89.1 Current smokers (%) 0 ICS (%): Drug 1: OM 100 Drug 2:Placebo 100	Withdrawals: Drug 1: OM 19 (7.1%) Drug 2: Placebo 34 (13.2%) Withdrawals due to adverse events: Drug 1: OM 2 (0.7%) Drug 2: Placebo 0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Busse et al. Finn et al. Lanier et al. 2001, 2003, 2005 + unpublished data (FDA) Multinational Multicenter Novartis Pharmaceuticals Corp. and Genetech Inc.		• Symptoms: [Median change in total symptom score from baseline to week 16: -1.5 vs. -1.1; P < 0.05; daily asthma scores over 28 weeks: significantly improved with OM: data NR; P < 0.01; median proportion of low symptom days for 28 week period: 0.03 vs. 0.01 (P = 0.04)] • Night symptoms: [Median change from baseline to week 16 in nocturnal asthma score: -0.4 vs. -0.2; P < 0.05] • Exacerbations: [number per patient, weeks 1-16: 0.28 vs. 0.54, P = 0.006; % of subjects experiencing 1 or more: 14.6% vs. 23.3%, P = 0.009; % of subjects with exacerbations during steroid reduction phase, weeks 17-28: 21.3 vs. 32.3, P = 0.004; number per subject, weeks 17-28: 0.39 vs. 0.66, P = 0.003] • Rescue med use: [Significant difference favoring OM in reduction in daily rescue medication use over 28 weeks (data reported in line graph only; P < 0.01)] • QoL: [Mean improvement in overall AQLQ score at week 16: 0.93 vs. 0.66, P < 0.01; mean improvement in overall AQLQ score at week 28: 0.97 vs. 0.7, P < 0.01; proportion of patients achieving a clinically meaningful improvement in overall QoL (i.e., increase in score of > 0.5 points): at 16 weeks, 64.1% vs. 51.7%, P<0.01; at 2 • Missed school: [Mean Number (± SD) of school days missed: 0.49 (± 2.1) vs. 0.59 • Missed work: [Mean (± SD) Number of work days missed: 0.38 (± 1.4) vs. 0.72 (± • ER/Urgent care: [Mean unscheduled medical contacts (± SD): 0.26 (0.65) vs. 0.2 • Hospitalization: [Exacerbations requiring hospitalization 1 (<1%) vs. 2 (<1%), P = EXTENSION PHASE: • Exacerbations: [Exacerbations per patient: 0.60 vs. 0.83, P = 0.023] • QOL: [improvement in mean overall AQLQ score: 1.19 vs. 0.91, P < 0.01; % of pa • Missed school: [Mean number (± SD) of school days missed: 0.40 (± 2.1) vs. 0.53

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Busse et al. Finn et al. Lanier et al. 2001, 2003, 2005 + unpublished data (FDA) Multinational Multicenter Novartis Pharmaceuticals Corp. and Genetech Inc.	Overall OM 89.2 Placebo 89.1 Severe OM 2.6 Placebo: 2.3 Urticari OM 1.5 Placebo 3.1 Injection site reaction: OM 8.6 Placebo 6.5 EXTENSION PHASE Overall OM 82.9 Placebo 82.5	NR	Fair

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
673	Busse et al.{Busse, 2001 #673} 2001 Multicenter, United States 50% primary care Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 12wk N = 338 Number screened: NR,NR,NR ITT Analysis: Unable to determine: Likely not, 9 patients from one site were excluded because of significant deviations from good clinical practice standards.	12 years and older with asthma who used a short-acting beta agoinst either scheduled or as needed for at least 6 weeks preceding the study, FEV1 between 50 and 80% of predicted and reversibility of FEV 1 >/= 12%. Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Busse et al.{Busse, 2001 #673} 2001 Multicenter, United States 50% primary care Glaxo Wellcome	Albuterol as needed for symptom relief or oral or parenteral corticosteroids for asthma exacerbations for >14 consecutive days.	Other: Life-threatening ashtma, significant and uncontrolled disease, diabetes, CAD, used tobacco products within the preceding year or had a smoking history of more than 10 pack years. If they received any systemic corticosteroids within 6 months of screening, any inhaled corticosteroid within 1 month of screening, or an LTRA within 1 week of screening.	Yes: 8 to 14 day run in to establish baseline respiratory function.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Busse et al.{Busse, 2001 #673} 2001 Multicenter, United States 50% primary care Glaxo Wellcome	Intervention: Drug 1: FP Drug 2: Zafirlukast Drug 3: Placebo Total daily dose: Drug 1: 176mcg Drug 2: 40mg Drug 3: NA Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: NA Drug 3: NA Delivery device: Drug 1: MDI Drug 2: tablet Drug 3: MDI/tablet Is dosing comparable between treatment groups? NA: ICS versus LTRA	# in group (n): Drug 1: 113 Drug 2: 111 Drug 3: 114 Mean age (years): Drug 1: NR Drug 2: NR Drug 3: NR Sex (% female): Drug 1: NR Drug 2: NR Drug 3: NR Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Optional - Previous ICS use (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Groups similar at baseline? Not reported	Number (%) withdrawn: Drug 1: NR (between 14-19% for all groups) Drug 2: NR Adverse events caused withdrawal (%): Drug 1: #2 Drug 2: #1 Drug 3: #1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Busse et al.{Busse, 2001 #673} 2001 Multicenter, United States 50% primary care Glaxo Wellcome	Intervention: Drug 1: FP Drug 2: Zafirlukast Drug 3: Placebo Number in group (n): Drug 1: 113 Drug 2: 111 Drug 3: 114	Rescue med use during 24 hour period: Drug 1 : mean baseline: 4.8 (0.3); mean change from baseline = -2.8 (0.27) Drug 2: 4.7 (0.3); -1.9 (0.27) Drug 3: 5.1 (0.3); -1.3 (0.23) P<0.05 for FP versus Zafirlukast and placebo, p<0.05 for zafirlukast versus placebo Asthma exacerbations: D1: 4% D2: 12% D3: 10% P: NS, NR Symptom control during 24 hour period: D1: symptom score change from baseline = -0.65 D2: -0.36 D3: -0.43 P<0.05 for FP versus Zafirlukast and placebo, others NS/NR Missed days of work: D1 : mean number of days that patients attended work or school with asthma symptoms = 1.8 D2: 3.8 D3: 4.4 P: P</= 0.03 for zafirulast and palcebo versus FP Nocturnal awakenings: D1: number per night, mean change from baseline = -0.32 D2: -0.23 D3: -0.17 P<0.05 for FP versus Zafirlukast and placebo, p<0.05, others NS/NR AQLQ - overall: D1: mean change from baseline = 0.6 D2: 0.3 D3: NR D2 endD3 baseD3 endP: p< 0.001 for FP vs placebo; p</= 0.033 for FP vs zafirlukast, NS/NR for zafirulakast vs placebo

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Busse et al.{Busse, 2001 #673} 2001 Multicenter, United States 50% primary care Glaxo Wellcome	Overall adverse events reported (%): Drug 1: NR Drug 2: NR Drug 3: NR Oral candidiasis- thrush (%): Drug 1: #3 Drug 2: #0 Drug 3: #2 Sore throat (%): Drug 1: throat irritation = 4 Drug 2: 3 Drug 3: 3 Headache (%): Drug 1: 3 Drug 2: 2 Drug 3: 2 Other (%): Drug 1: sinusitis = 12 Drug 2: 4 Drug 3: 4 Other (%): Drug 1: chest congestion = <1 Drug 2: 5 Drug 3: 0	Compliance Median compliance was 93% in each group for both inhaled and oral study medications.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
715	Busse et al.{Busse, 2001 #715} 2001 USA Multicenter - 52 sites Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 24wk N = 533 Number screened: 1428/NR/533 ITT Analysis: Yes	Age: >/= 15 yrs FEV 1 expressed as a percent of the predicted value: 50% to 80% Reversability of FEV1: 15% or more after inhalation of 2 puffs (180 mg) of albuterol at screening. Duration of condition: >/= 6 months Other: patients must have used an inhaled or oral short-acting B2-agonist on a regular or as-needed basis during the 3 months before screening. At randomization, patients were required to demonstrate that additional asthma therapy was warranted using the following criteria: an unmedicated FEV1 value of 50% to 80% of predicted normal that was within 15% of the FEV1 value obtained at screening, use of albuterol on 6 or more of the 7 days before randomization, and an asthma symptom score of 2 or more (on a scale of 0-5) on 4 or more of the 7 days before randomization. Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Busse et al.{Busse, 2001 #715} 2001 USA Multicenter - 52 sites Glaxo Wellcome	Albuterol as needed. Concurrent use of asthma meds was not allowed during the study. Use of meds for treatment of rhinitis was allowed	Pregnant or lactating Prior treatment: ICS use within 2 months of screening Smoking - current or former: use of tobacco products within previous year or a smoking history of 10 pack-years or more Other: hospitalization for asthma within 3 months of screening, respiratory tract infections within 4 weeks of screening, and hypersensitivity to any â2-agonist, sympathomimetic drug, leukotriene antagonist, or corticosteroid.	Yes: 8-14 day run-in to confirm eligibility and to obtain baseline data; all patients used albuterol as needed to relieve asthma symptoms during run-in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Busse et al.{Busse, 2001 #715} 2001 USA Multicenter - 52 sites Glaxo Wellcome	Intervention: Drug 1: FP Drug 2: ML Total daily dose: Drug 1: 176mcg Drug 2: 10 mg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: NA Delivery device: Drug 1: MDI (+ placebo capsule) Drug 2: capsule (+ placebo MDI)	# in group (n): Drug 1: 271 Drug 2: 262 Mean age (years): Drug 1: 35.4 Drug 2: 34.4 Sex (% female): Drug 1: 53% Drug 2: 58% Optional - Race (% white): Drug 1: 84% Drug 2: 82% Current smokers (%): Drug 1: 0 Drug 2: 0 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 77 (28%) Drug 2: 75 (29%) Optional - Withdrew due to lack of efficacy (%): Drug 1: 2% Drug 2: 4% Optional - Withdrew due to asthma exacerbations (%): Drug 1: 4% Drug 2: 6% Adverse events caused withdrawal (%): Drug 1: 4% Drug 2: 2% Optional - Lost to follow-up (%): Drug 1: 6% Drug 2: 5% Optional - Protocol violation (%): Drug 1: 3% Drug 2: 3% Optional - Consent withdrawn (%): Drug 1: 4% Drug 2: 4% Optional - Other reasons for withdrawal (%): Drug 1: 6% Drug 2: 4%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Busse et al.{Busse, 2001 #715} 2001 USA Multicenter - 52 sites Glaxo Wellcome	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: ML Drug 2 Endpoint: ML Number in group (n): Drug 1- baseline: 271 Drug 1- endpoint: 271 Drug 2- baseline: 262 Drug 2- endpoint: 262	Rescue med use day: Drug 1- baseline: 5.07 (0.17) Drug 1 -endpoint: -3.10 (0.17) Drug 2 - baseline: 5.29 (0.16) Drug 2 - endpoint: -2.31 (0.17) P value: <0.001 Symptom control during 24 hour period: D1 base: % of days symptom free D1 end: 32% D2 end: 18.4% P < 0.001 Asthma exacerbations: D1 end: 4% D2 end: 8% P: NS (NR) Nocturnal awakenings: D1 base: subset analysis only AQLQ - overall: D1 base: See below, box #86 Other: D1 base: % rescue-free days: 2.5 (0.4) D1 end : 45.9 (2.5) D2 base: 2.5 (0.1) D2 end: 31.2 (2.3) P: <0.001 Other: D1 base: Mean symptom score: 1.65 (0.05) D1 end : -0.85 (0.06) D2 base: 1.69 (0.05) D2 end: -0.60 (0.06) P: <0.001 Other:

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Busse et al.{Busse, 2001 #715} 2001 USA Multicenter - 52 sites Glaxo Wellcome	Overall adverse events reported (%): Drug 1: 71% Drug 2: 68% Serious adverse events (%): Drug 1: 2.2% Drug 2: 0.76% Oral candidiasis- thrush (%): Drug 1: 1% Drug 2: 0 Sore throat (%): Drug 1: 2% Drug 2: 2% Headache (%): Drug 1: 3% Drug 2: 1% Hoarseness (%): Drug 1: 2% Drug 2: 0 Additional adverse events and comments: One death (ML group) attributed to myocardial infarction, occurred in this study. Asthma exacerbations were experienced by 12 (4%) and 21 (8%) patients in the FP and ML treatment groups, respectively. The difference between treatment groups was not statistically significant.	Compliance Mean values for patient-reported compliance with the MDI and capsules were 91.4% or more.	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4748	Busse et al.{Busse, 2003 #4748} 2003 USA Multicenter GlaxoSmithKline	Study design: RCT Double-blind Duration: 12 weeks (plus 12 more) N=558 Enrolled: NR/760/558 ITT? Yes	Male and female patients aged 12 years and older; asthma for at least 6 months and been treated with a medium dose of ICS on a scheduled basis for at least 30 days before screening, such a dose being defined as any one of the following: BDP, 504-840 µg/day; BUD, 400-800 µg/day; FP, 440-660 µg/day; FLUN, 1000-1500 ìg/day; TAA, 1200-1600 µg/day. At the screening visit, required to have an FEV1 between 65% and 95% of predicted normal and an increase in FEV1 of at least12% within 30 minutes of inhaling 2 to 4 puffs of albuterol. Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Busse et al.{Busse, 2003 #4748} 2003 USA Multicenter GlaxoSmithKline		Other: pregnancy and/or lactation; life-threatening asthma; asthma hospitalization within 3 months of screening; a change in asthma regimen 30 days before screening; significant concurrent diseases, including a recent upper or lower respiratory tract infection. Medications prohibited throughout the study included oral or parenteral corticosteroids, theophylline or other bronchodilators, anticholinergics, LM, cromolyn, nedocromil, SM, and FM. Patients had not used oral or parenteral corticosteroids for at least 30 day	Yes- There were 3 run-in periods; During run-in period 1, patients received FP 220 ìg bid or the equivalent for 10 to 14 days. Controlled patients moved to run-in period 2 (5-28 days), which assessed asthma stability on FP 100 ìg bid administered via Diskus. Only patients who became unstable on FP 100 ìg bid were eligible to enter run-in period 3 (26-30 days), during which they were placed on FP 250 ìg bid and those regaining asthma control were eligible for randomization

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Busse et al.{Busse, 2003 #4748} 2003 USA Multicenter GlaxoSmithKline	Intervention: Drug 1: FP/SM Drug 2: FP Total daily dose: Drug 1: 200/100 Drug 2: 500 Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: medium Delivery device: Drug 1: Diskus Drug 2: Diskus Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 281 Drug 2: 277 Mean age (years): Drug 1: 38 Drug 2: 39 Sex (% female): Drug 1: 59 Drug 2: 57 Current smokers (%): Drug 1: NR Drug 2: NR Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 46(16) Drug 2: 54(19) Overall: 100 (18%) Adverse events caused withdrawal (%): Drug 1: <1% Drug 2: 1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Busse et al.{Busse, 2003 #4748} 2003 USA Multicenter GlaxoSmithKline	Intervention: Drug 1 Baseline: FP/Sal Drug 1 Endpoint: FP/Sal Drug 2 Baseline: FP Drug 2 Endpoint: FP Number in group (n): Drug 1- baseline: 281 Drug 2- baseline: 277	Rescue med use during 24 hour period:(SEM) Drug 1- baseline: mean puffs/24h of albuterol: 0.83 Drug 1-endpoint: mean change from baseline to 24 weeks: -0.43 (0.11) Drug 2-baseline: 0.92 Drug 2-endpoint: -0.21 (0.07) P values: P = 0.022 Rescue med use day: Drug 1- baseline: mean Percent rescue free days: 64.9 Drug 1 -endpoint: mean change from baseline to 24 weeks: 14.9 (3.2) Drug 2 - baseline: 62.1 Drug 2 - endpoint: 8.3 (2.7) P value: P = 0.032 Day time symptom control: D1 - base: mean Percent symptom free days: 44.5 D1 - end: mean change from baseline 11.6 (3.0) D2 - base: 43.0 D2 - end: 6.2 (2.9) P = 0.078 Nocturnal awakenings: D1 base: mean: 0.49 D1 end: mean change from baseline: -0.37 (0.05) D2 base: 0.49 D2 end: -0.43 (0.09) : P = 1.00 Asthma Control Score: D1 base: mean Daily Asthma symptom score: 1.0 D1 end: mean change from baseline: -0.22 (0.06) D2 base: 1.06 D2 end: -0.14 (0.06) : P =0.137

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Busse et al.{Busse, 2003 #4748} 2003 USA Multicenter GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 50% over first 12 weeks Drug 2: 56 Additional adverse events and comments: Of the 266 patients who continued for an additional 12 weeks, 44% of the FP100/SM-treated patients and 47% of the FP250-treated patients reported 1 or more adverse events. Upper respiratory tract infection was the most frequently reported adverse event. Drug-related adverse events occurred in 4% and 5% of patients treated with FP100/SM and FP250, respectively, during weeks 1 through 12 of double-blind treatment and in <1% and 3% of patients treated with FP100/SM and FP250, respectively, during weeks 13 through 24. In the subset of patients in which cortisol data were available at baseline and at Week 52 (n = 194), the geometric mean of the cortisol/creatinine ratio (nmol/mmol) at these time points was 3.74 versus 3.04 for SM/FP (n = 102) and 3.92 versus 2.85 for FP (n = 92). No statistical differences between treatments at Week 52 were observed (p = 0.318; 95% CI, 0.92, 1.31). For patients who received the highest dose of corticosteroid (500 µg twice a day), the geometric	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
659	Calhoun et al.{Calhoun, 2001 #659} 2001 USA Multicenter Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 12wk N = 423 Number screened: 1217 screened, 423 randomised ITT Analysis: Yes	: Male and female patients aged 15 yr and older, with asthma for at least 6 months and had been treated with an oral or inhaled short-acting B2-agonist on a scheduled or as-needed basis for at least 6 wk before screening. At the screening visit, all patients were required to have an FEV1 between 50 and 80% of the predicted normal value and an increase in FEV1 of at least 12% within 30 min of the inhalation of two puffs (180 mcg) of albuterol. Asthma Severity: Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Calhoun et al.{Calhoun, 2001 #659} 2001 USA Multicenter Glaxo Wellcome		Other: NR	Yes: Eligible patients entered an 8 to 14-d screening period. Before this period, all oral and inhaled short-acting B2 -agonists were replaced with inhaled albuterol. Baseline information related to asthma control was obtained duringthe screening period. Patients were considered symptomatic and, thus, eligible for randomization, if they required rescue albuterol on five or more days during the 7 d preceding randomization or if they had a diary card symptom score of >/=2 on three or more days for chest tightness, wheezing, or shortness of breath.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Calhoun et al.{Calhoun, 2001 #659} 2001 USA Multicenter Glaxo Wellcome	Intervention: Drug 1: FP/SM Drug 2: ML Total daily dose: Drug 1: 200mcg Drug 2: 10mg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: NA Delivery device: Drug 1: Diskus DPI Drug 2: tablet Is dosing comparable between treatment groups? NA: ICS versus LTRA	# in group (n): Drug 1: 211 Drug 2: 212 Mean age (years): Drug 1: 37 Drug 2: 36 Sex (% female): Drug 1: 50 Drug 2: 49 Optional - Race (% white): Drug 1: 81 Drug 2: 76 Current smokers (%): Drug 1: NR Drug 2: NR Current use of ICS at baseline (%): Drug 1: NR Drug 2: NR Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 26 (12) Drug 2: 38 (18) Adverse events caused withdrawal (%): Drug 1: 3 Drug 2: 4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Calhoun et al.{Calhoun, 2001 #659} 2001 USA Multicenter Glaxo Wellcome	Intervention: Drug 1 Baseline: FP/SM Drug 1 Endpoint: FP/SM Drug 2 Baseline: ML Drug 2 Endpoint: ML Number in group (n): Drug 1- baseline: 211 Drug 1- endpoint: 211 Drug 2- baseline: 213 Drug 2-endpoint: 213	Rescue med use during 24 hour period: Drug 1- baseline: 4.8 Drug 1-endpoint: -3.3 Drug 2-baseline: 1.8 Drug 2-endpoint: -1.9 P </= 0.001 for FP/Sal versus ML at endpoint Rescue med use day: Drug 1- baseline: % rescue free days = 5.9 Drug 1 -endpoint: 53 Drug 2 - baseline: 6.8 Drug 2 - endpoint: 26.2 P </= 0.001 for FP/Sal versus ML at endpoint Asthma exacerbations: D1 end: 0 (0%) D2 end: 11 (5%) P < 0.001 for FP/Sal versus ML at endpoint Symptom control during 24 hour period: D1 base: Combined symptom score = 1.6 D1 end: -1 D2 base: 1.6 D2 end: -0.6 P </= 0.001 for FP/Sal versus ML at endpoint Day time symptom control: D1 - base: % symptom free days = 3.9 D1 - end: 48.9 D2 - base: 5.8 D2 - end: 21.7 P </= 0.001 for FP/Sal versus ML at endpoint Night time symptom control: D1 - base: % nights with no awakenings = 66.7 ; % nights with no awakenings in patients with >/= 2 awakenings/week at baseline = 32.1 D1 - end: 23; 49.2 D2 - base: 62.4 ; 33.9 D2 - end: 15.5 ; 31.4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Calhoun et al.{Calhoun, 2001 #659} 2001 USA Multicenter Glaxo Wellcome	Overall adverse events reported (%): Drug 1: 61 Drug 2: 62 Serious adverse events (%): Drug 1: 0 Drug 2: 0.5 Headache (%): Drug 1: 2 Drug 2: 2 Hoarseness (%): Drug 1: 2 Drug 2: 0	Compliance Compliance with the Diskus device and with the oral capsules was similar between treatment groups and was approximatley 98% with the Diskus and 99% with the capsules.	Fair: Minimal methods reported Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
2259	Campbell et al.{Campbell, 1999 #2259} 1999 United Kingdom and Ireland 110 General practice and 2 hospitals Astra Pharmaceuticals	Study design: RCT Double-blind Duration: 8 weeks N=469 Enrolled: 600 eligible/ 469 enrolled ITT Analysis: No another type of analysis was used (define): APT, all patients treated	: documented diagnosis of asthma and have been receiving at least 200 µg day inhaled steroid at a constant dose for at least the 4 weeks prior to entering the study. In addition the patients must have been using a short-acting b-agonist as required and in the opinion of the investigator have a requirement for the addition of a long-acting beta agonist. Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Campbell et al.{Campbell, 1999 #2259} 1999 United Kingdom and Ireland 110 General practice and 2 hospitals Astra Pharmaceuticals		Other: significant disease past or present or clinically relevant laboratoryresult which, in the opinion of the investigator, would interfere with the study. Those with documented or suspected diagnosis of irreversible chronic airways obstruction as judged by the investigator	Yes: 7 to 14 days to establine baseline characteristics

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Campbell et al.{Campbell, 1999 #2259} 1999 United Kingdom and Ireland 110 General practice and 2 hospitals Astra Pharmaceuticals	Intervention: Drug 1: Eformeterol Drug 2: SM Drug 3: SM Total daily dose: Drug 1: 24 µg Drug 2: 100 µg Drug 3: 100 µg Delivery device: Drug 1: Turbohaler Drug 2: Accuhaler Drug 3: pMDI Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 230 Drug 2: 119 Drug 3: 111 Mean age (years): Drug 1: 40.3 Drug 2: 40.4 Drug 3: 39.9 Sex (% female): Drug 1: 63 Drug 2: 55 Drug 3: 57 Current smokers (%): Drug 1: 24 Drug 2: 20 Drug 3: 23 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 34 (15) Drug 2: 17 (14) Drug 3: 19 (17)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Campbell et al.{Campbell, 1999 #2259} 1999 United Kingdom and Ireland 110 General practice and 2 hospitals Astra Pharmaceuticals	Intervention: Drug 1: Eformetrol Drug 2: SM Accuhaler Drug 3: SM pMDI Number in group (n): Drug 1- endpoint: 240 Drug 2- endpoint: 119 Drug 3- endpoint: 111	Symptom control during 24 hour period: D1 base: % of days symptom free and no rescue med use: D1 end: 32.8% D2 end: 24.1% D3 end: 28.0 P: P = NS Day time symptom control: D1 - base: only reported at 4 weeks Exacerbations: No difference [mean (SD) number of episodes of worsening of asthma per patient: 0.12 (0.35) vs. 0.13 (0.36) vs. 0.12 (0.32), P=0.9144 for eFM vs. SM DPI, P=0.9041 for eFM vs. SM MDI; % of patients with worsening asthma: 11 vs. 12 vs. 12; P=NR; number of episodes of worsening asthma resulting in short course of oral or nebulised steroids: 13 vs. 5 vs. 11; P=NR] Courses of steroids: D1 base: number and % with short courses of oral or nebulized steroids: D1 end: 13 (46%) D2 end: 5 (33%) D3 end: 11 (85%) P: NR Hospitalizations: D1 base: hospital admission or visit to A & E: D1 end: 1 (4%) D2 end: 1 (7%) D3 end: 2 (15%) Other Relevant Health Outcome Results: Number (%) of patients with worsening of asthma: 26 (11%) vs 14 (12%) vs 13 (12%); Patients in all the treatment groups gained an additional l-l.5 nights undisturbed by asthma per week, observed in both the analyses after 4 and 8 week

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Campbell et al.{Campbell, 1999 #2259} 1999 United Kingdom and Ireland 110 General practice and 2 hospitals Astra Pharmaceuticals	Overall adverse events reported (n): Drug 1: 526 Drug 2: 266 Drug 3: 257 Cough (%): Drug 1: 2% Drug 2: 4% Drug 3: 5% Headache (%): Drug 1: 8% Drug 2: 5% Drug 3: 6% Respiratory infection (%): Drug 1: 17% Drug 2: 17% Drug 3: 19% Pharyngitis: Drug 1: 5% Drug 2: 3% Drug 3: 8% Asthma aggravated: Drug 1: 28% Drug 2: 33% Drug 3: 25%	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
262	Ceylan et al.{Ceylan, 2004 #262} 2004 Turkey University clinic NR	Study design: RCT :not specified only says randomly assigned Duration: 2 months N = 48 Number screened: NR, NR, 48 ITT Analysis: Yes	: Moderately persistent asthma who presented to the Clinic for Chest Diseases of the Harran University Faculty of Medicine. Patients were diagnosed with asthma according to the diagnostic criteria of the international asthma consensus report. The patients who were included in the study had had persistent asthma symptoms for at least 1 year, had used ICS for at least 6 months, were 15–60 years of age and did not smoke. Asthma Severity: Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Ceylan et al.{Ceylan, 2004 #262} 2004 Turkey University clinic NR	short-acting ß2 agonist (salbutamol 100 Ìg/puff) for symptomatic treatment	Smoking - current or former: only nonsmokers enrolled Other?: Pregnant or lactating women, patients with life-threatening asthma, patients hospitalized due to asthma within the previous 3 months and patients with accompanying upper or lower respiratory infections were not included in the study. Oral or parenteral corticosteroid treatment, theophylline, anticholinergics, oral ß2 agonists, all types of antihistamines, drugs which contain sodium cromoglycate or nedocromil sodium, and drugs that can make study complex were prohibited.	Yes: 200 mcg of BUD twice a day was given to all patients for 4 weeks (training period) at the beginning of the study.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Ceylan et al.{Ceylan, 2004 #262} 2004 Turkey University clinic NR	Intervention: Drug 1: BUD/FM Drug 2: BUD/ML Total daily dose: Drug 1: 400mcg / 18mcg Drug 2: 400mcg / 10mg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Delivery device: Drug 1: DPI Drug 2: DPI	# in group (n): Drug 1: NR (20 completed) Drug 2: NR (20 completed) Mean age (years): Drug 1: 39.1 Drug 2: 33.2 Sex (% female): Drug 1: 50% Drug 2: 55% Current smokers (%): Drug 1: 0 Drug 2: 0 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Other: Drug 1: history of allergic rhinitis = 12 Drug 2: 14 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: NR Drug 2: NR Overall: Total 8 = (17%) Optional - Lost to follow-up (%): Drug 1: NR Drug 2: NR Overall: 2 (4%) Optional - Other reasons for withdrawal (%): Drug 1: NR Drug 2: NR Overall: acute exacerbation or use of other drugs = 6 (13%)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Ceylan et al.{Ceylan, 2004 #262} 2004 Turkey University clinic NR	Intervention: Drug 1 Baseline: BUD/ FM Drug 1 Endpoint: BUD/ FM Drug 2 Baseline: BUD/ ML Drug 2 Endpoint: BUD/ ML Number in group (n): Drug 1- baseline: NR Drug 1- endpoint: 20 Drug 2- baseline: NR Drug 2- endpoint: 20	Rescue med use during 24 hour period: Drug 1- baseline: puffs per day = 2.4 Drug 1-endpoint: puffs/day after treatment: 0.5; change from baselin: 1.9 Drug 2-baseline: 2.4 Drug 2-endpoint: 1.9/0.5 P < 0.0001; p<0.0001 Day time symptom control: D1 - base: morning symptom scores = 3.1 D1 - end: after treatment/change from baseline: 0.5/2.6 D2 - base: 3.2 D2 - end: 2.4/0.8 P < 0.0001; p <0.0001 Other Relevant Health Outcome Results: The percentage of asymptomatic days during 8 weeks was significantly higher in the FB group than in the MB group (P < 0.0001). The number of days on which the patients did not use salbutamol was statistically lower in the FB group than in the MB group at all measurement times (P <0.0001).

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Ceylan et al.{Ceylan, 2004 #262} 2004 Turkey University clinic NR	Oral candidiasis- thrush (%): D1: #1 D2: #1 Dysphonia D1: #2 D2: #1 Sore throat D1: #2 D2: #1 Headache: D1: #1 D2: #1	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
609	Chuchalin al.{Chuchalin 2002 #609} 2002 EPOCH Study Group Russia Research Institute - Pulmonology Astra Zeneca NR (?)	Study design: RCT Double-blind Other: 3rd group was open control group of non-ICS treatment (thoephylline, cromolyn, etc) Duration: 12 weeks N=338 Enrolled: 338 randomised for run-in; after run in 333 met inclusion and exclusion and continued treatment. ITT Analysis: Yes	: Adults with mild to moderate asthma, diagnosed at least six months before the study. Baseline FEV1 was between 50 to 85% of predicted and they demonstrated >/= 15% reversibility. Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Chuchalin al.{Chuchalin 2002 #609} 2002 EPOCH Study Group Russia Research Institute - Pulmonology Astra Zeneca NR (?)	Concomitant antihistamines (oral, nasal, or ocular), immunotherapy, and nasal glucocorticoids were allowed if dosage remained constant throughout study. Terbutaline as needed for rescue. Mucolytics and expectorants not containing bronchodilators and nasal, oral or ocular formulations of sodium cromoglycate or nedocromil sodium as needed.	Other: Smoking history of >/= 10 pack years or if they were current or recent users of inhaled, oral, or IV corticosteroids, oral LTRA, nedocromil sodium, sodium cromoglycate, beta-blockers (including eye drops). Females must be postmenopausal, surgically sterile, or using medically approved contraceptive measures. Previous asthma meds had to be withdrawn at the following minimum times before first clinic visit: LABA 72 hours, xanthines 36 hours, inhaled anticholinergics 8 hours, short-course oral or IV corticosteroids 30 days, regular inhaled or oral steroids 3 months, depot IV steroids 2 months, LTRA, inhaled nedocromil sodium, or inhaled sodium cromoglycate 30 days.	Yes: 2 week period in which terbutaline was used as needed and patients were randomised to FM plus BUD, BUD, or non ICS treatement.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Chuchalin al.{Chuchalin 2002 #609} 2002 EPOCH Study Group Russia Research Institute - Pulmonology Astra Zeneca NR (?)	Intervention: Drug 1: FM / BUD Drug 2: BUD Total daily dose: Drug 1: 400mcg Drug 2: 400mcg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Delivery device: Drug 1: Turbuhaler / Turbuhaler (separate inhalers) Drug 2: Turbuhaler Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 111 Drug 2: 114 Overall: 225 (plus 108 for non-ICS group) Mean age (years): Drug 1: 44 Drug 2: 47 Sex (% female): Drug 1: 78 Drug 2: 72 Current smokers (%): Drug 1: NS - # NR Drug 2: NS - # NR Optional - Previous ICS use (%): Drug 1: NR, but very low Drug 2: NR, but very low Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: NR Drug 2: NR Overall: 17 (5%) (including non-ICS group) Adverse events caused withdrawal (%): Drug 1: 1 Drug 2: 1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Chuchalin al.{Chuchalin 2002 #609} 2002 EPOCH Study Group Russia Research Institute - Pulmonology Astra Zeneca NR (?)	Intervention: Drug 1: FM/BUD Drug 2: BUD Number in group (n): Drug 1: 111 Drug 2: 114	Rescue med use during 24 hour period: Drug 1: mean improvement in times per day using: 2.51 Drug 2: 1.64 P values: p = 0.0001 AQLQ - overall: data shown in figure P: all form/BUD versus BUD were NS (NR), except form/BUD was greater in the emotional domain than BUD. General QOL instrument: SF-36: data NR, shown in figures P: NS differences between BUD/FM or BUD for SF-36 overall or increases in individual domain scores except BUB/FM greater for the physical domain. Other: D1 : symptom score reduction from baseline: cough 0.57 (+/-0.10); wheeze when resting 0.59 (+/-0.11); wheeze on activity 0.72 (+/-0.12); sleep disturbance 0.56 (+/-0.11); problems with normal daily activities 0.57 (+/-0.12) D2 : symptom score reduction from baseline: cough 0.52 (+/-0.14); wheeze when resting 0.46 (+/- 0.11); wheeze on activity 0.58 (+/- 0.13); sleep disturbance 0.41 (+/- 0.11); problems with normal daily activities 0.39 (+/-0.12) P: all "greater" for FM/BUD versus BUD; P = NR Other Relevant Health Outcome Results: Reported as part of their AEs: aggravation or exacerbation of asthma = n=1 for BUD/FM vs 4 for BUD; P = NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Chuchalin al.{Chuchalin 2002 #609} 2002 EPOCH Study Group Russia Research Institute - Pulmonology Astra Zeneca NR (?)	Overall adverse events reported (%): Drug 1: 36.0 Drug 2: 35.1 Serious adverse events (%): Drug 1: 0 Drug 2: 2 Respiratory infection (%): Drug 1: respiratory system disorder = 7 Drug 2: 11 Other (%): Drug 1: aggravation or exacerbation of asthma = 1 Drug 2: 4 Other (%): Drug 1: common cold = ~ 40% Drug 2: ~ 40% Other (%): Drug 1: tremor = 10 Drug 2: 2	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1078	Condemi et al.{Condemi , 1997 #1078} 1997 USA Multicenter (24 outpatient centers) Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 24 weeks N=291 Enrolled: 378/291/291 ITT Analysis: Yes	Age: >/= 12 FEV1 expressed as a percent of the predicted value: 50-80% predicted Reversability of FEV1: 15% or greater Previous use of corticosteroids: for at least 4 weeks prior to study Other: had asthma (defined in accordance with American Thoracic Society criteria) and had required maintenance ICS therapy for at least 4 weeks preceding the study; reversibility of airway obstruction was demonstrated by an increase of 15% or greater within 15 minutes after administration of 2 to 4 puffs of albuterol; had at least one documented urgent or emergent care visit or home treatment for asthma within the 12 months before screening. At the end of screening, eligible patients were required to meet the following criteria on the basis of the 7-day period immediately preceding the day of random assignment to study group: asthma stability defined as no more than 3 days' use of more than 12 puffs/day of as-needed albuterol, 4 or fewer mornings when PEF decreased more than 20% from the previous evening's PEF, and 3 or fewer nights with awakenings caused by asthma requiring inhaled albuterol; FEV1 between 50% and 8 Asthma Severity: Mild Moderate Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Condemi et al.{Condemi , 1997 #1078} 1997 USA Multicenter (24 outpatient centers) Glaxo Wellcome	Albuterol as needed; theophylline if part of an established fixed dosage regimen	Pregnant or lactating "significant concommitents illnes" : any other prescription or over-the-counter medication that might affect the course of asthma or interact with sympathomimetic amines Smoking - use of methotrexate or gold salts for control of asthma; use of inhaled cromolyn or inhaled nedocromil; use of oral, intranasal, or injectable corticosteroids within 4 weeks; significant concomitant illness; immunotherapy requiring a change in dosage regimen within 12 weeks	Yes: 1 week screening/run-in period during which patients continued their usual inhaled corticosteroid dosage regimens (open-label BDPdipropionate or TAA aerosols, 8 to 12 actuations daily). In addition, they received placebo FP powder through the Diskhaler twice daily. Previous bronchodilator therapy was replaced with albuterol aerosol, to be used only as needed for relief of acute symptoms; and if already part of their currenttherapeutic regimen, theophylline was continued at a fixed dosage.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Condemi et al.{Condemi , 1997 #1078} 1997 USA Multicenter (24 outpatient centers) Glaxo Wellcome	Intervention: Drug 1: FP + placebo Drug 2: TAA + placebo Drug 3: placebo Total daily dose: Drug 1: 500 mcg Drug 2: 800 mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Delivery device: Drug 1: Diskhaler (DPI) Drug 2: MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 95 Drug 2: 101 Drug 3: 95 Mean age (years): Drug 1: 34 Drug 2: 37 Drug 3: 37 Sex (% female): Drug 1: 46 Drug 2: 58 Drug 3: 48 Optional - Race (% white): Drug 1: 91 Drug 2: 89 Drug 3: 93 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100	Number (%) withdrawn: Drug 1: 32 (34%) Drug 2: 45 (45%) Drug 3: 69 (73%) Overall: 146 (50%) Optional - Withdrew due to lack of efficacy (%): Drug 1: 17% Drug 2: 27% Drug 3: 60% Adverse events caused withdrawal (%): Drug 1: 4% Drug 2: 5% Drug 3: 8% Optional - Other reasons for withdrawal (%): Drug 1: 16% Drug 2: 14% Drug 3: 11%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Condemi et al.{Condemi , 1997 #1078} 1997 USA Multicenter (24 outpatient centers) Glaxo Wellcome	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: TAA Drug 2 Endpoint: TAA Drug 3 Baseline: placebo Drug 3 Endpoint: placebo Number in group (n): Drug 1- baseline: 95 Drug 1- endpoint: 95 Drug 2- baseline: 101 Drug 2- endpoint: 101 Drug 3- baseline: 95 Drug 3- endpoint: 95	Rescue med use day: Drug 1- baseline: 3.0 (0.3) Drug 1 -endpoint: -0.9 (0.3) Drug 2 - baseline: 3.3 (0.7) Drug 2 - endpoint: -0.2 (0.7) Drug 3 - baseline: 3.2 (0.3) Drug 3 - endpoint: 1.6 (0.3) P value: <0.05, FP vs. TTA Symptom control during 24 hour period: D1 base: Overall symptom score: 1.7 (0.1) D1 end: -0.3 (0.1) D2 base: 1.8 (0.1) D2 end: -0.1 (0.1) D3 base: 1.7 (0.1) D3 end: 0.7 (0.2) P: <0.05, FP vs. placebo and TTA vs. placebo Nocturnal awakenings: D1 base: 0.09 (0.02) D1 end: -0.03 (0.03) D2 base: 0.10 (0.02) D2 end: -0.01 (0.03) D3 base: 0.08 (0.02) D3 end: 0.27 (0.05) P: <0.05, FP vs. placebo and TTA vs. placebo Other: D1 base: rescue-free days (%): 34 (4) D1 end : 14 (4) D2 base: 34 (4) D2 end: 1 (3) D3 base: 32 (4) D3 end: -11 (4) P: <0.05, FP vs. TTA Other: D1 base: Symptom-free days (%): 33 (4) D1 end : 14 (5) D2 base: 23 (3) D2 end: 12 (3) D3 base: 25 (3) D3 end: -5 (3) P: <0.05. FP vs. placebo and TTA vs. placebo Other Relevant Health Outcome Results: Only 27% of patients in the placebo group remained in the study for the entire 24 weeks compared with 66% and 55% of patients in the FP and TAA groups, respecti

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Condemi et al.{Condemi , 1997 #1078} 1997 USA Multicenter (24 outpatient centers) Glaxo Wellcome	Overall adverse events reported (%): Drug 1: 15% Drug 2: 8% Drug 3: 13% P = 0.174 (FP vs. TTA) Oral candidiasis- thrush (%): Drug 1: 8% Drug 2: 3% Drug 3: 1% P = 0.035 (FP vs. placebo) Sore throat (%): Drug 1: 3% Drug 2: 1% Drug 3: 0% Headache (%): Drug 1: 1% Drug 2: 0 Drug 3: 2% Hoarseness (%): Drug 1: 3% Drug 2: 0 Drug 3: 0 Other (%): Drug 1: Candidiasis, unspecified site: 2% Drug 2: 0 Drug 3: 0% Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: The numbers of patients with postrandomization morning plasma cortisol concentrations less than 5 Fg/dl in each treatment group were one (1%), three (3%), and one (1%) in the placebo, TAA, and FP treatment groups, respectively.	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
936	Condemi et al.{Condemi, 1999 #936} 1999 USA Multicenter (36 centers) Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 24 weeks N=437 Enrolled: 516/NR/437 ITT Analysis: Yes	Age: >/= 12 FEV1 expressed as a percent of the predicted value: 40%-80% Reversability of FEV1: 15% or greater increase Duration of condition: >/= 6 months of asthma as defined by ATS Other: reversible airways disease as demonstrated by a 15% or greater increase in FEV1 from baseline after the inhalation of 180 mcg of albuterol, had an FEV1 of 40%-80% of their predicted value, and used a short acting bronchodilator on a regular basis for at least 3 months; at end of screening period, patients had to have an FEV1 of 40% to 65% of predicted normal or an FEV1 of 65% to 85% of predicted normal with at least one of the following over the 7 days prior to randomization: an average of >/=4 puffs of albuterol per day, 2 or more days when the evening to mornign PEF variation was >/= 20%, 2 or more nights with awakenings due to asthma, or 3 or more days with scores >/-2 for any of the daytime symptoms of wheeze, chest tightness, shortness of breath, and cough Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Condemi et al.{Condemi, 1999 #936} 1999 USA Multicenter (36 centers) Glaxo Wellcome	Albuterol as needed	Pregnant or lactating Prior treatment with: oral or paenteral corticosteroid stherapy within 30 days of screening; oral or long-acting inhaled bronchodilators within 48 hours of screening; cromolyn or nedocromil within 30 days of screening Smoking - current or former: current tobacco use Other: a hospital admission for asthma in the past 30 days, or an upper or lower respiratory tract infection within 30 days. Patients were excluded during screening if they had an asthma exacerbation, an upper or lower respiratory tract infection, required any change in their use of asthma meds, or were unwilling or unable to carefully maintain their diary card	Yes: 2-4 week screening period where all patients used 88 mcg open-label fluticasone twice daily and albuterol as needed (total 144mcg/d)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Condemi et al.{Condemi, 1999 #936} 1999 USA Multicenter (36 centers) Glaxo Wellcome	Intervention: Drug 1: FP + SM Drug 2: FP (higher dose) Total daily dose: Drug 1: 196 mcg + 84 mcg Drug 2: 440 mcg Steroid dosing range (Low, medium or high): Drug 1: Low Drug 2: medium Delivery device: Drug 1: MDI Drug 2: MDI Is dosing comparable between treatment groups? NA: comparing two appropriate clinical options (adding LABA to low dose ICS vs increasing ICS dose)	# in group (n): Drug 1: 221 Drug 2: 216 Mean age (years): Drug 1: 36.9 Drug 2: 36.8 Sex (% female): Drug 1: 62 Drug 2: 60 Optional - Race (% white): Drug 1: 86 Drug 2: 83 Current smokers (%): Drug 1: 0 Drug 2: 0 Optional - Disease duration (years): Drug 1: > 10 yrs: 76% Drug 2: 78% Other: Drug 1: FEV1: mean % predicted: 60.9 Drug 2: 61.7 Other: Drug 1: % of symptom free days: 10 Drug 2: 15.3 Is dosing comparable between treatment groups? NA: comparing two appropriate clinical options (adding LABA to low dose ICS vs increasing ICS dose)	Number (%) withdrawn: Drug 1: 19 (9%) Drug 2: 30 (14%) Optional - Withdrew due to lack of efficacy (%): Drug 1: <1% Drug 2: 3% Adverse events caused withdrawal (%): Drug 1: 0 Drug 2: 2% Optional - Lost to follow-up (%): Drug 1: 1% Drug 2: 1% Optional - Other reasons for withdrawal (%): Drug 1: 6% Drug 2: 7%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Condemi et al.{Condemi, 1999 #936} 1999 USA Multicenter (36 centers) Glaxo Wellcome	Intervention: Drug 1 Baseline: FP + SM Drug 1 Endpoint: FP + SM Drug 2 Baseline: FP (higher dose) Drug 2 Endpoint: FP (higher dose) Number in group (n): Drug 1- baseline: 221 Drug 1- endpoint: 221 Drug 2- baseline: 216 Drug 2- endpoint: 216	Rescue med use day: Drug 1- baseline: daily supplemental albuterol use (mean # of puffs (SE)): 4.66 (0.22) Drug 1 -endpoint: -2.51 (0.17) (thus, over weeks 1-24 daily use of supplemental albuterol was reduced by 51%) Drug 2 - baseline: 4.57 (0.19) Drug 2 - endpoint: -1.55 (0.15); over weeks 1-24 daily use reduced by 29% P value: <0.001 Asthma exacerbations: D1 end: Patients with at least 1 exacerbation/patients with >1: 21 (10%)/4 (2%) D2 end: 31 (14%)/7 (3%) P: 0.140/0.377 Nocturnal awakenings: D1 base: % nights with no awakenings, mean: 71.7 (2.4) D1 end: mean change: 14.9 (1.9) D2 base: 76.6 (2.2) D2 end: 10.1 (1.8) P: 0.008 Other: D1 base: % symptom-free days, mean: 10.0 (1.5) D2 base: 15.3 (2.0) Other Relevant Health Outcome Results: Daytime symptom scores, mean change (SE) from baseline (FP + SM vs. FP higher dose); Wheezing: -0.40 (0.04) vs. -0.26 (0.05); P=0.15; Shortness of breath: -0.52 (0.05) vs. -0.25 (0.05); P<0.001; Chest tightness: -0.55 (0.05) vs. -0.29 (0.04); P=0.002; Cough: -0.25 (0.04) vs. -0.23 (0.05); P=0.858; Combined symptom score: -0.43 (0.04) vs. -0.26 (0.04); P<0.001; combined sympto

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Condemi et al.{Condemi, 1999 #936} 1999 USA Multicenter (36 centers) Glaxo Wellcome	Overall adverse events reported (%): Drug 1: 86% Drug 2: 86% Serious adverse events (%): Drug 1: 0.5% (n=1) Drug 2: 0.5% (n=1) Oral candidiasis- thrush (%): Drug 1: <1% Drug 2: 5% Sore throat (%): Drug 1: 3% Drug 2: 4%	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
5082	Condemi J{Condemi, 2001 #5082} 2001 USA Multicenter Novartis	Study design: RCT open-label parallel-group study Duration: 26 weeks N=528 ITT Analysis:	outpatients between the ages of 18 and 75 years with moderate to moderately severe asthma diagnosed at least 1 year before screening; receiving low-dose inhaled corticosteroids at 400 lxg/d

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Condemi J{Condemi, 2001 #5082} 2001 USA Multicenter Novartis	NR	Pregnant or nursing women were excluded Childbearing potential who were not practicing reliable contraception; respiratory diseases unrelated to asthma or other serious medical conditions; if they had required a dose increase in inhaled corticosteroids to treat an acute exacerbation of asthma within 1 month or had any history of allergy to sympathomimetic amines, aerosols, or inhaled lactose; taking beta-receptor-blocking medications, drugs that prolong the cardiac QT interval, tricyclic antidepressants, monoamine oxidase derivatives, or nonpotassium- sparing diuretics	None

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Condemi J{Condemi, 2001 #5082} 2001 USA Multicenter Novartis	Intervention: Drug 1: FM Drug 2: SM Total daily dose: Drug 1: 24µg Drug 2: 100µg Steroid dosing range: Delivery device: Drug 1: Aerolizer Drug 2: Diskus	# in group (n): Drug 1: 256 Drug 2: 260 Mean age (years): NR Sex (% female): NR	Number (%) withdrawn: Drug 1: 14.5 Drug 2: 11.3 Adverse events caused withdrawal (%): Drug 1: 5.7 Drug 2: 3.4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Condemi J{Condemi, 2001 #5082} 2001 USA Multicenter Novartis	Intervention: Drug 1: FM Drug 2: SM Number in group (n): Drug 1: 256 Drug 2: 260	See adverse events

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Condemi J{Condemi, 2001 #5082} 2001 USA Multicenter Novartis	Total no. of patients 262 (100) vs. 266 (100) No. with at least 1 adverse event 202 (77.1) vs. 201 (75.6) Adverse event Upper respiratory tract infection 68 (26.0) vs. 51 (19.2) Asthma 53 (20.2) vs. 49 (18.4) Viral infection 50 (19.1) vs.52 (19.5) Sinusitis 37 (14.1) vs. 40 (15.0) Bronchitis 19 (7.3) vs. 23 (8.6) Headache 18 (6.9) vs. 13 (4.9) Rhinitis 17 (6.5) vs. 11 (4.1) Cough 11 (4.2) vs.15 (5.6) Pharyngitis 7 (2.7) vs. 15 (5.6) Back pain 4 (1.5) vs. 19 (7.1)	No	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
403	Corren et al.{Corren, 2003 #403} 2003 USA Multicenter (17 centers) Schering-Plough	Study design: RCT Double-blind Double-dummy Duration: 8 weeks N=262 Enrolled: NR/NR/262 ITT Analysis: Yes	Age: >/= 12 Previous use of corticosteroids: daily ICS use for at least 30 days before screening and maintained a stable ICS regimen within recommended dose ranges for 2 weeks before screening Duration of condition: >/= 6 months Other: At screening and baseline, patients had to demonstrate a baseline FEV1 >/= 50% and </= 85% of normal predicted values for age, gender and height after all restricted medications had been withheld for appropriate intervals; Each patient needed to demonstrate an increase in FEV1 of >/= 12% of pre-bronchodilator value, with an absolute volume increase of >/= 200 ml at screening or within the past 12 months Asthma Severity: Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Corren et al.{Corren, 2003 #403} 2003 USA Multicenter (17 centers) Schering-Plough	antihistamines and/or nasal corticosteroids if on a stable regimen for 2 weeks before screening; theophylline if taken at stable dose for 2 weeks before screening	Pregnant or lactating Smoking - current or former : required oral corticosteroid treatment for more than a total of 14 days during the 6 months immediately before screening; required a burst of systemic steroids within the month before screening; been treated with leukotriene modifiers within 2 weeks before screening; received treatment with methotrexate, cyclosporin, gold, or other immunosuppressive agents within the past 3 months; required emergency hospital treatment for asthma twice in the previous six months; been hospitalized for an asthma exacerbation within the previous 3 months; required ventilatory support for asthma within previous 5 years; had clinical evidence of other respiratory or clinically significant disease other than asthma; had smoked within previous 6 months or demonstrated a clinical condition requiring daily use of nebulized B2-adrenergic agonists	Yes: screening period, which is distnguished from baseline but not described otherwise

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Corren et al.{Corren, 2003 #403} 2003 USA Multicenter (17 centers) Schering-Plough	Intervention: Drug 1: MOM Drug 2: BUD Drug 3: placebo Total daily dose: Drug 1: 400 mcg Drug 2: 320 mcg Drug 3: N/A Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: low Delivery device: Drug 1: DPI Drug 2: DPI Drug 3: DPI Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 104 Drug 2: 106 Drug 3: 51 Mean age (years): Drug 1: 37 Drug 2: 39 Drug 3: 37 Sex (% female): Drug 1: 71% Drug 2: 57% Drug 3: 61% Optional - Race (% white): Drug 1: 89% Drug 2: 88% Drug 3: 92% Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Optional - Disease duration (years): Drug 1: 19 (5) Drug 2: 20 (15) Drug 3: 20 (13) Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100	Number (%) withdrawn: Drug 1: NR Drug 2: NR Drug 3: NR Overall: 19% Optional - Withdrew due to lack of efficacy (%): Drug 1: 6% Drug 2: 10% Drug 3: 35% overall: 13%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Corren et al.{Corren, 2003 #403} 2003 USA Multicenter (17 centers) Schering-Plough	Intervention: Drug 1 Baseline: MOM Drug 1 Endpoint: MOM Drug 2 Baseline: BUD Drug 2 Endpint: BUD Drug 3 Baseline: placebo Drug 3 Endpoint: placebo Number in group (n): Drug 1- baseline: 104 Drug 1- endpoint: 104 Drug 2- baseline: 106 Drug 2- endpoint: 106 Drug 3- baseline: 51 Drug 3- endpoint: 51	Rescue med use day: Drug 1- baseline: 2.85 (0.26) Drug 1 -endpoint: -0.91 (0.23) Drug 2 - baseline: 2.86 (0.26) Drug 2 - endpoint: -0.21 (0.23) Drug 3 - baseline: 2.46 (0.37) Drug 3 - endpoint: 1.09 (0.34) P value: P<0.01 MF vs. placebo and BUD vs. placebo; P<0.05 MF vs. BUD Day time symptom control: D1 - base: Morning total asthma score: 1.59 (0.14) D1 - end: -0.42 (0.12) D2 - base: 1.36 (0.14) D2 - end: -0.12 (0.11) D3 - base: 1.42 (0.20) D3 - end: 0.16 (0.17) P: P<0.01 MF vs. placebo Night time symptom control: D1 - base: Evening total asthma score: 1.64 (0.13) D1 - end: -0.46 (0.12) D2 - base: 1.38 (0.13) D2 - end: -0.11 (0.12) D3 - base: 1.23 (0.19) D3 - end: 0.24 (0.17) P: P<0.01 MF vs. placebo; P<0.05 MF vs. BUD Nocturnal awakenings: D1 base: patients with no nocturnal awakenings (%): 68.3 D1 end: 78.8 D2 base: 70.8 D2 end: 81.1 D3 base: 66.7 D3 end: 60.8 Other: D1 base: Asthma symptom-free days over course of study (%): D1 end : 39.7 (3.4) D2 baseD2 end: 26.8 (3.3)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Corren et al.{Corren, 2003 #403} 2003 USA Multicenter (17 centers) Schering-Plough	Overall adverse events reported (%): Drug 1: 8% Drug 2: 9% Drug 3: 8% Additional adverse events and comments: No differences among groups in overall incidence of AEs. Most frequently reported treatment-related AEs were headache and pharyngitis (both 4% or less: data by treatment arm NR). Treatment-related AEs were mild to moderate in intensity except for one report of severe headache with BUD; none was life-threatening. There was only one report of oral candidiasis in one MF-reated patient. There were no clinically relevant changes in vital signs, physical examinations or lab tests from baseline to endpoint for any treatment group.	Compliance Compliance over course of study: MF 96% vs. BUD 97% vs. placebo 88%	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4799	Corren et al.{Corren, 2007 #4799} 2007 USA Multicenter (56) AstraZeneca	Study design: Head to head - straight forward comparison RCT Double-blind Double-dummy Duration: 12 weeks N=480 Enrolled: NR/NR/480 ITT Analysis: Yes	Male and female patients aged >12 years with a documented diagnosis of asthma of >6 months' duration, low to medium doses of ICSs, either aloneor in combination with other asthma maintenance medications, consistently for >4 weeks and to have a prebronchodilator forced expiratory volume in 1 second (FEV1) of >60% to <90% of predicted normal on ICS at screening and of 50% to 85% of predicted normal after discontinuation of ICS during a 2-week run-in period. At screening, eligible patients had reversibility from baselineFEV 1 (prealbuterol value) of at least 12% and at least 0.20 L within 15 to 30 minutes after administration of a standard dose of albuterol pMDI (2-4 inhalations [90 pg per inhalation]). In addition, eligible patients were capable of performing the necessary maneuvers and proceduresrequired for participation in the study Asthma severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Corren et al.{Corren, 2007 #4799} 2007 USA Multicenter (56) AstraZeneca	Disallowed medications included other ICSs, LABAs, leukotriene antagonists, nebulized albuterol, and systemic corticosteroids.	Pregnant or lactatingSmoking - current or formerOther? (Please list all): severe asthma (as judged by the investigator), asthma requiring hospitalization once or emergency treatment more than once within 6 months or requiring treatment with systemic corticosteroids within the 4 weeks before screening, and/or a >10-pack-year smoking history; pregnant or breastfeeding.	Yes- elucidate....: 7-21 days; must have daytime or nighttime symptom score >0 on >=3 of 7 consecutive days

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Corren et al.{Corren, 2007 #4799} 2007 USA Multicenter (56) AstraZeneca	Intervention: Drug 1: Bud/For Drug 2: Bud Drug 3: Form Drug 4: Placebo Total daily dose: Drug 1: 320/18 Drug 2: 320 Drug 3: 18 Drug 4: NA Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Drug 3: NA Delivery device: Drug 1: pMDI Drug 2: pMDI Drug 3: DPI Drug 4: NA Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 123 Drug 2: 121 Drug 3: 114 Drug 4: 122 Mean age (years): Drug 1: 37.2 Drug 2: 37.1 Drug 3: 35.3 Drug 4: 36.1 Sex (% female): Drug 1: 62.6 Drug 2: 62.0 Drug 3: 63.2 Drug 4: 61.5 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Drug 4: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 18 (14.6%) Drug 2: 18(14.9%) Drug 3: 35 (30.7%) Drug 4: 62 (50.8%) Overall: 27% Adverse events caused withdrawal (%): Drug 1: 3 Drug 2: 2 Drug 3: 2 Drug 4: 9

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Corren et al.{Corren, 2007 #4799} 2007 USA Multicenter (56) AstraZeneca	Intervention: Drug 1: Bud/For Drug 2: Bud Drug 3: Form Drug 4: Placebo # in group (n): Drug 1: 123 Drug 2: 121 Drug 3: 114 Drug 4: 122	Rescue med use during 24 hour period: Drug 1- baseline: change from baseline mean Drug 1-endpoint: -2.01 (2.36) Drug 2-baselineDrug 2-endpoint: -1.86 (2.59) Drug 3 - baselineDrug 3- endpoint: -1.30 (2.81) P values: mean difference between groups(95% CI; p value): -0.23(-0.80 to 0.34; NS) ; -0.80(-1.38 to -0.23; P < 0.01) Asthma exacerbations: D1 baseD1 end: 0.8% D2 baseD2 end: 2.5% D3 baseD3 end: 4.4% P: Odds Ratio (95% CI): Bud/FM minus BUD 0.32 (0.03 to 3.14); BUD/FM minus FM 0.18 (0.02 to 1.55); BUD/FM minus PBO 0.04 (0.01 to 0.32) Symptom control during 24 hour period: D1 base: % symptom-free days: change from baseline, mean D1 end: 26.47 (39.46) D2 baseD2 end: 29.77 (38.19) D3 baseD3 end: 18.10 (37.57) P: mean difference between groups(95% CI; p value): -2.66(-12.26 to 6.93; NS); 9.97(0.19 to 19.74; p<=0.05) Day time symptom control: D1 - base: Daytime symptom score change from baseline mean D1 - end: -0.41 (0.52) D2 - baseD2 - end: -0.44 (0.58) D3 - baseD3 - end: -0.27(0.61) P: mean difference between groups(95% CI; p value): 0.04 (-0.10 to 0.18; p NS) ; -0.15 (-0.29 to 0.00; P < 0.05)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Corren et al.{Corren, 2007 #4799} 2007 USA Multicenter (56) AstraZeneca	NR	Compliance - A compliance rate of _>80% was reported in 85.8% of patients, with similar compliance rates observed	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4749	Cumming et al.{Cumming, 1997 #4749} 1997 Australia Population-based cohort Australian dept of Health and Family Services	Study design: Observational Cohort study Duration: NA N=3654 Enrolled: NA ITT Analysis: NA	: all permanent residents with birthdates before January 1, 1943, were invited to attend a local clinic for a detailed eye examination. Of 4433 eligible people identified at our census, 3654 attended from 1992 to 1994 (82.4% participation rate).

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Cumming et al.{Cumming, 1997 #4749} 1997 Australia Population-based cohort Australian dept of Health and Family Services		NA	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Cumming et al.{Cumming, 1997 #4749} 1997 Australia Population-based cohort Australian dept of Health and Family Services	Intervention: Drug 1: ICS (glaucoma paper) Drug 2: No ICS Drug 3: Cumming ICS (cataract paper) Drug 4: Cumming No ICS Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 370 Drug 2: 3284 Drug 3: 241 Drug 4: 2784 Mean age (years): Drug 1: 62.4 Drug 2: 64.7 Drug 3: 66.1 Drug 4: 66.1 Sex (% female): Drug 1: 80 Drug 2: 70 Drug 3: 54 Drug 4: 56 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: 14 Drug 4: 15	NA

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Cumming et al.{Cumming, 1997 #4749} 1997 Australia Population-based cohort Australian dept of Health and Family Services	Intervention: Drug 1: ICS (glaucoma paper) Drug 2: No ICS Drug 3: Cumming ICS (cataract paper) Drug 4: Cumming No ICS Number in group (n): Drug 1: 370 Drug 2: 3284 Drug 3: 241 Drug 4: 2784	Other Relevant Health Outcome Results: For Mitchell paper (glaucoma) In persons with a glaucoma family history, strong association between ICSe and presence of either glaucoma or elevated IOP (odds ratio [OR], 2.6; 95% confidence interval, 1.2–5.8). The risk increased with higher doses (OR, 6.3; 95% CI, 1.0 –38.6) for persons who used more than four puffs per day. •Age and sex adjusted prevalence ratios compared to never users of corticosteroids: For CUmmings paper (cataract) Any use current or former ICS use: cortical 1.1 (95% CI: 0.9 to 1.3), nuclear 1.5 (95% CI: 1.2 to 1.9), post subcapsular 1.9 (95% CI: 1.3 to 2.8) Former Users: cortical 0.9 (95% CI: 0.7 to 2.2), nuclear 1.6 (95% CI: 1.1 to 2.3), post subcapsular 1.1 (95% CI: 0.6 to 2.0) Current Users: cortical 1.4 (95% CI: 1.1 to 1.7), nuclear 1.5 (95% CI: 1.1 to 2.0), post subcapsular 2.6 (95% CI: 1.7 to 4.0) •Higher cumulative lifetime doses of BDP were associated with higher risk of posterior subcapsular cataracts (P < 0.001); adjusting for oral steroid use did not change this significantly

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Cumming et al.{Cumming, 1997 #4749} 1997 Australia Population-based cohort Australian dept of Health and Family Services	See outcomes.	NR	

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
107	Dahl et al.{Dahl R, 2006 #107} 2006 Multicenter (178), Multinational (18); while outpatient, unclear whether primary care NR: 3 of 5 authors employed by GlaxoSmithKline, UK	Study design: RCT Double-blind Double-dummy Duration: 24 weeks N=1397 Enrolled: 1769, NR, 1397 ITT with LOCF, but excluded data from one site (n=6), also performed PP analysis	Age: >= 18yr; Reversability of FEV1: >=12% 15min s/p salbutamol 200-400mcg inh; asthma symptom score (day and night combined) of at least 2 (two or moreepisodes of symptoms during the day/night) on at least 4 of the last 7 evaluable days of the run-inperiod; Current 1000-2000mcg/day BDP or equivalent; Duration of condition: >=6mo Asthma Severity: Moderate Severe Other: unclear, although likely moderate to severe based on BDP dosing equivalent required for study inclusion

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Dahl et al.{Dahl R, 2006 #107} 2006 Multicenter (178), Multinational (18); while outpatient, unclear whether primary care NR: 3 of 5 authors employed by GlaxoSmithKline, UK	rescue beta-agonist	Prior treatment with: oral corticosteroids within 4 weeks or depot steroids within 12 weeks of beginning of run-in period Concommitant diseases: suffered an upper or lower respiratorytract infection or an acute asthma exacerbation(requiring emergency treatment or hospitalisation) within 4 weeks of the beginning of the run-in period Smoking - current or former: >=10PY Other? (Please list all): pre-bronchodilator FEV1 of <=50% of the predicted value	Yes- 2wks where patients continued ICS use with salbutamol prn. additionally, patients on coimbination therapy switched to ICS for 4 wks prior to study-unclear whether prior to run-in or randomization

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Dahl et al.{Dahl R, 2006 #107} 2006 Multicenter (178), Multinational (18); while outpatient, unclear whether primary care NR: 3 of 5 authors employed by GlaxoSmithKline, UK	Intervention: Drug 1: SM/FP Drug 2: FM/BUD Total daily dose: Drug 1: 100/500mcg Drug 2: 24/800mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Delivery device: Drug 1: Diskus Drug 2: Turbuhaler Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 694 Drug 2: 697 Mean age (years): Drug 1: 45.6 Drug 2: 47.1 Sex (% female): Drug 1: 56 Drug 2: 59 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Other: Drug 1: # exacerbations in past year requiring: antibiotics/ICS, hospitalization 0.6, 0.1 Drug 2: 0.6, 0.1 Other: Drug 1: % symptom-free days 8.2 Drug 2: 7.3 Other: Drug 1: % symptom-free nights 31.5 Drug 2: 35 Groups similar at baseline? No -	Number (%) withdrawn: Drug 1: 10.2 Drug 2: 8.9 Overall: 133 (9.6) Optional - Withdrew due to lack of efficacy (%): Drug 1: 0.7 Drug 2: 0.3 Adverse events caused withdrawal (%): Drug 1: 1.9 Drug 2: 1.4 Optional - Lost to follow-up (%): Drug 1: 2.3 Drug 2: 1.9 Optional - Protocol violation (%) Drug 1: 1.9 Drug 2: 1.7 Optional - Consent withdrawn (%): Drug 1: 1.6 Drug 2: 2.1 Optional - Other reasons for withdrawal (%): Drug 1: includes those who did not fulfill entry criteria 1.9 Drug 2: 1.4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Dahl et al.{Dahl R, 2006 #107} 2006 Multicenter (178), Multinational (18); while outpatient, unclear whether primary care NR: 3 of 5 authors employed by GlaxoSmithKline, UK	Intervention: Drug 1 Baseline: SM/FP Drug 1 Endpoint: SM/FP Drug 2 Baseline: FM/BUD Drug 2 Endpoint: FM/BUD Number in group (n): Drug 1- baseline: 697 Drug 1- endpoint: 694 Drug 2- baseline: 700 Drug 2- endpoint: 697	Rescue med use during 24 hour period: Drug 1- baseline: median % rescue-free days 0 Drug 1-endpoint: 82 Drug 2-baseline: 0 Drug 2-endpoint: 81 P = NS Asthma exacerbations: D1 end: 2.69 D2 end: 2.79 ratio 0.96, 95%CL (0.84, 1.10), pvalue 0.571 Day time symptom control: D1 - base: median % symptom-free days 0 D1 - end: 63 D2 - base: 0 D2 - end: 60 P =:NR Night time symptom control: D1 - base: median % symptom-free nights 14 D1 - end: 85 D2 - base: 25 D2 - end: 86 P = NR Other Relevant Health Outcome Results: More detailed explanation of asthma exacerbations: For the primary endpoint, the adjusted mean rate of all exacerbations over 24 weeks, as recorded by the investigators, was similar in both treatment groups (2.69 for SM/FP and 2.79 for FM/BUD). The majority of exacerbations were mild. Further analysis of all exacerbations adjusting for time interval, revealed a significant effect of time, such that the rate of all exacerbations across both treatment groups showed a 30% reduction in weeks 9–16 (95% CI 24–36%; P<0.001) and a 36% reduction in weeks 17–24 (95% CI 30–42%; P<0.001) compared with weeks 1–8. From approxi

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Dahl et al.{Dahl R, 2006 #107} 2006 Multicenter (178), Multinational (18); while outpatient, unclear whether primary care NR: 3 of 5 authors employed by GlaxoSmithKline, UK	Overall adverse events reported (%): Drug 1: 55 Drug 2: 54 Serious adverse events (%): Drug 1: rare Drug 2: rare Oral candidiasis- thrush (%): Drug 1: 2 Drug 2: 1 Dysphonia (%): Drug 1: /hoarseness 2 Drug 2: 2 Headache (%): Drug 1: 1 Drug 2: 2 Death (%): Drug 1: 0 Drug 2: 0 Other (%): Drug 1: drug-related <10 Drug 2: <10	NR Only reported withdrawals; see above	Good Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4730	de Benedictis et al.{de Benedictis, 2001 #4730} 2001 Multinational (7 countries) Multicenter (32) GlaxoSmithKline	Study design: RCT Double-blind parallel group Duration:52 weeks (not including 2 week run-in period) N=343 (277 for the growth population) Enrolled: 403 enrolled, 343 randomized ITT Analysis: No another type of analysis was used (define): exluded 66 patients from growth population	: Boys (aged 4-11 years) or girls (aged 4-9 years) with a sexual maturity rating of Tanner stage 1 (prepubertal), required treatment with inhaled FP, 100 to 200 µg/d, or BDP or BUD, 200 to 500 µg/d, for at least the previous 8 weeks, at a constant dosage for at least 4 weeks before the run-in period. After 2-week run-in period, randomized to treatment if they demonstrated a mean morning PEF during the last 7 days of the run-in period of no greater than 85% of their maximum achievable response after inhalation of albuterol sulfate, 400 µg, via a metered dose inhaler. Patients also had to have an asthma symptom score of at least 1 or require albuterol at least once daily on at least 4 of the last 7 days of the run-in period. Asthma Severity: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
de Benedictis et al.{de Benedictis, 2001 #4730} 2001 Multinational (7 countries) Multicenter (32) GlaxoSmithKline	Patients were permitted to continue with the following antiasthma treatments, providing that the dose remained constant during the course of the study: cromolyn sodium, nedocromil sodium, methylxanthines, ketotifen fumarate, anticholinergics, and oral or long-acting beta-agonists. In addition, the following treatments were permitted□ for use as needed: oral corticosteroids for asthma exacerbations, intranasal corticosteroids, decongestants, antihistamines, and antibiotics.	Patients with intermittent asthma or disorders that could affect growth, patients receiving oral or parenteral steroids, and patients admitted to a hospital with respiratory disease in the 4 weeks before the run-inperiod were excluded from the study.	Yes: During the 2-week run-in period, patients continued to receive their existing inhaled corticosteroid treatment and albuterol sulfate from a metered-dose or dry-powder inhaler on an as-needed basis. Patients were randomized to treatment if they demonstrated a mean morning peak expiratory flow (PEF) during the last 7 days of the run-in period of no greater than 85% of their maximum achievable response after inhalation of albuterol sulfate, 400 ìg, via a metered dose inhaler. Patients also had to have an asthma symptom score of at least 1 or require albuterol at least once daily on at least 4 of the last 7 days of the run-in period.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
de Benedictis et al.{de Benedictis, 2001 #4730} 2001 Multinational (7 countries) Multicenter (32) GlaxoSmithKline	Intervention: Drug 1: FP Drug 2: BDP Total daily dose: Drug 1: 400mcg Drug 2: 400mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Delivery device: Drug 1: Diskhaler (DPI) Drug 2: Diskhaler (DPI) Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 170 Drug 2: 173 Mean age (years): Drug 1: 7.6 (1.7) Drug 2: 7.6 (2.0) Sex (% female): Drug 1: 33.5 Drug 2: 22 Optional - Race (% white): Drug 1: 82.9 Drug 2: 84.4 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 95.3 Drug 2: 96 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100	Number (%) withdrawn: Drug 1: NR Drug 2: NR Adverse events caused withdrawal (%): Drug 1: NR Drug 2: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
de Benedictis et al.{de Benedictis, 2001 #4730} 2001 Multinational (7 countries) Multicenter (32) GlaxoSmithKline	Intervention: Drug 1: FP Drug 2: BDP Number in group (n): Drug 1: 170 Drug 2: 173	Asthma exacerbations: D1 : #47 D2: #52 P = NS Other Relevant Health Outcome Results: There were no significant differences between treatment groups for any assessment period with respect to diary-card symptoms or the as-needed use of albuterol. There was no significant difference between treatments in the total number of exacerbations (47 in the FPgroup vs 52 in the BDP group) and the percentage of patients who experienced at least 1 exacerbation (16% of patients in the FPgroup vs 19% of patients in the BDP group).

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
de Benedictis et al.{de Benedictis, 2001 #4730} 2001 Multinational (7 countries) Multicenter (32) GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 80 Drug 2: 80.9 Cough (%): Drug 1: 5.3 Drug 2: 8.1 Upper respiratory tract infection (%): Drug 1: 13.5 Drug 2: 14.5 Rhinitis (%): Drug 1: 25.3 Drug 2: 11.6 Other (%): Drug 1: asthma = 15.3 Drug 2: 19.1 Other (%): Drug 1: bronchitis = 14.1 Drug 2: 11.6 Other (%): Drug 1: ear, nose, and throat infection = 14.1 Drug 2: 9.2 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: Adjusted mean growth velocity greater in FLUP treated subjects (4.76 cm/year (0.28)) than BDP treated subjects (4.06 cm/year (0.29)) (Difference 0.70 (95% CI: 0.13 to 1.26 cm, P < 0.02)); ;no significant changes from baseline in morning serum cortisol levels in either treatment group, despite a trend toward reduced levels in both groups. A significant reduction from baseline in overnight urinary cortisol levels was found in the BDP group; however, the differences between treatments were not statistically significant Additional adverse events and comments: pharyngitis/throat infection = 12.4; 14.5 ; viral infection = 11.8; 7.5 ; vi	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
58	Deykin et al.{Deykin, 2007 #58} 2007 USA Multicenter National Heart, Lung, and Blood Institute of the National Institutes of Health	Study design: RCT Double-blind Duration: 14 weeks then washout 4 weeks then crossover and another 14 weeks N=192 Enrolled: 254/192 ITT Analysis: No another type of analysis was used (define)	Age: 12-65 FEV1 expressed as a percent of the predicted value: at least 40% Reversability of FEV1: 12% or greater Asthma Severity: Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Deykin et al.{Deykin, 2007 #58} 2007 USA Multicenter National Heart, Lung, and Blood Institute of the National Institutes of Health		Smoking - current or former: within 12 months or more than 10 pack-years or within past 12 months Other: respiratory tract infection, or asthma exacerbation (i.e., a need for oral corticosteroid or urgent care visit) within the previous 6 weeks.	Yes: 4-week run-in period, single-blind treatment with beclomethasone hydrofluoroalkane (HFA) (80 µg twice daily) and ML (10 mg

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Deykin et al.{Deykin, 2007 #58} 2007 USA Multicenter National Heart, Lung, and Blood Institute of the National Institutes of Health	Drug 1: All Is dosing comparable between treatment groups? NA: LTRA vs ICS	# in group (n): Drug 1: 192 Mean age (years): Drug 1: 34.3 Sex (% female): Drug 1: 61 Optional - Race (% white): Drug 1: 54.7 black 28.6 Asian 5.2 hispanic 10.9 other 0.5 Current smokers (%): Drug 1: 0 Optional - Rescue medication use (puffs per day): Drug 1: 0.24 Current use of ICS at baseline (%): Drug 1: 66 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 98 (51%) - 39% due to trial being stopped early Adverse events caused withdrawal (%): Drug 1: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Deykin et al.{Deykin, 2007 #58} 2007 USA Multicenter National Heart, Lung, and Blood Institute of the National Institutes of Health		Other Relevant Health Outcome Results: In the 60 white individuals, more subjects experienced a longer time to treatment failure when using BDP and SM in combination than when using ML and SM in combination (10 vs. 2, p 0.039). Thirty-two subjects identified themselves as African American. In these subjects, more individuals experienced a longer time to treatment failure when using BDP and SM in combination than when using ML and SM in combination (15 vs. 3, p 0.0075). There was no difference in proportion of white subjects with preferential protection against treatment failure while using an ICS/LABA (relative to an LTRA/LABA) as compared with that in the African-American subjects (p = 1.0). Of the 110 subjects eligible for the prespecified primary analysis, 73 (66%) did not fail while receiving either therapy. Ten subjects (9%) failed while receiving an ICS and an LABA, and 29 individuals (26%) met treatment failure criteria while receiving an LTRA and an LABA.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Deykin et al.{Deykin, 2007 #58} 2007 USA Multicenter National Heart, Lung, and Blood Institute of the National Institutes of Health	NR	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
2243	Edelman et al.{Edelman, 2000 #2243} 2000 USA Treatment centers (17) Merck	Study design: RCT Double-blind Duration: 18 weeks N=191 Enrolled: NR	: Male and female patients 15 to 45 years of age with a history of chronic asthma were enrolled. All patients had an FEV1 of at least 65% of the predicted value at rest and a decrease in FEV1 of at least 20% after a standardized exercise challenge on two occasions during the baseline period; nonsmokers for at least 1 year and had a smoking history of less than 15 pack-years. Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Edelman et al.{Edelman, 2000 #2243} 2000 USA Treatment centers (17) Merck	albueterol	Other: upper respiratory infection or exacerbation of asthma requiring emergency carewithin the past month or were hospitalized for asthma in the past 3 months were excluded. Use of oral or ICS, theophylline, cromolynsodium, nedocromil, oral b-agonist, and longacting antihistamines was prohibited before and during the study	Yes: 2 week

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Edelman et al.{Edelman, 2000 #2243} 2000 USA Treatment centers (17) Merck	Intervention: Drug 1: ML Drug 2: SM Total daily dose: Drug 1: 10 mg Drug 2: 100 ug Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 97 Drug 2: 94 Mean age (years): Drug 1: 26.5 Drug 2: 26.0 Sex (% female): Drug 1: 53 Drug 2: 43 Current smokers (%): Drug 1: 0 Drug 2: 0 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 6 (6%) Drug 2: 8 (9%) Adverse events caused withdrawal (%): Drug 1: 1 Drug 2: 5

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Edelman et al.{Edelman, 2000 #2243} 2000 USA Treatment centers (17) Merck	Intervention: Drug 1: ML Drug 2: SM Number in group (n): Drug 1: 97 Drug 2: 94	Mortality: 0 vs. 1, P = NR Most reported results were intermediate outcomes evaluating exercise-induced bronchoconstriction

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Edelman et al.{Edelman, 2000 #2243}	Overall adverse events reported (%): Drug 1: 41 Drug 2: 40	NR	Fair Fair No
2000 USA Treatment centers (17) Merck	Headache (%): Drug 1: 5 Drug 2: 6 Upper respiratory tract infection (%): Drug 1: 14 Drug 2: 10 Death (%): Drug 1: 0 Drug 2: n=1 Other (%): Drug 1: asthma: 3 Drug 2: 7		

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
352	Everden et al.{Everden, 2004 #352} 2004 FACT study UK and Republic of Ireland Multicenter (56 general practice centers) Astra Zeneca UK (see p. 42)	Study design: RCT Other: open, parallel-group comparator study Duration: 12 weeks N=156 Enrolled: NR/NR/208 enrolled/156 randomized ITT Analysis: Yes	: outpatients, aged 6–17 years, with a clinical diagnosis of moderate, persistent asthma according to GINA criteria; patients had to have been receiving ICS for asthma at a constant dose for >/=4 weeks prior to enrollment, be currently using inhaled shortacting B2-agonists for relief of asthma symptoms (chest tightness, cough, wheeze, shortness of breath or activity-induced), and have had asthma symptoms occurring on >/=3 days or nights out of the past 7 days prior to enrollment. For randomization, patients needed to have continued to experience asthma symptoms as above during the run-in period and to have used >/=7 actuations of short-acting B2-agonists in the last 7 days or nights for relief of asthma symptoms. Asthma Severity: Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Everden et al.{Everden, 2004 #352} 2004 FACT study UK and Republic of Ireland Multicenter (56 general practice centers) Astra Zeneca UK (see p. 42)	Rescue med	Other: PEF < 50% of predicted, asthma symptoms requiring immediate treatment, significant concurrent disease or health problems, or a requirement foradditional medication (e.g. beta-blocker therapy, nebulized therapy, oral steroids or oral short-acting B2-agonists) which may have interfered with the evaluation of the study drug	Yes: run-in period of 7-10 days with patients receiving their regular ICS and short-acting B2-agonists but no study medication.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Everden et al.{Everden, 2004 #352} 2004 FACT study UK and Republic of Ireland Multicenter (56 general practice centers) Astra Zeneca UK (see p. 42)	Intervention: Drug 1: eFM Drug 2: SM Total daily dose: Drug 1: 24 mcg Drug 2: 100 mcg Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: NA Delivery device: Drug 1: Turbohaler Drug 2: Accuhaler Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 79 Drug 2: 76 Mean age (years): Drug 1: 11.7 Drug 2: 11.8 Sex (% female): Drug 1: 37 Drug 2: 50 Current smokers (%): Drug 1: 0 Drug 2: 0 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 21 (26) Drug 2: 12 (15.8) Optional - Withdrew due to lack of efficacy (%): Drug 1: 6.3 Drug 2: 5.3 Adverse events caused withdrawal (%): Drug 1: 5 Drug 2: 1.3

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Everden et al.{Everden, 2004 #352} 2004 FACT study UK and Republic of Ireland Multicenter (56 general practice centers) Astra Zeneca UK (see p. 42)	Intervention: Drug 1 Baseline: eFM Drug 1 Endpoint: eFM Drug 2 Baseline: SM Drug 2 Endpoint: SM Number in group (n): Drug 1- baseline: 79 Drug 1- endpoint: NR Drug 2- baseline: 76 Drug 2- endpoint: NR	Rescue med use during 24 hour period: Drug 1- baseline: 3.69 (2.48) Drug 1-endpoint: change from run-in: -2.45 (2.29) Drug 2-baseline: 4.22 (2.40) Drug 2-endpoint: -2.05 (2.50) P values: Adjusted mean difference (95% CI): -0.70 (-1.37, -0.03); P=0.043 Rescue med use day: Drug 1 -endpoint: change from run-in: -1.85 (1.90) Drug 2 - endpoint: -1.72 (2.02) P value: Adjusted mean difference (95%CI): -0.46 (-0.97, +0.05); P=0.081 Rescue med use at night: Drug 1- baseline: 0.84 (1.06) Drug 1 - endpoint: change from run-in: -0.56 (0.83) Drug 2 - baseline: 0.85 (0.88) Drug 2 - endpoint: -0.39 (0.69) P value: Adjusted mean difference (95%CI): -0.17 (-0.42, +0.09); P=0.251 Asthma exacerbations: D1 base: mild exacerbations (#/patient/12 weeks): D1 end: 7.8 D2 end: 12.2 P: ratio 0.63; P=0.051 Day time symptom control: D1 - base: poorly controlled days (#/patient/12 weeks): D1 - end: 12.4 D2 - end: 17.0 P: ratio 0.73; P=0.107 Nocturnal awakenings: D1 base: nights/week, change from run-in: D1 end: -1.03 (1.96) D2 end: -1.31 (1.94) P: mean txt difference (95%CI): +0.28 (-0.36, +0.92); P=0.632 Other

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Everden et al.{Everden, 2004 #352} 2004 FACT study UK and Republic of Ireland Multicenter (56 general practice centers) Astra Zeneca UK (see p. 42)	Overall adverse events reported (%): Drug 1: 55 Drug 2: 59 Drug 5: P=NR Serious adverse events (%): Drug 1: 1 Drug 2: 1 Headache (%): Drug 1: 18 Drug 2: 22 Upper respiratory tract infection (%): Drug 1: 9 Drug 2: 12 Other (%): Drug 1: asthma aggravation: 10 Drug 2: 13 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: NR	Compliance Compliance (at least 75% of doses of study medication taken) was similar in both groups (eFM: 90% of patients; SM: 88%).	Fair--overall attrition (21%); differential attrition is approx. 10%; open label Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1259	Fabbri et al.{Fabbri, 1993 #1259} 1993 Multicentre (25) Multinational (10 European) Glaxo	Study design: RCT Double-blind Duration:12 months N=274 Enrolled: 274 randomized ITT Analysis: Yes	Age: 12-80 FEV1 expressed as a percent of the predicted value: at least 2 of: PEF during last 7 d of run-in of <=70 pred; 15% reversibility of FEV1 after salbutamol during run in or within 3 months of start of study; >=20% diurnal variation on PEF on at least four of 7 days of run-in period; Reversability of FEV1: among "2 of the following criteria" Previous use of corticosteroids: at least 1000 µg/d of BDP or BUD : meet criteria during run-in Asthma Severity: ModerateSevereNot or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Fabbri et al.{Fabbri, 1993 #1259} 1993 Multicentre (25) Multinational (10 European) Glaxo	other asthma meds continued during run-in		Yes: during the 2 week run in; all patients got 1.5 mg/ day of inhaled BD; if they achieved criteria for randomization during that time, then they entered the double blind part of the study.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Fabbri et al.{Fabbri, 1993 #1259} 1993 Multicentre (25) Multinational (10 European) Glaxo	Interventiom: Drug 1: FP Drug 2: BD Total daily dose: Drug 1: 1500 µg Drug 2: 1500 gu Steroid dosing range (Low, medium or high): Drug 1: high Drug 2: high Delivery device: Drug 1: MDI Drug 2: MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 142 Drug 2: 132 Mean age (years): Drug 1: 17-77 Drug 2: 19-80 Sex (% female): Drug 1: 36% Drug 2: 52% Optional - Race (% white): Drug 1: 96% Drug 2: 98% Current smokers (%): Drug 1: 13% Drug 2: 8% Optional - Disease duration (years): Drug 1: >1 yr:FP 98% v BD 98 %; >10 yr: 49 v 45 % Drug 2: 98% Optional - Previous ICS use (%): Drug 1: 100% Drug 2: 100% Optional - Current use of LABA (%): Drug 1: n/a - pre LABA Drug 2: n/a Current use of ICS at baseline (%): Drug 1: 100% Drug 2: 100% Optional - Current methylxanthine (i.e. theophylline) use (%):	Number (%) withdrawn: Drug 1: 25 (18) Drug 2: 18 (14) Optional - Withdrew due to asthma exacerbations (%): Drug 1: 4 Drug 2: 1 Adverse events caused withdrawal (%): Drug 1: 8 Drug 2: 8

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Fabbri et al.{Fabbri, 1993 #1259} 1993 Multicentre (25) Multinational (10 European) Glaxo	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: BD Drug 2 Endpoint: BD Number in group (n): Drug 1- baseline: 142 Drug 1- endpoint: 142 Drug 2- baseline: 132 Drug 2- endpoint: 132	Rescue med use during 24 hour period: Drug 1- baseline: mean % rescue free days: run-in 20% Drug 1-endpoint: 29% over the 12 weeks Drug 2-baseline: 13% during run-in Drug 2-endpoint: 19% over the 12 weeks P values: NS Asthma exacerbations: D1 base: NA D1 end: total 33 exacerbations reported; 23 (16%) of pts w/ any exacerbation; 3 (2 %) w/ severe exacerbation D2 base: NA D2 end: 62 exacerbations reported; 37 (28%) patients w/ an exacerbation; 13 (10%) of pts had severe exacerbations; D3 baseD3 endP: p < 0.05 for # of patients with exacerbation; p < 0.02 for # of patients with severe exacerbation Day time symptom control: D1 - base: Mean % sx free days during run-in: 19% D1 - end: 38 % over 12 wks D2 - base: 22% D2 - end: 41% over 12 weeks D3 - baseD3 - endP: mean differences NS Night time symptom control: D1 - base: mean % sx free nights: 47% D1 - end: 61% at 12 wks D2 - base: 50% D2 - end: 63% D3 - baseD3 - endP: NS Asthma Control Score: D1 base: collected ashtma sx score, but did not report these data completely, just sx free days and nights, which were not different D1 endD2 baseD2 endD3 baseD3 endP Other Relevant Health Outcome Results: Statistically significantly fewer patients in FP group had exacerbations; but 15 pts,

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Fabbri et al.{Fabbri, 1993 #1259} 1993 Multicentre (25) Multinational (10 European) Glaxo	Overall adverse events reported (%): Drug 1: 70 Drug 2: 73 Serious adverse events (%): Drug 1: 16% Drug 2: 23% Oral candidiasis- thrush (%): Drug 1: 4% Drug 2: 7% Sore throat (%): Drug 1: 5% Drug 2: 2% Headache (%): Drug 1: 4% Drug 2: 5% Upper respiratory tract infection (%): Drug 1: 6% Drug 2: 5% Respiratory infection (%): Drug 1: 15% Drug 2: 11% Hoarseness (%): Drug 1: 6% Drug 2: 3% Other (%): Drug 1: influenza 4% Drug 2: 5% Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: several HPA axis measures, not diff; cortisol values below lower limit of normal: Baseline 19% vs 16%; 12 months 16% vs 17%; NS; Tetracosactrin test (similar to cosyntropin test) done in 35 and 30 patients respectively and all were normal responses.	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
691	Fairfax et al.{Fairfax, 2001 #691} 2001 UK and Ireland Multicenter (30 general practice sites) 3M Pharmaceuticals	Study design: RCT Double-blind Double-dummy Duration: 6 weeks N=172 Enrolled: 234/172/172 ITT Analysis: Yes	Age: 18-65 : taking FP 100-250 mcg daily, displayed signs and symptoms of active disease, at least a 4-week past history of clinically diagnosed asthma and a morning PEFR of 50%-90% of predicted after withholding B2-agonist therapy for 4 hours; otherwise healthy with any concurrent medical condition judged as stable. During last 4 full days of run-in, had to demonstrate mean baseline AM PEFR >50% predicted; reversibility >/=15% above mean baseline AM PEFR value obtained within 30 minutes of inhalation of B2-agonist at the end of clinic visit; one or more specified symptoms of asthma (defined as a sleep disturbance score >1 on at least 1 night, a mean daily use of two or more puffs of B2-agonist as rescue therapy, or a daily asthma score of 2 or more on at least 3 days for either wheeze, cough, shortness of breath, or chest tightness. Asthma Severity: Mild Moderate Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Fairfax et al.{Fairfax, 2001 #691} 2001 UK and Ireland Multicenter (30 general practice sites) 3M Pharmaceuticals	B-2 agonists as needed	Pregnant or lactating: evaluated with an additional significant respiratory disorder; had experienced a clinically significant acute upper or lower respiratory tract infection within past 2 weeks; had visible oral or pharyngeal candidiasis; use of intraarticular, intramuscular or injectable steroids, oral corticosteroids, monoamine xoidase inhibitors, tricyclic antidepressants, B-blockers, SM, or FM during past 4 weeks; known hypersensitivity or idiosyncratic reaction to sympathomimetic drugs or inhaled steroids; history (within 2 years) of alcholol or substance abuse; taking nasal steroid dose >400 mcg/day, or had taken an investigational drug within past 4 weeks	Yes: 5-9 day run-in during which they continued to use the same strength and dose of prescribed steroid inhaler that they had used before the study and asrequired B-agonist therapy

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Fairfax et al.{Fairfax, 2001 #691} 2001 UK and Ireland Multicenter (30 general practice sites) 3M Pharmaceuticals	Intervention: Drug 1: BDP extrafine Drug 2: FP Total daily dose: Drug 1: 400 mcg Drug 2: 400 mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Delivery device: Drug 1: HFA Drug 2: MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 88 Drug 2: 84 Mean age (years): Drug 1: 40.6 Drug 2: 39.5 Sex (% female): Drug 1: 59.1 Drug 2: 60.7 Overall: 60% Optional - Race (% white): Drug 1: NR Drug 2: NR Current smokers (%): Drug 1: 22.7 Drug 2: 26.2 Optional - Disease duration (years): Drug 1: <1 yr/1-5 yrs/>5 yrs (%): 4.5/28.4/67.0 Drug 2: 1.2/25.0/73.8 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100	Number (%) withdrawn: Drug 1: 8 (9.1%) Drug 2: 5 (6.0%) Overall: 13 (7.6%) Optional - Withdrew due to lack of efficacy (%): Drug 1: NR Drug 2: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Fairfax et al.{Fairfax, 2001 #691} 2001 UK and Ireland Multicenter (30 general practice sites) 3M Pharmaceuticals	Intervention: Drug 1 Baseline: BDP Drug 1 Endpoint: BDP Drug 2 Baseline: FP Drug 2 Endpoint: FP Number in group (n): Drug 1- baseline: 88 Drug 1- endpoint: 88 Drug 2- baseline: 84 Drug 2- endpoint: 84	AQLQ - overall: D1 : mean change from baseline +0.47 D2: +0.41 P = 0.002 for equivalence

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Fairfax et al.{Fairfax, 2001 #691} 2001 UK and Ireland Multicenter (30 general practice sites) 3M Pharmaceuticals	Overall adverse events reported (%): Drug 1: 41% Drug 2: 37% Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: Mean (SE) AM plasma cortisol levels at baseline were 432.3 (26.77 nmol/L) for BDP and 423.7 (29.8 nmol/L) for FP. Mean $ changes from baseline in AM plasma cortisol levels at week 6 were +17.7% for BDP and +4.2% for FP (90% CI for difference BDP minus FP of 1.43 to 25.51; P=0.066 for test difference). There was no significant difference between treatment groups with regard to transitions (from/to low, normal, or high relative to the reference range) in plasma cortisol from baseline to week 6 (P=0.998). Additional adverse events and comments: There were no statistically significant differences between groups for any of the individual AE categories or with regard to the incidence of acute asthma episodes or increased asthma symptoms (no data reported). No serious AEs or deaths were reported in either group during study.	Compliance inhalers were weighed initially and on return: considered compliant if the total # of actuations was +/- 40% predicted.; 87.5% patients compliant in BDP group vs 83.3% FP; P NR	Good Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
945	Ferguson et al.{Ferguson, 1999 #945} 1999 Multinational (6 countries: Canada, Denmark, Finland, Netherlands, Indonesia, South Africa) Multicenter GlaxoSmithKline	Study design: RCT Double-blind Double-dummy Duration: 20 weeks N=333 Enrolled: NR/442/333 ITT Analysis: Yes	Ages: 4 to 12 yrs moderate to severe asthma; a Sexual Maturity Rating of 1 (prepubertal); using inhaled b-adrenergic medication for relief of symptoms when necessary and were able to demonstrate ability in using inhalation devices and peak flow meters and in completing diary cards with parental assistance; month preceding the study, none of the subjects had changed the dose of their inhaled or oral medications, and none had been admitted to the hospital for treatment of respiratory illness. Inclusion at the end of the run-in period, (1) daily symptom score of 1 or greater on at least 4 of the last 7 consecutive days before randomization and (2) a mean morning PEF, on 4 of the last 7 consecutive days of the run-in period, that was less than or equal to 85% of the postbronchodilator PEF at the randomization visit or PEF =<85% of predicted value on at least 4 of the last 7 days before randomization or reversibility of 15% or greater of PEF or FEV1 in response to albuterol Asthma Severity: Moderate Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Ferguson et al.{Ferguson, 1999 #945} 1999 Multinational (6 countries: Canada, Denmark, Finland, Netherlands, Indonesia, South Africa) Multicenter GlaxoSmithKline	Concurrent asthma and non-asthma medications were permitted as long as the dose, frequency, and route remained fixed throughout the study.	combination bronchodilators or systemic corticosteroids, had any sign of serious disease other than asthma, or had received any investigational drugs	Yes: 2 week run-in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Ferguson et al.{Ferguson, 1999 #945} 1999 Multinational (6 countries: Canada, Denmark, Finland, Netherlands, Indonesia, South Africa) Multicenter GlaxoSmithKline	Intervention: Drug 1: FP Drug 2: BUD Total daily dose: Drug 1: 400 Drug 2: 800 Steroid dosing range (Low, medium or high): Drug 1: Med Drug 2: Med Delivery device: Drug 1: DPI (Diskus) Drug 2: DPI (Turbuhaler) Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 166 Drug 2: 167 Mean age (years): Drug 1: 8.2 Drug 2: 7.9 Sex (% female): Drug 1: 31.3 Drug 2: 34.7 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Disease duration (years): Drug 1: <1 y 3% 1-5 y 45% 6-10 y 49% >10 y 2% Unknown <1% Drug 2: <1 y 2%1-5 y 57%6-10 y 40%>10 y <1%Unknown <1% Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Other: Drug 1: % atopy 88 Drug 2: 86	Number (%) withdrawn: Drug 1: 15 (9%) Drug 2: 10 (6%) Optional - Protocol violation (%): Drug 1: 15/167 Drug 2: 10/167

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Ferguson et al.{Ferguson, 1999 #945} 1999 Multinational (6 countries: Canada, Denmark, Finland, Netherlands, Indonesia, South Africa) Multicenter GlaxoSmithKline	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: BUD Drug 2 Endpoint: BUD FP vs BUD Number in group (n): Drug 1: 166 Drug 2: 167	Rescue med use day: Drug 1- baseline: see below P value: P = 0.181 Rescue med use at night: Drug 1- baseline: see below P value: P = 0.59 Asthma exacerbations: D1 base: % and number of subjects: D1 end: 1% (2) D2 end: 5% (8) P: NR Day time symptom control: D1 - base: see below P: P = .729 Night time symptom control: D1 - base: see below P: P = 0.34 Other Relevant Health Outcome Results: Actual data NR for the following: no difference in improvement of daytime (P = 0.73) and nighttime (P = 0.34) asthma symptom scores; No difference in albuterol use for daytime (P = 0.181) and nighttime (P = 0.59)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Ferguson et al.{Ferguson, 1999 #945} 1999 Multinational (6 countries: Canada, Denmark, Finland, Netherlands, Indonesia, South Africa) Multicenter GlaxoSmithKline	Serious adverse events (%): Drug 1: 2 Drug 2: 6 Oral candidiasis- thrush (%): Drug 1: 0 Drug 2: 0 Upper respiratory tract infection (%): Drug 1: 28 Drug 2: 32 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: Baseline geometric mean serum cortisol levels were 227.6 ± 63 (SD) nmol/L for FP and 203 ± 74 nmol/L for BUD. The adjusted geometric means at end of treatment were 199 nmol/L and 183 nmol/L, respectively (treatment ratio = 1.09; 90% CI 0.98-1.21; P = .172). Thus in terms of morning serum cortisol levels, there was no difference between the 2 treatment groups From DERP ICS: No difference in serum cortisol levels Additional adverse events and comments: FP who had an adjusted mean increase in height of 2.51 cm compared with 1.89 for those receiving BUD. The difference was 6.2 mm (95% CI 2.9-9.6, P = .0003). The study was not designed to critically assess growth as an outcome factor; measurement of height was done primarily to calculate predicted values for spirometry. To further test the validity of the growth effect, we evaluated a subgroup of 154 children whose heights had been measu Fropm DERP ICS, linear growth velocity was statistically greater for F	Compliance Compliance was calculated as the number of days or nights when each study medication was used, divided by the number of days of recorded data, multiplied by 100. There was no significant difference between treatment groups (P = .977). The compliance rate was almost 100% for both FP and BUD groups.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
670	Fish et al.{Fish, 2001 #670} 2001 Multicenter (71 centers in United States and Puerto Rico) Glaxo Wellcome	Study design: RCT Double-blind Other: 2 randomized trials Duration: 12 weeks N = 948 Number screened: NR, NR, NR ITT Analysis: No another type of analysis was used (define): Inferential analyses	: Male patients and nonpregnant, nonlactating female patients >/= 15 years old, had a diagnosis of asthma for at least 6 months and were symptomatic despite receiving ICS for at least 6 weeks prior to screening, and at a constant dosage for 30 days prior to screening. Patients had a baseline FEV1 of 50 to 80% of predicted after withholding bronchodilator therapy for 6 h and had at least a 12% increase in FEV1 30 min following inhalation of 180 mg of albuterol. After a 7-day to 14-day run-in period to assess symptoms, diary card completion, and patient proficiency with inhaler use, patients whose FEV1 remained within 50 to 80% of predicted normal values were eligible for enrollment. Patients were also required to meet one or more of the following criteria during the 7 days prior to randomization: use of an average of >/=4 puffs per day of albuterol, a symptom score of >/=2 on >/= 3 days, and >/= 3 nights when the patient awakened due to asthma symptoms. Asthma Severity: Moderate Severe Not or poorly controlled Other: symptomatic despite ICS

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Fish et al.{Fish, 2001 #670} 2001 Multicenter (71 centers in United States and Puerto Rico) Glaxo Wellcome	Albuterol inhalers for relief.	Other: Use of all other inhaled or oral bronchodilators, systemic corticosteroids, cromolyn, nedocromil, ipratropium, or LM was prohibited. Concurrent use of theophylline during the study or use of any medication that could potentially interact with sympathomimetic amines or ML was not allowed (ie, b-blockers, polycyclic antidepressants, monoamineoxidase inhibitors, phenobarbital, and rifampin).	Yes: 7-14 day to assess symptoms, diary card completion, and patietn proficiency with inhaler use.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Fish et al.{Fish, 2001 #670} 2001 Multicenter (71 centers in United States and Puerto Rico) Glaxo Wellcome	Intervention: Drug 1: SM Drug 2: ML Total daily dose: Drug 1: 100mcg Drug 2: 10mg Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: NA Delivery device: Drug 1: Diskus DPI Drug 2: tablet Is dosing comparable between treatment groups? NA: baseline ICS appears similar between groups - randomization treatment LABA versus LTRA	# in group (n): Drug 1: 476 Drug 2: 472 Mean age (years): Drug 1: 40 Drug 2: 40 Sex (% female): Drug 1: 61 Drug 2: 62 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 61 (13) Drug 2: 70 (15) Adverse events caused withdrawal (%): Drug 1: 13 (3) Drug 2: 13 (3) Overall: 26 (3)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Fish et al.{Fish, 2001 #670} 2001 Multicenter (71 centers in United States and Puerto Rico) Glaxo Wellcome	Intervention: Drug 1 Baseline: SM Drug 1 Endpoint: SM Drug 2 Baseline: ML Drug 2 Endpoint: ML Number in group (n): Drug 1- baseline: 476 Drug 1- endpoint: 452 Drug 2- baseline: 472 Drug 2- endpoint: 448	Rescue med use during 24 hour period: Drug 1- baseline: # of puffs: 4.37 Drug 1-endpoint: mean change from baseline = -1.9 Drug 2-baseline: 4.66 Drug 2-endpoint: -1.66 P = 0.004 (all comparing change from baseline) Rescue med use day: Drug 1- baseline: 3.62 Drug 1 -endpoint: mean change from baseline = -1.51 Drug 2 - baseline: 3.79 Drug 2 - endpoint: -1.31 P ≤ 0.010 Rescue med use at night: Drug 1- baseline: 0.76 Drug 1 - endpoint: mean change from baseline = -0.39 Drug 2 - baseline: 0.88 Drug 2 - endpoint: -0.35 P ≤ 0.012 Asthma exacerbations: D1 end: 26/476 = 6% of patients D2 end: 23/472 = 5% P = NR Symptom control during 24 hour period: D1 base: % of symptom free days = 8 D1 end: change: 24% greater D2 base: 10 D2 end: 16 P <0.001 Day time symptom control: D1 - base: Wheezing = 1.21 ; shortness of breath = 1.55 ; chest tightness = 1.42 ; all symptoms = 1.4 D1 - end: change from baseline = -0.47 ; -0.59 ; -0.60 ; -0.55 D2 - base: 1.19 ; 1.51 ; 1.34 ; 1.34 D2 - end: change from baseline = -0.37 ; -0.44 ; -0.42 ; -0.41

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Fish et al.{Fish, 2001 #670} 2001 Multicenter (71 centers in United States and Puerto Rico) Glaxo Wellcome	Overall adverse events reported (%): Drug 1: 7 Drug 2: 6 Serious adverse events (%): Drug 1: # 5 Drug 2: # 5 Headache (%): Drug 1: 1 Drug 2: 1 Other (%): Drug 1: insomnia = 1 Drug 2: 0	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
218 Combo	Fitzgerald and Price {#4724} 2005 CONCEPT Trial How do you want this cited? I searched ID#4724 in TrialStat and the date is 2007... -Rachael Multicenter (91) Multinational (15) GlaxoSmithKline	Study design: RCT Double-blind Double-dummy Duration: 52 weeks N=688 (568 completed AQLQ at least once) Enrolled: 905/738/706 ITT Analysis: Yes	Age: 18-70 FEV1 expressed as a percent of the predicted value: 60-90% Previous use of corticosteroids: ICS at a dose equivalent to 200 to 500 µg/d BDP combined with a LABA, or an ICS alone at a dose equivalent to >500 to 1000 µg/d BDP for >12 weeks Asthma severity: Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Fitzgerald and Price {#4724} 2005 CONCEPT Trial How do you want this cited? I searched ID#4724 in TrialStat and the date is 2007... -Rachael Multicenter (91) Multinational (15) GlaxoSmithKline		Prior treatment with: systemic corticosteroids within 1 month Current treatment with....: inhaled cromones, leukotriene modifiers,beta2-agonists (except salbutamol provided as rescuemedication), xanthines, and inhaled anticholinergics. Smoking - current or former: more than 10 pack years Other? (Please list all): lower respiratory tract infectionwithin 1 month changes to regular asthma therapy within 12 weeks of study entry, and any significant disorder that in the investigator's opinion,might put the patient at risk or influence the study	Yes- elucidate....: 2 weeks on ild meds

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Fitzgerald and Price {#4724} 2005 CONCEPT Trial How do you want this cited? I searched ID#4724 in TrialStat and the date is 2007... -Rachael Multicenter (91) Multinational (15) GlaxoSmithKline	Intervention: Drug 1: SM/FP Drug 2: FM/BUD Total daily dose: Drug 1: 50/250 Drug 2: 6/200 Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Delivery device: Drug 1: Diskus Drug 2: Turbuhaler Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 344 Drug 2: 344 Mean age (years): Drug 1: 46 Drug 2: 44 Sex (% female): Drug 1: 59 Drug 2: 63 Optional - Current use of LABA (%): Drug 1: 44 Drug 2: 41 Current use of ICS at baseline (%): Drug 1: 100 (mean 509µg) Drug 2: 100 (mean 515µg) Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 80 (23.2) Drug 2: 93(27) Optional - Withdrew due to lack of efficacy (%): Drug 1: .9 Drug 2: 1.2 Optional - Withdrew due to asthma exacerbations (%): Drug 1: did not meet step down criteria 14.2 Drug 2: 15.1 Adverse events caused withdrawal (%): Drug 1: 1.7 Drug 2: 3.2 Optional - Lost to follow-up (%): Drug 1: 1.2 Drug 2: .6 Optional - Protocol violation (%): Drug 1: 1.2 Drug 2: 2 Optional - Consent withdrawn (%): Drug 1: 3.2 Drug 2: 1.7 Optional - Other reasons for withdrawal (%): Drug 1: .9 Drug 2: 2.6

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Fitzgerald and Price {#4724} 2005 CONCEPT Trial How do you want this cited? I searched ID#4724 in TrialStat and the date is 2007... -Rachael Multicenter (91) Multinational (15) GlaxoSmithKline	Intervention: Drug 1 Baseline Drug 1 Endpoint: SM/FP Drug 2 Baseline Drug 2 Endpoint: FM/BUD Number in group (n): Drug 1- baseline Drug 1- endpoint: 344- 158 (AQLQ) Drug 2- baseline Drug 2-endpoint: 344 - 155(AQLQ)	Rescue med use during 24 hour period: Drug 1t: % free 90.5 use 0.11 Drug 2% free 85.6 use 0.18 Asthma exacerbations: D1 end: 11.3% D2 end: 17.7% AQLQ - overall: D1: mean change from baseline 1.1 D2 : 0.9 Other: D1 : symptom free 58.8% D2: 52.1% Other: D1 Daily symptom score 0.8 D2 : 0.9

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Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Fitzgerald and Price {#4724} 2005 CONCEPT Trial How do you want this cited? I searched ID#4724 in TrialStat and the date is 2007... -Rachael Multicenter (91) Multinational (15) GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 48.6 Drug 2: 53.3 Serious adverse events (%): Drug 1: 0.06% (2 pts) Drug 2: 0.08% (3 pts)	Compliance	Good No

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	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4732	Garbe et al.{Garbe, 1998 #4732} 1998 Canada Elderly population of Quebec contained in the provincial health insurance plan database (RAMQ). Fonds de la Recherche en Sante du Quebec	Study design: Observational Case-control Duration: 6.4 and 6.3 years respectively for case and control. N=3677 cases; 21868 controls = total 25545 Enrolled: 10214; NR; 3677 ITT Analysis: NA	: Registration within the RAMQ database (includes all prescription drugs and medical services for all individuals 65 years and older, 97.3% of this population is registered in the database); at least 5 years of history in the RAMQ database; study represents 10% random sample of this population Asthma Severity: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Garbe et al.{Garbe, 1998 #4732} 1998 Canada Elderly population of Quebec contained in the provincial health insurance plan database (RAMQ). Fonds de la Recherche en Sante du Quebec	NR	NA	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Garbe et al.{Garbe, 1998 #4732} 1998 Canada Elderly population of Quebec contained in the provincial health insurance plan database (RAMQ). Fonds de la Recherche en Sante du Quebec	Intervention: Drug 1: ICS Drug 2: Non-exposed Total daily dose: Drug 1: NR - variable Drug 2: NR Steroid dosing range (Low, medium or high): Drug 1: low to high Drug 2: N/A Delivery device: Drug 1: NR Drug 2: NR Is dosing comparable between treatment groups? Not applicable- ICS versus control	# in group (n): Drug 1: 3677 Drug 2: 21868 Mean age (years): Drug 1: 70-74 = 21%; 75-84 = 41.3%, >/= 85 = 37.8% Drug 2: 70-74 = 36.6%; 75-84 = 37.4%, >/= 85 = 25.9% Overall: CI 1 ; 1.6 - 2 ; 2 -2.5 Sex (% female): Drug 1: 67.4 Drug 2: 57.1 Overall: CI 1.4-1.6 Current smokers (%): Drug 1: NR Drug 2: NR Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 0 Optional - Current use of Cromolyn Sodium (%): Drug 1: >10 physician claims in the year before index date = 74.2% Drug 2: 39.2% Overall: 3.7 - 4.3 Other: Drug 1: DM - treated with oral agents = 11.3%; treated with insulin = 2.9% Drug 2: 8.7% ; 1.6% Overall: 1-1.2 ; 1.1 - 1.7 Other: Drug 1: previous use of ocular	Number (%) withdrawn: Drug 1: NA Drug 2: NA Adverse events caused withdrawal (%): Drug 1: NA Drug 2: NA

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Garbe et al.{Garbe, 1998 #4732} 1998 Canada Elderly population of Quebec contained in the provincial health insurance plan database (RAMQ). Fonds de la Recherche en Sante du Quebec	Intervention: Drug 1: ICS Drug 2: Non-exposed # in group (n): Drug 1: 3677 Drug 2: 21868	See adverse events

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Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Garbe et al.{Garbe, 1998 #4732} 1998 Canada Elderly population of Quebec contained in the provincial health insurance plan database (RAMQ). Fonds de la Recherche en Sante du Quebec	Additional adverse events and comments: Adjusted OR for cataract extraction according to average daily dose and cumulative treatment duration of ICS (reference group is no treatment): < 1 year: Low to Medium dose (< 1000 mcg/day of BDP) 0.94 (95% CI: 0.76 to 1.16); High dose (> 1000 mcg/day of BDP) 0.86 (95% CI: 0.65 to 1.12) 1-2 years: Low to Medium dose (< 1000 mcg/day of BDP) 0.79 (95% CI 0.35 to 1.52); High dose (> 1000 mcg/day of BDP) 0.85 (95% CI: 0.35, 2.08) >2 years: Low to Medium dose (< 1000 mcg/day of BDP) 1.63 (95% CI: 0.85 to 3.13); High dose (> 1000 mcg/day of BDP) 3.40 (95% CI: 1.49 to 7.76) Adjusted OR for cataract extraction according to cumulative treatment duration with oral steroids (reference group is no treatment): Up to 1 year: 1.27 (95% CI: 0.85 to 1.12) 1-3 years: 1.98 (95% CI: 1.44 to 2.71) > 3 years: 2.33 (95% CI: 1.61 to 3.38)	NR	Fair Good

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
194	Garcia et al.{Garcia, 2005 #194} 2005 The MOSAIC Study Multinational (104 sites in 24 countries in Asia, Africa, North America, and South America) Primary Care Merck and Co.	Study design: RCT Double-blind Double-dummy Duration: 12 months N = 994 Number screened: 1432 screened / 994 randomized ITT Analysis: No another type of analysis was used (define): did not include if did not receive at least on dose.	: Male or female between 6 and 14 years of age with clinical history of asthma of >/= 12 months which was mild persistent. FEV1 of >/= 80% of predicted while beta receptor agonist was whithheld for >/= 6 hours at least twice in the run-in period and FEV1 or PEF of >/= 70% of predicted at visit 3. Mild asthma was defined on an increase in FEV1 or PEF rate of >/= 12% after inhaled beta agonist, a positive methacholine or histamie provocation causing a 20% decrease in FEV1 of </=8mg/mL, or a decrease in FEV1 of >/= 15% after an exercise challenge. Had to demonstrate symptoms requiring beat agonist use on >/= 2 and </= 6 days of the week for 2 weeks before visit 3. Good general health for asthma. Asthma Severity: Mild

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Garcia et al.{Garcia, 2005 #194} 2005 The MOSAIC Study Multinational (104 sites in 24 countries in Asia, Africa, North America, and South America) Primary Care Merck and Co.	Beta agoinst alone or a controlled medication and a short acting beta againsnt. Immunotherapy at a stable dose if it had been initiated 3 months before the study. Systemic corticosteroids for resuce or if asthma symtoms were not controlled adequatley, any other controller medication at the investigator's discretion.	Other: Use of systemic cortiocsteroids (except as specified in asthma action plan), intravenously gamma gloculin or immunosuppressants within 1 month of visit 1; combination medication containing theophylline/aminophylline/caffeine or a beta againsnt (except as specified in asthma action plan); beta blocking agents; aspirin or NSAIDS for sensitive individuals for 2 weeks before visit 1; antiasthma medications for >7 days after visit 1 or antibiotics for > 7 consecutive days in the 4 weeks before visit 1 or duing the placebo run-in period.	Yes: 4 week, single-blind, placebo run in were patients discontinued any asthma controller medicationand received image-matching, single-blind, ML and FP and an open-label, short acting beta agonist as needed. Those meeting inclusion criteria would be randomized.

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Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Garcia et al.{Garcia, 2005 #194} 2005 The MOSAIC Study Multinational (104 sites in 24 countries in Asia, Africa, North America, and South America) Primary Care Merck and Co.	Intervention: Drug 1: ML Drug 2: FP Total daily dose: Drug 1: 5mg Drug 2: 200mcg Steroid dosing range (Low, medium or high): Drug 1: N/A Drug 2: medium Delivery device: Drug 1: tablet Drug 2: MDI Is dosing comparable between treatment groups? NA: non-steroid vs steroid	# in group (n): Drug 1: 495 Drug 2: 499 Overall: 994 Mean age (years): Drug 1: 9 Drug 2: 9 Sex (% female): Drug 1: 35 Drug 2: 42 Optional - Race (% white): Drug 1: 64 Drug 2: 64 Optional - Rescue medication use (puffs per day): Drug 1: 0.7 Drug 2: 0.7 (n=495 patients) Optional - % of rescue free days: Drug 1: n=494 ; 64 Drug 2: n=495 ; 64 Other: Drug 1: weight (kg) n=493; 33 Drug 2: n=499; 33 Other: Drug 1: height (cm); 136 Drug 2: 135 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 36 (7) Drug 2: 33 (7) Overall: 69 (7) Optional - Withdrew due to lack of efficacy (%): Drug 1: 0.4 Drug 2: 0.2 Optional - Withdrew due to asthma exacerbations (%): Drug 1: 0 Drug 2: 0 Adverse events caused withdrawal (%): Drug 1: 1 Drug 2: 0.2 Optional - Lost to follow-up (%): Drug 1: 1 Drug 2: 1 Optional - Protocol violation (%): Drug 1: 2 Drug 2: 3 Optional - Consent withdrawn (%): Drug 1: 2 Drug 2: 1 Optional - Other reasons for withdrawal (%): Drug 1: 0.5 Drug 2: 1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Garcia et al.{Garcia, 2005 #194} 2005 The MOSAIC Study Multinational (104 sites in 24 countries in Asia, Africa, North America, and South America) Primary Care Merck and Co.	Intervention: Drug 1 Baseline: ML Drug 1 Endpoint: ML Drug 2 Baseline: FP Drug 2 Endpoint: FP Number in group (n): Drug 1- baseline: 495 Drug 1- endpoint: varied Drug 2- baseline: 499 Drug 2- endpoint: varied	Rescue med use during 24 hour period: Drug 1-endpoint: all change from baseline (%); n=439; -22.7 Drug 2-endpoint: n=442; -25.4 P values = 0.003 Asthma exacerbations: D1 end: 32.2% D2 end: 25.6% Relative Risk 1.26 CI (1.04 to 1.52) favoring FP Missed days of school: D1 end: parents lost >/= 1 day of work = 2.9% (n-13); lost > 3 days 0.4% D2 end: 2.0% (n=9); 0.2% P = NR Courses of steroids: D1 end: n=482; 17.8% D2 end: n=484; 10.5% P: </=0.001 Other Asthma QOL instrument: D1 end: Pediatric AQLQ: change from baseline in overall score; n=263; 0.92 D2 end: n=278; 1.05 P = 0.036 Asthma Control Score: D1 base: control domain of the Pediatric Asthma Therapy Assessment Questionnaire; 1.8 D1 end: 0.7 D2 base: 1.7 D2 end: 0.4 Difference in least squares was 0.2 (CI 0.1 to 0.4) favoring FP Other: D1 end : all change from baseline % Rescue Free Days; n=482; 22.4 D2 end: n=484; 25.2 CI (-4.7% to -0.9%) Other:

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Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Garcia et al.{Garcia, 2005 #194} 2005 The MOSAIC Study Multinational (104 sites in 24 countries in Asia, Africa, North America, and South America) Primary Care Merck and Co.	Overall adverse events reported (%): Drug 1: 22 (4.4%) Drug 2: 16 (3.2%) Serious adverse events (%): Drug 1: 0 Drug 2: 0 Growth: Drug 1: 6.18cm/year Drug 2: 5.81cm/year P = 0.018 Headache (%): Drug 1: 2.2 Drug 2: 1 Other (%): Drug 1: asthma 0.6 Drug 2: 0.4	Compliance similar in 2 groups. average % of says fully compliant for ML were 97.8% and 98.1% for placebo and active arms and for FP were 97.5% and 98% for placebo and active arms.	Fair: variable numbers of patients included in analyses for our variables of interest Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1230	Greening et al.{Greening, 1994 #1230} 1994 REFID # 1186 (Hyland 1995) abstracted with this UK General practice Centers (99) Allen & Hanburys Limited UK Study Group	Study design: RCT Double-blind Double-dummy Duration: 21 weeks N=429 Enrolled: NR/NR/429 ITT Analysis: Yes	: aged 18 years and over with symptomatic asthma completed the baseline period and were randomly assigned study treatment; reversibility of at least 15% of PEF or FEV1 to an inhaled beta2-agonist, period variation in PEF (over 1 week) of at least 15%(highest evening PEF minus lowest morning PEF as a percentage of the highest value), FEV, of at least 50% of predicted normal, symptoms on at least 4 of 7 days during the second baseline week, and no courses of oral corticosteroids during the previous 6 weeks or more than four short courses during the past year. Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Greening et al.{Greening, 1994 #1230} 1994 REFID # 1186 (Hyland 1995) abstracted with this UK General practice Centers (99) Allen & Hanburys Limited UK Study Group		Other: maintenance oral corticosteroids, received a short course of oral steroids in the 6 weeks before the start of the study, or > 4 short courses over the past year, FEV 1 < 50% predicted, and those who had changed asthma therapy in the 6 weeks prior to the start of the study	Yes: 2 weeks, patients took BDP 200ug BID and salbutamol prn

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Greening et al.{Greening, 1994 #1230} 1994 REFID # 1186 (Hyland 1995) abstracted with this UK General practice Centers (99) Allen & Hanburys Limited UK Study Group	Intervention: Drug 1: SM/BDP Drug 2: BDP Total daily dose: Drug 1: 100/400 Drug 2: 1000 Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: high Delivery device: Drug 1: Dikhaler Drug 2: Diskhaler Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 220 Drug 2: 206 Mean age (years): Drug 1: 48 Drug 2: 47 Sex (% female): Drug 1: 54 Drug 2: 59 Current smokers (%): Drug 1: 27 Drug 2: 26 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 71 (32%) did not complete 6 months Drug 2: 65 (32%) Adverse events caused withdrawal (%): Drug 1: 8 Drug 2: 11

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Greening et al.{Greening, 1994 #1230} 1994 REFID # 1186 (Hyland 1995) abstracted with this UK General practice Centers (99) Allen & Hanburys Limited UK Study Group	Intervention: Drug 1 Baseline: SM/BDP Drug 1 Endpoint: SM/BDP Drug 2 Baseline: BDP Drug 2 Endpoint: BDP Number in group (n): Drug 1- baseline: 220 Drug 2- baseline: 206	Rescue med use day: Drug 1- baseline: mean use of relief med daytime: 3.0 Drug 1 -endpoint: week 21: 2.1 Drug 2 - baseline: 3.3 Drug 2 - endpoint: 2.4 P value: 0.553 Rescue med use at night: Drug 1- baseline: mean use of relief med: 0.7 Drug 1 - endpoint: week 21: 0.4 Drug 2 - baseline: 0.6 Drug 2 - endpoint: 0.5 P =0.086 Asthma exacerbations: D1 base: See below for more. Rate per patient per 28 days: D1 end: 0.21 D2 end: 0.29 P=0.42 Symptom control during 24 hour period: D1 base: symptom incidence (from QOL diary)= proportion of when a symptom was reported: 1.00 D1 end: 0.52 (change -0.35) D2 base: 0.86 D2 end: 0.53 (change -0.26) P: NS Day time symptom control: D1 - base: dAYTIME ASTHMA SYMPTOMS 87% D1 - end: at week 21: 56% D2 - base: 87% D2 - end: 61% P = NS Nocturnal awakenings: D1 base: night wakings (from QOL diary): proportion of nights: 0.50 D1 end: 0.24 (change -0.20) D2 base: 0.43

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Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Greening et al.{Greening, 1994 #1230} 1994 REFID # 1186 (Hyland 1995) abstracted with this UK General practice Centers (99) Allen & Hanburys Limited UK Study Group	Serious adverse events (%): Drug 1: non-respiratory serious AEs: 3 Drug 2: 1.5	Compliance Patients were 90% or more compliant. no differences between groups	Fair Fair No

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	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4733	Gross et al.{Gross, 1998 #4733} 1998 United States Multicenter (24 respiratory care or allergy University Clinics) GlaxoSmithKline	Study design: RCT Double-blind Double-dummy Duration:24 weeks N=304 Enrolled: 386 screened, 304 eligible and randomized ITT Analysis: Yes	: at least 12 years old with asthma, required BDP or TAA for at least 4 weeks before the study, FEV1 50-80% of predicted normal values, reversibility of airway obstruction by 15% or greater increase in FEV1 within 15 minutes after 2-4 ufs of albuterol, at least one documented urgent or emergent care visit or home treatment for asthma within the 12 months before screening. After run-in had to meet: asthma stability defined as fewer than 4 days usage of mroe than 12 puffs/day of PRN albuterol, four or fewer mornings when the morning PEF decreased more than 20% from the previous evening's PEF, three or fewer nights with awakenings because of asthma requiring inhaled albuterl; FEV1 between 50-80% of predicted values and within 15% of screening FEV1 and adequate compliance. Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Gross et al.{Gross, 1998 #4733} 1998 United States Multicenter (24 respiratory care or allergy University Clinics) GlaxoSmithKline		prenancy or lactiation; use of methotrexate or gold salts; use of inhaled cromolyn dosium or inhaled nedocromil; use of oral, intranasal, or injectable corticosteroids within 4 weeks; significant concomitant illness; immunotherapy requiring a change in dosage regimen within 12 weeks, concurrent use of any other prescription or OTC medication that might affect the course of asthma or interact with sympathomimetic amines. Post-randomization exclusion: lack of treatment efficacy if they met: clinical exacerbation requiring emergency treatmetn, hospitalization, or asthma medication not allowed by protocol, 20% decrease from the predose FEV1 at randomiazation, 20% decrease from mean moring baseline PEF on more than 3 of 7 days before visit, more than 12 albuterol puffs per day on more than 3 of 7 days before visit, mor ethan 3 nighttime awakenings because of asthma symptoms that required albuterol during the week before a visit.	Yes: 3 week screening period were each patient continued their usual inhaled corticosteroid dosage regimens and in addition received placebo FPpowder via inhalation

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Gross et al.{Gross, 1998 #4733} 1998 United States Multicenter (24 respiratory care or allergy University Clinics) GlaxoSmithKline	Intervention: Drug 1: placebo Drug 2: TAA Drug 3: FP Total daily dose: Drug 2: 800 mcg Drug 3: 500 mcg Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: medium Drug 3: medium Delivery device: Drug 1: oral inhaler and Diskhaler Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 103 Drug 2: 101 Drug 3: 100 Mean age (years): Drug 1: 38 (13-84) Drug 2: 38 (12-81) Drug 3: 38 (13-77) Sex (% female): Drug 1: 42 Drug 2: 45 Drug 3: 49 Optional - Race (% white): Drug 1: 92 Drug 2: 92 Drug 3: 91 Current smokers (%): Drug 1: tobacco use: 25 Drug 2: 35 Drug 3: 35 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100	Number (%) withdrawn: Drug 1: 79 Drug 2: 49 Drug 3: 33 Optional - Withdrew due to lack of efficacy (%): Drug 1: 65 Drug 2: 33 Drug 3: 17 Optional - Withdrew due to asthma exacerbations (%): Drug 1: (Part of lack of efficacy) 20 Drug 2: 13 Drug 3: 9 Adverse events caused withdrawal (%): Drug 1: 9 Drug 2: 7 Drug 3: 9 Optional - Other reasons for withdrawal (%): Drug 1: 15 Drug 2: 15 Drug 3: 10

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Gross et al.{Gross, 1998 #4733} 1998 United States Multicenter (24 respiratory care or allergy University Clinics) GlaxoSmithKline	Intervention: Drug 1: placebo Drug 2: TAA Drug 3: FP Number in group (n): Drug 1: 103 Drug 2: 101 Drug 3: 100	Rescue med use during 24 hour period: Drug 1: mean puffs/d: baseline: 3.3/change from baseline 1.9 Drug 2: 3.2/0.6 Drug 3 3.2/-0.6 P < 0.018 versus placebo for both; P < 0.016 for FP versus TAA for change from baseline Nocturnal awakenings: D1 : mean per week; baseline/change from baseline: 0.10/0.26 D2: 0.09(0.02)/0.11 D3: 0.09/-0.04 P < 0.018 versus placebo for both; P <0.016 for FP versus TAA AQLQ - overall: D1 : mean increase in global score: -0.5 D2: 0.0 D3: 0.4 P < 0.001versus baseline for placebo; P = 0.802 versus baseline for TAA; P < 0.001 (versus baseline for FP and versus placebo and P < 0.007 versus TAA) Other: D1 : mean asthma symptom score (0-9): baselin/change = 1.6/0.8 D2 : 1.7/-0.1 D3: 1.7-0.3 P < 0.018 versus placebo for both; NS TAA vs FP Other: D1 : mean % symptom free days; baselin/change = 30/-10 D2 : 32/5 D3: 23/18 P < 0.018 versus placebo for both; NS for TAA vs FP Other: D1 : mean % symptom free days; baselin/change = 30/-10 D2 : 32/5 D3: 23/18 P <0.018 versus placebo for both; NS for TAA vs FP Other:

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Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Gross et al.{Gross, 1998 #4733} 1998 United States Multicenter (24 respiratory care or allergy University Clinics) GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 5 Drug 2: 5 Drug 3: 20 P < 0.001 for FP vs. placebo and TAA Serious adverse events (%): Drug 1: 2.9 Drug 2: 1 Drug 3: 1 Oral candidiasis- thrush (%): Drug 1: 0 Drug 2: 0 Drug 3: 5 Sore throat (%): Drug 1: 2 Drug 2: 2 Drug 3: 3 Headache (%): Drug 1: 2 Drug 2: 1 Drug 3: 1 Hoarseness (%): Drug 1: 0 Drug 2: 0 Drug 3: 3 Other: Drug 1: migraine = 0 Drug 2: 0 Drug 3: 2 The number of patietns with post-randomization morning cortisol concentrations of less than 5 mcgdl were 1 (1%), 2 (2%), and 2 (2%) for the placebo, TAA, and FP respectively.	NR	Fair Fair No

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	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1258	Gustafsson et al.{Gustafsson, 1993 #1258} 1993 Multinational Multicenter GlaxoSmithKline	Study design: RCT Double-blind Duration: 6 weeks N=398 Enrolled: NR	: ages 4 to 19 yrs; childhood asthma being treated with up to 400 µg of cocorticosteroid or were inadequetley controlled on other trmt; During run-in, had to have night time sx on at least 1 of 7 days, or ashtma sx at least 3 out of 7 days, or PEFR less than 80% pred, or more than 15% reversibility of FEV1 after salbutamol. Asthma Severity: Moderate Controlled Not or poorly controlled

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Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Gustafsson et al.{Gustafsson, 1993 #1258} 1993 Multinational Multicenter GlaxoSmithKline		Change in meds in last month; in hospital for asthma , taken oral corticosteroids in last month; lower respiratory tract infection in last 14 days; asthma became unstable during run-in	Yes: 2 week

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Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Gustafsson et al.{Gustafsson, 1993 #1258} 1993 Multinational Multicenter GlaxoSmithKline	Intervention: Drug 1: FP Drug 2: BDP Total daily dose: Drug 1: 200 Drug 2: 400 Delivery device: Drug 1: Pressurized inhaler Drug 2: Pressurized inhaler Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 197 Drug 2: 201 Mean age (years): Drug 1: 10 Drug 2: 11 Sex (% female): Drug 1: 44 Drug 2: 43 Current smokers (%): Drug 1: 0 I hope Drug 2: 0 Current use of ICS at baseline (%): Drug 1: 72 Drug 2: 62	Number (%) withdrawn: Drug 1: 4 (2) Drug 2: 5 (2) Optional - Withdrew due to asthma exacerbations (%): Adverse events caused withdrawal (%): Drug 1: 0 Drug 2: 0

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Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Gustafsson et al.{Gustafsson, 1993 #1258} 1993 Multinational Multicenter GlaxoSmithKline	Intervention: Drug 1: FP Drug 2: BDP Number in group (n): Drug 1: 197 Drug 2: 201	Day time symptom control: D1: at week 6, daytime sx the same or better 83% D2: 81% P: NS Night time symptom control: D1 : at week 6, % that showed the same or better night time sx 83% D2: 82% P: NS Other Relevant Health Outcome Results: • No difference in % with symptom free days or nights • % with symptom-free exercise: FP 87%, BDP 81% (P = 0.04)"scores stratified by region" (not sure if this is the same as "adjusted according to country" which is what they say in the analysis section) • No difference in changes in median day, night, or exercise symptom scores • Increase in % of rescue beta-2 agonist free days: FP 87%, BDP 80% (P = 0.01) • Use of rescue medication per day: patients that showed an improvement over baseline FP 87%, BDP 84% (P = 0.04)*

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Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Gustafsson et al.{Gustafsson, 1993 #1258} 1993 Multinational Multicenter GlaxoSmithKline	Oral candidiasis- thrush (%): Drug 1: 0 Drug 2: 1 Sore throat (%): Drug 1: 8 Drug 2: <1 P < 0.001 Upper respiratory tract infection (%): Drug 1: 15 Drug 2: 16 Rhinitis (%): Drug 1: 5 Drug 2: 6 Hoarseness (%): Drug 1: 1 Drug 2: <1 Other (%): Drug 1: Asthma and related events 9 Drug 2: 11 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: Low cortisol FP vs. BDP baseline 10% vs 6% after trmt 9% and 4%	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
870	Heinig et al.{Heinig, 1999 #870} 1999 Multinational (Belgium, Canada, Denmark, the Netherlands) Multicenter (47) GlaxoSmithKline	Study design: RCT Double-blind Double-dummy Duration: 24 weeks N=395 Enrolled: 548/nr/395 ITT Analysis: Yes	Age: 18-75 Reversability of FEV1: 15% or more Previous use of corticosteroids: BDP, BUD or FP Duration of condition: history of reversible airways disease in the previous 12 months Other: After the run-in, patients were allocated to study treatment if there was demonstrable reversible airways disease; their mean morning PEF during the last 7 days ofthe run-in period was <85% of the post-salbutamolchallenge PEF; the mean daytime symptom score was 22on at least 7 days during the run-in period; and theinvestigator was satisfied that the patient was able to usethe Diskhaler@ and Turbuhalera correctly. Asthma Severity: Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Heinig et al.{Heinig, 1999 #870} 1999 Multinational (Belgium, Canada, Denmark, the Netherlands) Multicenter (47) GlaxoSmithKline	methylxanthines, anticholinergics, nedochromil, sodium cromoglycate, ketotifen and long-acting P-agonists on the understanding that the dose remained unchanged during the study. Intranasal corticosteroids anti-fungal lozenges for the treatment of oropharyngeal candidiasis.	Pregnant or lactating: Patients with serious uncontrolled systemic disease (including bonedisease) at the start of the run-in period, and patientswho had required treatment with oral steroids or werebeing treated with research medication within 1 month ofthe start of the run-in period, were not considered eligible.	Yes

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Heinig et al.{Heinig, 1999 #870} 1999 Multinational (Belgium, Canada, Denmark, the Netherlands) Multicenter (47) GlaxoSmithKline	Intervention: Drug 1: FP Drug 2: BUD Total daily dose: Drug 1: 2000 Drug 2: 2000 Steroid dosing range (Low, medium or high): Drug 1: High Drug 2: High Delivery device: Drug 1: Diskhaler (DPI) Drug 2: Turbuhaler (DPI) Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 198 Drug 2: 197 Mean age (years): Drug 1: 49 Drug 2: 47 Sex (% female): Drug 1: 50 Drug 2: 49 Optional - Race (% white): Drug 1: 97 Drug 2: 96 Current smokers (%): Drug 1: 12 Drug 2: 18 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100	Number (%) withdrawn: Drug 1: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Heinig et al.{Heinig, 1999 #870} 1999 Multinational (Belgium, Canada, Denmark, the Netherlands) Multicenter (47) GlaxoSmithKline	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: BUD Drug 2 Endpoint: BUD Number in group (n): Drug 1: 198 Drug 2: 197	Asthma exacerbations: % of patients D1 end: 33.8 D2 end: 28.4 P = NS Symptom control during 24 hour period: mean % of symptom free days D1 end: 31.5 D2 end: 22.8 P = 0.02 Missed days of work: D1 end: 4.2 D2 end: 7.6 P = 0.012 Other: mean % of rescue free days: D1 end : 42.7 D2 end: 33.7 P = 0.02 Other: % of patients remaining exacerbation free after 180 days: D1 end : 60 D2 end: 68 P = NS

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Heinig et al.{Heinig, 1999 #870} 1999 Multinational (Belgium, Canada, Denmark, the Netherlands) Multicenter (47) GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 78% Drug 2: 77% Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: The pre-treatment serum cortisol levels for FP and BUD were 356.7 (SD 192.3) and 380.5 (SD 231.7) nmol 1-l respectively, and these decreased over the treatment period by 16.7% for patients receiving FP and by 13.9% for those receiving BUD (P = 0.43). After 24 weeks of treatment the mean cortisol levels were 285.5 (SD 189.4) and 315.0 (SD 184.3) mmol 1-l with FP and BUD, respectively.	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1123	Hoekx et al.{Hoekx, 1996 #1123} 1996 Multinational (4) Multicenter (22) NR: 2 of authors are Glaxo employees	Study design: RCT Double-blind Double-dummy Duration: 8 weeks N=229 Enrolled: 285 recruited; 229 randomized ITT Analysis: Unable to determine: not enough detail reported to determine (8 post-randomization exclusions and not explained if ITT or how these were handled in analysis)	Age: prepubescent patients Reversability of FEV1: see other Days with asthma symptoms: see other Previous use of corticosteroids: 100% Other: Outpatient children using 200-400 mcg/d of ICS and using B-agonist therapy as required; meet at least 2 of the following criteria during run-in: 1) daytime or night-time symptoms on 4 out of 7 days; 2) wakening during the night or early morning on 1 or more occasions; 3) PEFR <= 75% predicted on 4 of 7 days; 4) at least 15% reversibility in FEV1 or PEFR in response to B-agonist therapy. Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Hoekx et al.{Hoekx, 1996 #1123} 1996 Multinational (4) Multicenter (22) NR: 2 of authors are Glaxo employees		Prior treatment with: oral or parenteral steroids prior 3 months; any investigational drug within prior 1 month : unable to use the delivery devices; unable to use the mini-Wright peak flow meter with our w/o parental help; if they suffered infection, seasonal allergy, or any other disease likely to affect their asthma during the trial; known or suspected hypersensitivity to corticosteroids. Asthma Severity: Mild Moderate	Yes: 2 week run-in preceeded randomization. During run-in, patients were required to meet 2/4 of the inclusion criteria listed above.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Hoekx et al.{Hoekx, 1996 #1123} 1996 Multinational (4) Multicenter (22) NR: 2 of authors are Glaxo employees	Intervention: Drug 1: FP Drug 2: BUD Overall: Total (both groups) Total daily dose: Drug 1: 400 mcg Drug 2: 400mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: low Delivery device: Drug 1: Diskhaler (DPI) Drug 2: Turbuhaler (DPI) Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 119 Drug 2: 110 Mean age (years): Drug 1: NR, range 5-13 Drug 2: NR, range 4-12 Sex (% female): Drug 1: 32 Drug 2: 32 Optional - Disease duration (years): Drug 1: 3% <1yr; 63% 1-5yr; 33% 6-10 yr; <1% >10yr Drug 2: 2% <1yr; 55% 1-5yr; 38% 6-10 yr; 5% >10yr Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Optional - Current use of LABA (%): Drug 1: 2 Drug 2: <1 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Optional - Current methylxanthine (i.e. theophylline) use (%): Drug 1: 3 Drug 2: <1 Optional - Current use of Cromolyn Sodium (%): Drug 1: 8 Drug 2: 13	Number (%) withdrawn: Drug 1: NR Drug 2: NR Overall: 8 (3.5%) Adverse events caused withdrawal (%): Drug 1: 2 (1.7%) Drug 2: 3 (2.7%) overall: 5 (2.2%) Optional - Other reasons for withdrawal (%): Drug 1: authors report that 3 patients withdrew due to not meeting study entry criteria, though they do not specific which treatment groups these came from. overall: 3 (1.3%) did not meet study entry criteria

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Hoekx et al.{Hoekx, 1996 #1123} 1996 Multinational (4) Multicenter (22) NR: 2 of authors are Glaxo employees	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FLU Drug 2 Baseline: BUD Drug 2 Endpoint: BUD Number in group (n): Drug 1- baseline: 119 Drug 2- baseline: 110	Rescue med use day: Drug 1- baseline: median % rescue free days: 0 Drug 1 -endpoint: 43 (over weeks 1-8) Drug 2 - baseline: 0 Drug 2 - endpoint: 44 (over weeks 1-8) P value: NR Symptom control during 24 hour period: D1 base: symptom free days and nigts: difference between groups NS (numbers NR) Missed days of school: D1 base: NS difference between groups (numbers NR) Missed days of work: D1 base: for parents: NS difference between groups (numbers NR) Nocturnal awakenings: D1 base: sleep distubance (NS difference between groups; numbers NR) Other Relevant Health Outcome Results: no statistically significant difference in % of symptom free days and nights, % of days with normal activity, mean symptom or activity scores, % of rescue medication free days. Parent report of impact of asthma: no difference in sleep or days of missed school or parental work. FLU group had significantly less disruption in physical activities after 8 weeks as compared to BUD group (p=0.03) [In the past 2 months, how often has you child been prevented from doing or had to stop doing certain activities b/c of his/her asthma? FLU group 4% often, 24 some

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Hoekx et al.{Hoekx, 1996 #1123} 1996 Multinational (4) Multicenter (22) NR: 2 of authors are Glaxo employees	Overall adverse events reported (%): Drug 1: 63 Drug 2: 69 Serious adverse events (%): Drug 1: 0.8 (n=1) Drug 2: 0.9 (n=1) Oral candidiasis- thrush (%): Drug 1: 3 Drug 2: <1 Cough (%): Drug 1: 6 Drug 2: 4 Sore throat (%): Drug 1: 4 Drug 2: 5 Headache (%): Drug 1: 3 Drug 2: 7 Upper respiratory tract infection (%): Drug 1: 12 Drug 2: 15 Rhinitis (%): Drug 1: 11 Drug 2: 12 Hoarseness (%): Drug 1: 0 Drug 2: 4 Other (%): Drug 1: asthma and related events: 24 Drug 2: 25 Other (%): Drug 1: eye disorders: 13 Drug 2: 9 Other (%): Drug 1: allergic skin reaction: <1 Drug 2: 5	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
340 5106	Holgate et al.{Holgate, 2004 #340} 2004 + unpublished data (FDA) Multinational Multicenter Novartis Pharma AG, Basel, Switzerland and Genentech, South San Francisco, CA	Study design: RCT, DB Duration: 32 wks (16 weeks add-on after FP optimization followed by 16 weeks of FP reduction) N = 246	Patients age 12-75; required high dose FP (between 1000 and 2000 mcg/day) for symptom control stabalized 4 wks prior to randomization; demonstrated positive SPTs to aeroallergen(s); had serum total IgE 30–700 IU/mL Asthma Severity: Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Holgate et al.{Holgate, 2004 #340} 2004 + unpublished data (FDA) Multinational Multicenter Novartis Pharma AG, Basel, Switzerland and Genentech, South San Francisco, CA	Short-acting B2-agonists were allowed as needed, along with continued use of long-acting B2-agonists.	Patients taking theophylline or anti-leukotrienes, or with a history of anaphylaxis, recent near-fatal asthma, respiratory infection within 4 weeks of the study, parasitic infection or an elevated serum total IgE for reasons other than atopy	Yes; 6–10-week run-in period, during which all patients underwent inhaled fluticasone optimization

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Holgate et al.{Holgate, 2004 #340} 2004 + unpublished data (FDA) Multinational Multicenter Novartis Pharma AG, Basel, Switzerland and Genentech, South San Francisco, CA	Intervention: Drug 1: OM 0.016 mg/kg IgE IU/mL per 4 weeks SQ n=126 Drug 2: Placebo NA n=120	Age: Drug 1: OM 41.1 Drug 2: Placebo 40.5 Sex (% female): Drug 1: OM 64.3 Drug 2: Placebo 57.5 Current smokers (%) 0 ICS use at baseline (%): Drug 1: OM 100 Drug 2: Placebo 100	Withdrawals: Drug 1: OM 9 (8.7%) Drug 2: Placebo 11 (9.2%) Withdrawals due to AEs (%): Drug 1: OM 0 Drug 2: Placebo 1.7

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Holgate et al.{Holgate, 2004 #340} 2004 + unpublished data (FDA) Multinational Multicenter Novartis Pharma AG, Basel, Switzerland and Genentech, South San Francisco, CA	Intervention: Drug 1: OM Drog 2: Placebo Number in group (n): Drug 1: 126 Drug 2: 120	• Symptoms: OM led to improvements in symptoms scores over both the stable steroid and stable reduction phases (data NR; P < 0.05 at weeks 16 and 32) • Exacerbations: OM patients had lower mean number of exacerbations per patient during stable steroid phase (weeks 1-16): 0.15 vs. 0.23 (P = 0.57) and during steroid reduction phase: 0.19 vs. 0.34 (P = 0.15) • Rescue med use: OM led to improvements in rescue med use over both phases of study (data NR; P < 0.05 at week 16; P < 0.01 at week 32) • QoL: Overall, 58% of OM patients vs. 39% of placebo patients had a clinically detectable improvement in asthma-related QoL (P<0.01); 16% had a large improvement compared to 6%with placebo (P<0.05). These differences were also reflected in various QoL domain scores • Mean change in score ≥ 0.5 and ≥ 1.5 taken to represent clinically detectable and large differences in asthma related QoL respectively. • Change in overall AQLQ score (0.52 vs. 0.28) at 16 weeks • Change in overall AQLQ score (0.68 vs. 0.26) at 32 weeks •Adherence: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Holgate et al.{Holgate, 2004 #340} 2004 + unpublished data (FDA) Multinational Multicenter Novartis Pharma AG, Basel, Switzerland and Genentech, South San Francisco, CA	Overall OM 76.2% Placebo 82.5% Serious OM <1% Placebo 4.2% Severe OM 6.3% Placebo 18.3% Injection site reaction OM 20.4% Placebo 10.3% Urticaria OM <1% Placebo 2.5%	NR	Good

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
254	Humbert et al.{Humbert, 2005 #254} 2005 INNOVATE Multinational Multicenter (hospital clinics) NR (1 author employed by Novartis)	Study design: RCT Duration: 28 wks N: 482	Patients aged 12-75; severe persistent allergic asthma; positive skin prick test to >1 perennial aeroallergen, severe persistent asthma requiring regular treatment with >1000 mcg/day BDP or equivalent and LABA; FEV1 > 40 to <80% of predicted normal value and continuing asthma symptoms; FEV1 reversibility >12% from baseline within 30 min of inhaled (up to 400 mcg) or nebulized (up to 5 mg) salbutamol; despite high-dose ICS and LABA use at least two asthma exacerbations requiring systemic corticosteroids, or one severe exacerbation resulting in hospitalization or ER treatment in past 12 months. Asthma Severity: Severe or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Humbert et al.{Humbert, 2005 #254} 2005 INNOVATE Multinational Multicenter (hospital clinics) NR (1 author employed by Novartis)	Additional asthma medications, taken regularly from >4 weeks prior to randomization, including theophyllines, oral b2-agonists and antileukotrienes. Maintenance oral corticosteroids (maximum 20 mg/d) were permitted providing at least one of the exacerbations in the previous 12 months had occurred while on this therapy. SABA rescue medication permitted as required.	Smokers or smoking history of >10 pack-years; treatment for an exacerbation within 4 weeks of randomization (the run-in could be extended if necessary); use of methotrexate, gold salts, troleandomycin or cyclosporin within 3 months of the first visit; prior OM treatment.	8 week run-in; during the first 4 weeks of the run-in period, each subject's asthma management was reviewed to include advice on allergen avoidance, theophylline monitoring if applicable and inhaler technique. Asthma medication could be adjusted to achieve the best control, but no further adjustments were permitted in the last 4 weeks of the run-in prior to randomization.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Humbert et al.{Humbert, 2005 #254} 2005 INNOVATE Multinational Multicenter (hospital clinics) NR (1 author employed by Novartis)	Intervention: Drug 1: OM 0.016 mg/kg IgE IU/mL per 4 weeks SQ n=209 Drug 2: Placebo NA n=210	Age: Drug 1: OM 43.4 Drug 2: Placebo 43.3 Sex (% female): Drug 1: OM 67.5 Drug 2: Placebo 65.7 Current smokers (%) 0 ICS use at baseline (%): Drug 1: OM 100 Drug 2: Placebo 100	Withdrawals: Drug 1: OM 30 (12%) Drug 2: Placebo 22 (9%) Withdrawals due to AEs: Drug 1: OM 11 (5%) Drug 2: Placebo 4 (2%)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Humbert et al.{Humbert, 2005 #254} 2005 INNOVATE Multinational Multicenter (hospital clinics) NR (1 author employed by Novartis)	Intervention: Drug 1: OM Drog 2: Placebo Number in group (n): Drug 1: 209 Drog 2: 210	• Symptoms: Mean change from baseline in total symptom score significantly greater with OM (data NR; P = 0.039) • Exacerbations: After adjustment for baseline differences, statistically significant difference in OM group in clinically significant asthma exacerbation rate (0.68 vs. 0.91; P = 0.042; rate ratio 0.738 [95% CI: 0.552, 0.998]. Treatment group difference (rate ratio 0.806, P = 0.153) did not reach statistical significance in analysis without adjustment for previous exacerbation difference at baseline; however, similar magnitude of effect was seen (19% reduction). NNT for 1 year to save one clinically significant exacerbation = 2.2. • Severe exacerbations significantly lower in OM group (0.24 vs. 0.48; P = 0.002). NNT for 1 year to save one severe exacerbation was 2.2. • Rescue med use: OM patients used approximately 0.5 puffs/day less of rescue medication compared with placebo at endpoint (P = NS) • QoL: Significantly greater improvements in overall AQLQ score in OM patients: (LSM: 0.91 vs. 0.46; LSM difference: 0.45; P < 0.001). Significantly greater proportion of OM patients achieved a clinically meaningful (≥ 0.5 point) improvemer • ER/Urgent care: OM patients had statistically significantly lower rates for total em

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Humbert et al.{Humbert, 2005 #254} 2005 INNOVATE Multinational Multicenter (hospital clinics) NR (1 author employed by Novartis)	Overall OM 72.2 Placebo 75.5 Injection site reaction: OM 5.3 Placebo 1.3	NR	Fair

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
314	Ilowite et al.{Ilowite, 2004 #314} 2004 USA Multicenter - 132 Merck	Study design: RCT Double-blind Double-dummy Duration: 48 weeks N=1473 Enrolled: 2879 screened 1957 eligible 1473 enrolled ITT Analysis: Yes	: 14 to 73 years; clinical history of asthma for at least a year; FEV 50 to 90%; reversibility of at least 12% and symptoms that required B agonist trmt once a day; ICS for at least 8 weeks; average symptom score of 4 Asthma Severity: Mild Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Ilowite et al.{Ilowite, 2004 #314} 2004 USA Multicenter - 132 Merck	Rescue albuterol	Other: Treated in an emergency room w/in last month; hospitalized w/in 3 months; upper respirtory infection w/in 3 weeks; corticosteroids w/in 1 month; cromolyn, nedocromil, anticholinergics, LTRA, or LABAs w/in 2 weeks; theophylline w/in 1 week	Yes: 4 week run-in all patients swithched to FP

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Ilowite et al.{Ilowite, 2004 #314} 2004 USA Multicenter - 132 Merck	Intervention: Drug 1: ML/ FP Drug 2: SM /FP Total daily dose: Drug 1: 10 mg / 220mcg Drug 2: 84 mcg / 220mcg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Delivery device: Drug 1: tablet / MDI Drug 2: MDI / MDI Is dosing comparable between treatment groups? NA: LTRA vs LABA	# in group (n): Drug 1: 743 Drug 2: 730 Mean age (years): Drug 1: 39.0 Drug 2: 38.1 Sex (% female): Drug 1: 58.8 Drug 2: 62.5 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 128 (17.2%) Drug 2: 113 (15.5%) Adverse events caused withdrawal (%): Drug 1: 2.4 Drug 2: 1.2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Ilowite et al.{Ilowite, 2004 #314} 2004 USA Multicenter - 132 Merck	Intervention: Drug 1 Baseline: ML/ FP Drug 1 Endpoint: ML/ FP Drug 2 Baseline: SM/ FP Drug 2 Endpoint: SM/FP Trmt difference (95% CI) Number in group (n): Drug 1- baseline: 743 Drug 1- endpoint: 734 Drug 2- baseline: 730 Drug 2- endpoint: 718	Rescue med use during 24 hour period: Drug 1- baseline: 3.34 (2.30) Drug 1-endpoint: change from baseline = -1.15 (0.06) Drug 2-baseline: 3.55 (2.41) Drug 2-endpoint: change from baseline = -1.66 (0.06) 0.52 (0.36 to 0.68) Day time symptom control: D1 - base: 2.28 (0.89) D1 - end: change from baseline = -0.48 (0.03) D2 - base: 2.28 (0.88) D2 - end: change from baseline = -0.66 (0.03) 0.18 (0.10 TO 0.26) Courses of steroids: D1 end: 16.8% D2 end: 14.2% RR 1.18 CI (0.93-1.5) Nocturnal awakenings: D1 base: nights per week = 1.80 (2.19) D1 end: change from baseline = - 0.79 (0.05) D2 base: 1.94 (2.24) D2 end: -1.02 (0.05) 0.23 (0.10 TO 0.36) AQLQ - overall: D1 base: 4.74 (1.01) D1 end: change from baseline = 0.78 (0.03) D2 base: 4.79 (1.04) D2 end: 0.90 (0.03) -0.12 (-0.22 TO -0.02) Emergency room visits: D1 end: 2% D2 end: 2.2% RR = 0.92 CI (0.46-1.84) Hospitalizations:

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Ilowite et al.{Ilowite, 2004 #314} 2004 USA Multicenter - 132 Merck	Overall adverse events reported (%): Drug 1: clinical AE rated as related to drug = 8.6 Drug 2: 10.0 Serious adverse events (%): Drug 1: clinical = 3.0 Drug 2: 3.7 Dysphonia (%): Drug 1: 1.1 Drug 2: 0.3 Cough (%): Drug 1: asthma = 1.3 Drug 2: 1.4 Headache (%): Drug 1: 0.8 Drug 2: 1.5	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
454	Ind et al.{Ind, 2003 #454} 2003 Multicenter/national (100 - UK, Italy, Canada, Denmark, Iceland, Republic of Ireland) Hospitals and primary care centers Glaxo Wellcome	Study design:RCT Double-blind Double-dummy Duration: 24 weeks N=502 859 screened, 502 randomised ITT? Yes	Patients with asthma, aged between 16 and 75 years, who were currently symptomatic on BDP 500 - 800 mcg twice daily (or equivalent) delivered via a MDI. Had to demonstrate correct usage of an MDI and PEF meter, and at the first clinic visit, had to have a PEF of less than 85% of post-bronchodilator PEF determined 15min after inhalation of salbutamol(400 mg) via a Volumatic spacer. Patients were required to have at least two documented asthma exacerbations leading to a change in therapy or hospitalisation in the previous year with at least one of these episodes having occurred during the last 6 months. Other asthma medicationswere permitted (with the exception of additional inhaled ICS and b2-agonists). In order to enter the treatment phase of the study patients also had to demonstrate a period variation in PEF of at least 15% (highest eveningvalue-lowest morning value as a percentage of highest PEF) over the last 10 days and/or nights of the run-in period and to have sub-optimal PEF, with average PEF over the last 10 days of the run-in not exceeding 90% of postbronchodilator PEF. Asthma Severity: Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Ind et al.{Ind, 2003 #454} 2003 Multicenter/national (100 - UK, Italy, Canada, Denmark, Iceland, Republic of Ireland) Hospitals and primary care centers Glaxo Wellcome	Other asthma medications were permitted (with the exception of additional inhaled ICS and b2-agonists).	Receiving continuous oral corticosteroids, if they had any serious uncontrolledsystemic disease or their participation was deemed unsuitable by the physician.	Yes- During a 4-week initial run-in period patients were treated with FP 250mcg b.d. and used salbutamol as required for symptomatic relief. In order to minimise any non-speci¢c responses during this period, patients were unaware oftheir ICS dose. At the end of the run-in period, patients were randomised.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Ind et al.{Ind, 2003 #454} 2003 Multicenter/national (100 - UK, Italy, Canada, Denmark, Iceland, Republic of Ireland) Hospitals and primary care centers Glaxo Wellcome	Intervention: Drug 1: SM/FP Drug 2: FP 250 Drug 3: FP 500 Total daily dose: Drug 1: 500/100 mcg Drug 2: 500 mcg Drug 3: 1000 mcg Steroid dosing range: Drug 1: high Drug 2: high Drug 3: high Delivery device: Drug 1: MDI Drug 2: MDI Drug 3: MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 171 Drug 2: 160 Drug 3: 165 Mean age (years): Drug 1: 45 Drug 2: 46 Drug 3: 44 Sex (% female): Drug 1: 59 Drug 2: 51 Drug 3: 50 Current smokers (%): Drug 1: 13 Drug 2: 16 Drug 3: 24 Optional - Disease duration (years): Drug 1: 12 Drug 2: 11 Drug 3: 15 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 27 (16) Drug 2: 15 (9) Drug 3: 22 (13) Overall: 64 (13) Adverse events caused withdrawal (%): Drug 1: 4 Drug 2: 1 Drug 3: 4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Ind et al.{Ind, 2003 #454} 2003 Multicenter/national (100 - UK, Italy, Canada, Denmark, Iceland, Republic of Ireland) Hospitals and primary care centers Glaxo Wellcome	Intervention: Drug 1: SM/FP Drug 2: FP 250 Drug 3: FP 500 Number in group (n): Drug 1: 171 Drug 2: 160 Drug 3: 165	Rescue med use day: Drug 1: median % of days with no rescue = 53% Drug 2: 15% Drug 3: 9% : P =/< 0.001 for both combo versus each FP alone groups Rescue med use at night: Drug 1: median % of nights with no rescue = 90% Drug 2: 78% Drug 3: 77% P =/< 0.001 for both combo versus each FP alone groups Asthma exacerbations: D1 : severe exacerbations per patient per year = 0.05; moderate exacerbation rates = 0.77; % of pts with severe exacerbations during study = 3% D2: 0.23/0.95/8% D3: 0.16/0.95/6% P =0.16 for combo versus FP 500; 0.059 for combo versus FP 250 Symptom control during 24 hour period: D1 : median chage from baseline in % symptom free days = +21% D2: +1.5% D3 +0% P = 0.002 for both combo versus each FP alone groups Night time symptom control: D1 : median chage from baseline in % symptom free nights = +15% D2: +2% D3: +0% P =/< 0.002 for both combo versus each FP alone groups Other Relevant Health Outcome Results: There were also no differences between treatments in the number of patients experiencing at least one moderate or severe exacerbation during the treatment period: 27% (47 patients) with SM/FP250 compared with 31% (51) with FP500 and

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Ind et al.{Ind, 2003 #454} 2003 Multicenter/national (100 - UK, Italy, Canada, Denmark, Iceland, Republic of Ireland) Hospitals and primary care centers Glaxo Wellcome	NA	NR	Fair NR No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4735	Israel et al.{Israel, 2001 #4735} 2001 United States - Boston area, Massachusetts Hospitals and Health Plans National Heart, Lung, and Blood Institute and a General Clinical Research Center grant to Brigham and Women's Hospital from the National Center for Research Resources.	Study design: Observational Cohort Duration: 3 years N=109 Enrolled: 159, NR, 109 ITT Analysis: Unable to determine	: diagnosis of asthma from a physician, between 18 and 45 years old, 10 or more menstrual periods during the preceding year; prescribed inhaled glucocorticoids in a dose of four or more puffs per day and had received the same dose for at least six weeks. These women were subdivided into those taking four to eight puffs per day and those taking more than eight puffs per day. The women who were classified as not being treated with inhaled glucocorticoids had not received these drugs for at least six months. Asthma Severity: Controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Israel et al.{Israel, 2001 #4735} 2001 United States - Boston area, Massachusetts Hospitals and Health Plans National Heart, Lung, and Blood Institute and a General Clinical Research Center grant to Brigham and Women's Hospital from the National Center for Research Resources.	Oral contraceptives, calcium and vitamin d, otherwise NR	History of a disease affecting bone turnover, taking any drugs known to influence bone metabolism, and had smoked within the preceding year; abnormal serum thyrotropin concentrations,low 25-hydroxyvitamin D concentrations, high serum parathyroidhormone concentrations, high serum follicle-stimulating hormone concentrations, 24-hour urinary calcium excretion of more than 250 mg (6.2 mmol), or low bone density (z score, –2 orless), unless approved by a physician, and those who did not return for a postscreening visit; received more than two short courses (lasting two weeks or less) of oral or parenteral glucocorticoids in the preceding year or any oral orparenteral glucocorticoids in the preceding three months.	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Israel et al.{Israel, 2001 #4735} 2001 United States - Boston area, Massachusetts Hospitals and Health Plans National Heart, Lung, and Blood Institute and a General Clinical Research Center grant to Brigham and Women's Hospital from the National Center for Research Resources.	Intervention: Drug 1: Non-exposed Drug 2: 4-8 puffs Triamcinolone Drug 3: >8 puffs Triamcinolone Total daily dose: Drug 1: NA Drug 2: 400-800mcg Drug 3: > 800mcg Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: low- medium Drug 3: medium - high Delivery device: Drug 1: NA Drug 2: MDI Drug 3: MDI Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 28 Drug 2: 39 Drug 3: 42 Mean age (years): Drug 1: 34 Drug 2: 33 Drug 3: 37 Overall: p < 0.05 for the comparison among the three groups Sex (% female): Drug 1: 100 Drug 2: 100 Drug 3: 100 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Optional - Previous ICS use (%): Drug 1: current or past use of topical ICS (%) = 14 Drug 2: 62 Drug 3: 62 Overall: p <0.01 for comparison between three groups Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 100 Drug 3: 100 Other: Drug 1: history of oral glucocorticoid therapy (%) = 36 Drug 2: 76	Number (%) withdrawn: Drug 1: 8 (28.6%) Drug 2: 13 (33.3%) Drug 3: 15 (35.7%)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Israel et al.{Israel, 2001 #4735} 2001 United States - Boston area, Massachusetts Hospitals and Health Plans National Heart, Lung, and Blood Institute and a General Clinical Research Center grant to Brigham and Women's Hospital from the National Center for Research Resources.	Intervention: Drug 1: Non-exposed Drug 2: 4-8 puffs Triamcinolone Drug 3: >8 puffs Triamcinolone # in group (n): Drug 1: 28 Drug 2: 39 Drug 3: 42	see adverse events

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Israel et al.{Israel, 2001 #4735} 2001 United States - Boston area, Massachusetts Hospitals and Health Plans National Heart, Lung, and Blood Institute and a General Clinical Research Center grant to Brigham and Women's Hospital from the National Center for Research Resources.	Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: The urinary N-telopeptide, calcium, and cortisol values and the serum osteocalcin, calcium, cortisol, and parathyroid hormone values were not associated with the dose of inhaled glucocorticoids. Furthermore, these urinary and serum measurements and the changes in these values were not consistently correlated with the declines in bone density. Additional adverse events and comments: Each additional daily puff of the inhaled glucocorticoid was associated with a decline in bone density of 0.00044 g per square centimeter per year at both sites, but there was no significant association with the degree of decline at the femoral neck and spine (-0.00005 and -0.00008 g per square centimeter per year per puff, respectively [P=0.85 and P=0.68, respectively]). Even when we excluded these women and adjusted for age and the use of nasal glucocorticoids and oral contraceptives, each additional puff of inhaled glucocorticoid was still associated with an additional decline in the bone density of the total hip and trochanter of 0.00041 and 0.0(	Adherence	We tracked inhaled glucocorticoid use and the use of concomitant medications by means of monthly calendars that women mailed to the center. In order to encourage the keeping of accurate diary records, all women using inhaled glucocorticoids were issued a Chronolog monitoring monitoring device (Medtrac Technologies, Lakewood, Colo.), which electronically recorded all actuations of the glucocorticoid inhaler. Data from the device were reviewed with the women at the followup visits. In addition, empty canisters were mailed back to the center to be replaced by new canisters, and the returned canisters were weighed as another verification of medication use. We compared the number of puffs per day as calculated from the diary records with the number of actuations of the inhaler as recorded by the actuation monitor among 33 of the women. During the study,the maximal use of inhaled glucocorticoids during any period was 28 puffs per day. There was a direct linear correlation between the two values for the amount used. The intraclass correlation coefficient was 0.92, indicating that the do

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
497	Israel et al.{Israel, 2002 #497} 2002 USA Multicenter (64) Merck	Study design: RCT Double-blind Double-dummy Duration: 6 weeks N = 782 Number screened: NR ITT Analysis: Yes	: Male and female; at least 15 years; 1-year history of clinical symptoms of asthma; a negative serum β-human chorionic gonadotropin test; only short-acting b-agonist (albuterol); FEV1 of between 50% and 85% of the predicted value at rest and at least a 15% increase in FEV1 after albuterol administration; required to have average albuterol use of greater than 2 puffs per day; non-smokers for at least 1 year before enrollment, with a smoking history of no more than 7 pack-years Asthma Severity: Mild Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Israel et al.{Israel, 2002 #497} 2002 USA Multicenter (64) Merck	Inhaled albuterol for symptomatic relief of asthma and short-acting antihistamines were permitted. According to a standard action plan, up to 2 uses of rescue oral corticosteroid for the treatment of worsening asthma were allowed during the double-blind period. Patients who needed additional oral corticosteroid treatment discontinued study therapy.	Other: upper respiratory tract infections within the past 3 weeks, emergency care for asthma within 1 month, or hospitalization for asthma within 3 months; systemic corticosteroids were not allowed for 1 month before; ICSs were not allowed for 2 weeks; stop other antiasthma therapy 1 week before the first study visit.	Yes: 1-week prestudy screening period, a 2-week single-blind placebo baseline period

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Israel et al.{Israel, 2002 #497} 2002 USA Multicenter (64) Merck	Intervention: Drug 1: ML Drug 2: BDP Drug 3: Placebo Total daily dose: Drug 1: 10 mg Drug 2: 400 µg Drug 3: na Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: medium Drug 3: NA Delivery device: Drug 1: tablet Drug 2: MDI Drug 3: NA Is dosing comparable between treatment groups? NA: ICS versus LTRA	# in group (n): Drug 1: 339 Drug 2: 332 Drug 3: 111 Mean age (years): Drug 1: 33.5 Drug 2: 33.9 Drug 3: 33.3 Sex (% female): Drug 1: 52.2 Drug 2: 53.0 Drug 3: 51.4 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Optional - Rescue medication use (puffs per day): Drug 1: 5.6 Drug 2: 5.8 Drug 3: 5.7 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 11 (3.2) Drug 2: 14 (4.2) Drug 3: 5 (4.5)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Israel et al.{Israel, 2002 #497} 2002 USA Multicenter (64) Merck	Intervention: Drug 1 Baseline Drug 1 Endpoint: ML Drug 2 Baseline Drug 2 Endpoint: BDP Drug 3 Baseline Drug 3 Endpoint: Placebo P-values (Define comparison): m vs p. b vs p, m vs b Number in group (n): Drug 1- endpoint: 337 Drug 2-endpoint: 329 Drug 3- endpoint: 111	Rescue med use during 24 hour period: % change from baseline Drug 1-endpoint: -30.3 Drug 2-endpoint: -31.9 Drug 3- endpoint: -9.7 P values: < 0.001, <0.001, 0.621 Asthma exacerbations: patients without an asthma attack (%) D1 end: = 97 D2 end: 96.1 D3 end: 91.9 P: < 0.05, NS, NS Symptom control during 24 hour period: % days with asthma control D1 end: 41.4 D2 end: 41.1 D3 end: 26.8 P: < 0.001, <0.001, .929 Courses of steroids: patients without rescue steroids % = D1 end: 97.3 D2 end: 96.4 D3 end: 92.8 P: <0.05, NS, NS

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Israel et al.{Israel, 2002 #497} 2002 USA Multicenter (64) Merck	Other (%): Drug 1: Lab AEs= 3.9 Drug 2: 3.0 Drug 3: 4.5 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: NR The most frequently reported adverse experiences (>5% of patients) included upper respiratory tract infection, headache, and sinusitis, as well as asthma, and were not different among the treatment groups.	Adherence Adherence with treatment was measured at the last study visit on the basis of study medication tablet count and patient recall of inhaler use. Results NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4649	Jarjour et al.{Jarjour, 2006 #4649} 2006 US Multicenter GlaxoSmithKline, RTP NC Subanalysis 4748	Study design: RCT Double-blind Duration: 24 weeks N=88 Enrolled: 244/88/88 ITT? Yes	Age: >/= 18 : During the first part of the run-in period (run-in period 1), had stable symptoms with their prestudy medium doses of ICS (220 mcg of FP twice daily or equivalent) but whose asthma destabilized during a subsequent run-in period after a dose step-down to 100 mcg of FP twice daily (run-in period 2). During the final open-label run-in period, treatment was stepped up to 250 mcg of FP twice daily for 4 weeks (run-in period 3), at which time all patients had to re-establish asthma control to be included in the treatment phase of the study. This meant that subjects were not allowed to continue if they metany of the following asthma instability criteria: a 20% or greater decrease from the screening visit predose FEV1; a 20% or greater decrease from the mean morning baseline PEF on any one of 7 days immediately preceding a visit; a total symptom score of 8 or greater during any one week before run-in visit 1B; 18 or more puffs of albuterol during any 1 week before run-in visit 1B; or 2 or more nighttime awakenings caused by asthma requiring treatment with albuterol during any 1-week period. T Asthma Severity: Controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Jarjour et al.{Jarjour, 2006 #4649} 2006 US Multicenter GlaxoSmithKline, RTP NC Subanalysis 4748	Albuterol	current evidence of chronic bronchitis, emphysema, or respiratory diseases other than asthma. In addition, subjects with current tobacco use or a smoking history of more than 10 pack-years were excluded to ensure that those patients with possible COPD were not enrolled in the study.	Yes- Run-in period 1 (2 wks), Run-in period 2 (5-28 days), Run-in period 3 (4 weeks). Details described above in "other" inclusion criteria.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Jarjour et al.{Jarjour, 2006 #4649} 2006 US Multicenter GlaxoSmithKline, RTP NC Subanalysis 4748	Intervention: Drug 1: FSC Drug 2: FP Total daily dose: Drug 1: 200/100 mcg Drug 2: 500 mcg Delivery device: Drug 1: Diskus inhaler Drug 2: Diskus inhaler Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 40 Drug 2: 48 Mean age (years): Drug 1: 34.3 Drug 2: 35.3 Sex (% female): Drug 1: 58 Drug 2: 54 Optional - Race (% white): Drug 1: 95 Drug 2: 92 Current smokers (%): Drug 1: 0 Drug 2: 0 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: NR Drug 2: NR Optional - Withdrew due to asthma exacerbations (%): Drug 1: 0 Drug 2: 4%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Jarjour et al.{Jarjour, 2006 #4649} 2006 US Multicenter GlaxoSmithKline, RTP NC Subanalysis 4748	Drug 1 Baseline: FSC Drug 1 Endpoint: FSC Drug 2 Baseline: FP Drug 2 Endpoint: FP P-values (Define comparison): Treatment differences (95% CI)	Rescue med use during 24 hour period: **change????** Drug 1- baseline: 0.7 (0.11) Drug 1-endpoint: 0.42 (0.10) Drug 2-baseline: 1.1 (0.21) Drug 2-endpoint: 0.80 (0.22) tP values: -0.21 (-0.72 to 0.30); P=not statistically significant Symptom control during 24 hour period: D1 base: Daily asthma symptom score: 0.85 (0.14) D1 end: 0.60 (0.15) D2 base: 0.87 (0.12) D2 end: 0.71 (0.14) D3 endP: 0.05 (-0.26 to 0.36); P=not statistically significant Other: D1 base: % of symptom-free days: 47 (6.4) D1 end : 63.8 (7.2) D2 base: 47 (5.7) D2 end: 59.4 (6.3) D3 endP: 0.3 (-14.8 to15.4); P=not statistically significant Other: D1 base: percentage of rescue-free days: 56 (6.6) D1 end : 72.8 (6.1) D2 base: 55 (5.6) D2 end: 67.2 (5.8) D3 endP: 5.4 (-9.1 to 20.0); P=not statistically significant Other Relevant Health Outcome Results: An exacerbation was defined as worsening asthma requiring treatment beyond the blinded study drug and supplemental albuterol use. The number of subjects who experienced asthma exacerbations was low and similar in the 2 treatment groups. Five (13%) and 9 (19%) subjects treated with 100/50 mcg of FSC twice daily and 2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Jarjour et al.{Jarjour, 2006 #4649} 2006 US Multicenter GlaxoSmithKline, RTP NC Subanalysis 4748	Overall adverse events reported (%): Drug 1: 15 Drug 2: 17 Serious adverse events (%): Drug 1: 0 Drug 2: 0 Oral candidiasis- thrush (%): Drug 1: 2.5 Drug 2: 2.1 Headache (%): Drug 1: 2.5 Drug 2: 0 Additional adverse events and comments: Both of the treatments were well tolerated, and the incidence of common adverse events was similar in the 2 treatment groups. No adverse event occurred in more than one patient in each treatment group. The pharmacologically predictable adverse events included oral candidiasis (1 patient in each group), palpitation (1 patient in the FP group), and headache (1 patient in the FSC group). There were no serious drug-related adverse events during treatment.	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
53	Jat et al.{Jat, 2006 #53} 2006 India Pediatric Asthma Clinic NR	Study design: RCT Single-blind Duration: 12 weeks N = 71 Number screened: NR/71 ITT Analysis: No another type of analysis was used (define): patients after first two weeks of randomization	Age: 6-14 years : moderate asthma presenting to the Pedicatric Asthma Clinic of the Post Graduate Institute of Mecial Education and Research. Asthma Severity: Moderate Other: Persistant

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Jat et al.{Jat, 2006 #53} 2006 India Pediatric Asthma Clinic NR	salbutamol rescue therapy	Prior treatment with: in the last 30 days of systemic corticosteroids, theophylline, leukotrine modifiers, cromolyn or nedocromil sodium Other: purely exercise induced or aspirin-NSAID induce; pulmonary disease; history of upper and lower respiratory tract infections during last 4 weeks.	Yes: 1 week run-in during which education about asthma, training in inhalation therapy, and accurate recording of symptom score were reinforced.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Jat et al.{Jat, 2006 #53} 2006 India Pediatric Asthma Clinic NR	Intervention: Drug 1: BUD/ML Drug 2: BUD Total daily dose: Drug 1: 200mcg /5mg Drug 2: 400mcg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Delivery device: Drug 1: MDI spacer Drug 2: MDI spacer Is dosing comparable between treatment groups? NA: ICS versus ICS plus LTRA	# in group (n): Drug 1: 30 Drug 2: 33 Mean age (years): Drug 1: 10.13 Drug 2: 9.39 Sex (% female): Drug 1: 30 Drug 2: 27 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Disease duration (years): Drug 1: 2.36 months Drug 2: 2.29 months Current use of ICS at baseline (%): Drug 1: NR Drug 2: NR Other: Drug 1: previous hospitalisations-2.36 Drug 2: 2.29 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 18 Drug 2: 19 Adverse events caused withdrawal (%): Drug 1: NR Drug 2: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Jat et al.{Jat, 2006 #53}	Intervention:	Asthma exacerbations:
2006	Drug 1 Baseline: BUD/ML	D1 end: 13 in 10 subjects (33.3%)
	Drug 1 Endpoint: BUD/ML	D2 end: 3 (9.1%)
India	Drug 2 Baseline: BUD	P < 0.01
Pediatric Asthma Clinic	Drug 2 Endpoint: BUD	
		Symptom control during 24 hour period:
NR	Number in group (n):	Asthma Symptom Score
	Drug 1- baseline: 34	D1 base: 9.2
	Drug 1- endpoint: 30	D1 end: NR
	Drug 2- baseline: 37	D2 base: 8.36
	Drug 2- endpoint: 33	D2 end: NR
		P: NS

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Jat et al.{Jat, 2006 #53} 2006 India Pediatric Asthma Clinic NR	Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: NR	Adherence Evaluated by counting the number of tablets remaining at each visit for group A and calculating the duration for emptying the MDI for both groups. A high degree of adherence to prescribed treatment was reported during the study, with only 1 patietn voluntarily declaring nonadherence. tablet coutns for all the patients indicated that no doses had been missed. Similarly, calculation of days to empty the MDI suggested a good degree of adherence to therapy.	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
783	Jenkins et al.{Jenkins, 2000 #783} and Juniper et al. {Juniper, 2002 #523} 2000 and 2002 Multinational Multicenter (44 centers) Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 24 weeks N=353, subanalysis 113 for AQLQ Enrolled: NR/NR/353 randomized ITT? Yes	Age: >/=12 years with a documented history of reversible airways obstruction receiving ICSs for 4 or more weeks before 2-week run-in; during run-in period, had FEV1 or PEF between 50% and 85% of the predicted normal value, at least 15% increase in FEV1 or mean morning PEF </= 85% of maximum achievable after inhalation of a short-acting b2-agonist; used salbutamol more than twice a day or had a total daytime plus night-time symptom score at least 2 (defined as symptoms at least twice during the day or symptoms causing the patient to awake at least twice during the night) on 4 or more of 7 days. Asthma Severity: Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Jenkins et al.{Jenkins, 2000 #783} and Juniper et al. {Juniper, 2002 #523} 2000 and 2002 Multinational Multicenter (44 centers) Glaxo Wellcome	rescue salbutamol	in the 4 weeks before the run-in period they had had an acute exacerbation requiring hospitalization, had received oral, parenteral or depot corticosteroids, or had had a lower respiratory tract infection or change in asthma medication; treatment with a long-acting b2-agonist orslow-release bronchodilator in the 2 weeks before the run-in period; smoking history of at least 10 pack-years;Pregnant or lactating females	Yes- 2 week period during which all asthma medications were withdrawn except the patients' usual inhaled corticosteroid; and salbutamol was provided for symptomatic relief as required.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Jenkins et al.{Jenkins, 2000 #783} and Juniper et al. {Juniper, 2002 #523} 2000 and 2002 Multinational Multicenter (44 centers) Glaxo Wellcome	Intervention: Drug 1: SFC Drug 2: BUD Total daily dose: Drug 1: 100mcg/500mcg Drug 2: 1600mcg Steroid dosing range: Drug 1: medium Drug 2: medium Delivery device: Drug 1: Diskus Drug 2: Turbuhaler Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 180 Drug 2: 173 Mean age (years): Drug 1: 45 Drug 2: 48 Sex (% female): Drug 1: 50 Drug 2: 50 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 29 (16) Drug 2: 30 (17) Adverse events caused withdrawal (%): Drug 1: 1.7 Drug 2: 2.3 Adverse events caused withdrawal (%): Drug 1: 1.7 Drug 2: 2.3

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Jenkins et al.{Jenkins, 2000 #783} and Juniper et al. {Juniper, 2002 #523} 2000 and 2002 Multinational Multicenter (44 centers) Glaxo Wellcome	Intervention: Drug 1 Endpoint: SFC Drug 2 Endpoint: BUD Number in group (n): Drug 1- baseline: 180 Drug 1- endpoint: 180 (55 AQLQ) Drug 2- baseline: 173 Drug 2- endpoint: 173 (58 AQLQ)	Rescue med use at night: Drug 1 - endpoint: 90 Drug 2 - endpoint: 82 P = 0.029 95% CI 0 to 4 Asthma exacerbations: D1 base: % patients with >/= 1 exacerbation: D1 end: 30 D2 end: 30 P = NS Day time symptom control: D1 - base: median % symptom free days 0 D1 - end: 60 D2 - base: 0 D2 - end: 34 P = NR Night time symptom control: D1 - base: % symptom free nights (no baseline given) D1 - end: 86 D2 - end: 79 P = NS AQLQ - overall: D1 end: 0.89 (0.11) D2 end: 0.44 (0.10) P = 0.002; 95% CI: 0.17, 0.72 AQLQ - symptoms: D1 end: 1.11 (0.13) D2 end: 0.58 (0.13) P = 0.002; 95% CI: 0.21, 0.87 AQLQ - environment: D1 baseD1 end: 0.93 (0.13) D2 end: 0.52 (0.12) P = 0.014; 95% CI: 0.08, 0.73

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Jenkins et al.{Jenkins, 2000 #783} and Juniper et al. {Juniper, 2002 #523} 2000 and 2002 Multinational Multicenter (44 centers) Glaxo Wellcome	Serious adverse events (%): Drug 1: 3.3 Drug 2: 3.5 Oral candidiasis- thrush (%): Drug 1: 3 Drug 2: < 1 Sore throat (%): Drug 1: 2 Drug 2: 4 Hoarseness (%): Drug 1: 3 Drug 2: 5 Other (%): Drug 1: Candidiasis (unpecified site) < 1 Drug 2: 3 Other (%): Drug 1: Larangytis/pharyngitis 1 Drug 2: 2 Additional adverse events and comments: During the 24-week treatment period, 25 and 31 patients in the SFC BUD groups, respectively, reported adverse events which in the opinion of the investigators were related to study treatment.	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
204	Jenkins et al.{Jenkins, 2005 #204} 2005 Australia, research center Study funded by: Cooperative Research Centre for Asthma, which was funded by the Australian Federal Government and by industry, including AstraZeneca, Aventis Pharma, GlaxoSmithKline, Merck Sharp and Dohme and the New South Wales State Department of Health. These partners all contributed to the design of the present study protocol, but Merck Sharp and Dohme withdrew from involvement in the study prior to its commencement. H. Reddel is supported by the Asthma Foundation of New South Wales, Australia.	Study design: RCT Double-blind Double-dummy Duration: 6 weeks, 1 week washout, 6 weeks, 1 week washout, 6 weeks - total of 18 weeks treatment with 2 weeks washout - total 20 weeks. N=58 Enrolled: 99 assessed for eligibility; 58 randomised ITT Analysis: No another type of analysis was used (define): had to receive one dose of both meds	: aged 16–75 yrs, and had previously used a short-acting b2-agonist with/without an ICS </=500 mg beclomethasone equivalent. In all subjects, ICS treatment was ceased at entry to the study. During the 2-week run-in period, subjects were screened for the following inclusion criteria: FEV1 of 50–90% of predicted and/or a ratio of FEV1/forced vital capacity (FVC) </=70%, reversible airway obstruction (FEV1 increase >/=15% pred or >200 mL after 200 mg salbutamol) within the previous 6 months, asthma symptoms or shortacting b2-agonist use >/=4 days/week, and moderate AHR, defined as the provocative dose of methacholine causing a 20% fall in FEV1 (PD20) </=2 mmol at the end of a run-in period. Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Jenkins et al.{Jenkins, 2005 #204} 2005 Australia, research center Study funded by: Cooperative Research Centre for Asthma, which was funded by the Australian Federal Government and by industry, including AstraZeneca, Aventis Pharma, GlaxoSmithKline, Merck Sharp and Dohme and the New South Wales State Department of Health. These partners all contributed to the design of the present study protocol, but Merck Sharp and Dohme withdrew from involvement in the study prior to its commencement. H. Reddel is supported by the Asthma Foundation of New South Wales, Australia.		Other: Exclusion criteria included coexisting lung disease, recent asthma exacerbation or respiratory infection, and current smoking or smoking history>/=10 pack–yrs.	Yes: During the 2-week run-in period, subjects were screened for the following inclusion criteria: FEV 1 of 50–90% of predicted and/or a ratio of FEV1/forced vital capacity (FVC) </=70%, reversible airway obstruction (FEV1 increase >/=15% pred or >200 mL after 200 mg salbutamol) within the previous 6 months, asthma symptoms or shortacting b2-agonist use >/=4 days/week, and moderate airway hyperresponsiveness (AHR), defined as the provocative dose of methacholine causing a 20% fall in FEV1 (PD20) </=2 mmol at the end of a run-in period.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Jenkins et al.{Jenkins, 2005 #204} 2005 Australia, research center Study funded by: Cooperative Research Centre for Asthma, which was funded by the Australian Federal Government and by industry, including AstraZeneca, Aventis Pharma, GlaxoSmithKline, Merck Sharp and Dohme and the New South Wales State Department of Health. These partners all contributed to the design of the present study protocol, but Merck Sharp and Dohme withdrew from involvement in the study prior to its commencement. H. Reddel is supported by the Asthma Foundation of New South Wales, Australia.	Intervention: Drug 1: ML then eFM Drug 2: eFM then ML Drug 4: FP Total daily dose: Drug 1: 10mg then 24mcg Drug 2: 24mcg then 10mg Drug 4: 500mcg Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: NA Drug 4: medium Delivery device: Drug 1: tablet then turbuhaler Drug 2: turbuhaler then tablet Drug 4: Diskus Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 29 Drug 2: 29 Drug 3: 58 Drug 4: 58 Mean age (years): Drug 1: 41 Drug 2: 36 Drug 3: 39 Sex (% female): Drug 1: 55 Drug 2: 24 Drug 3: 40 Current smokers (%): Drug 1: former smoker 10 Drug 2: 28 Drug 3: 19 Optional - Rescue medication use (puffs per day): Drug 1: 5 Drug 2: 4 Drug 3: 5 Optional - % of rescue free days: Drug 1: symptom-free days (%) = 0 Drug 2: 0 Drug 3: 0 Optional - Previous ICS use (%): Drug 1: 52 Drug 2: 62 Drug 3: 57 Current use of ICS at baseline (%): Drug 1: 0 (required to stop at	Number (%) withdrawn: Drug 1: 1 (3) Drug 2: 4 (14) Drug 3: 6 (9) Drug 4: 1 (2) Adverse events caused withdrawal (%): Drug 1: 0 Drug 2: 3 Optional - Protocol violation (%): Drug 1: 0 Drug 2: 7 Optional - Consent withdrawn (%): Drug 1: 3 Drug 2: 3 Optional - Other reasons for withdrawal (%): Drug 4: 2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Jenkins et al.{Jenkins, 2005 #204} 2005 Australia, research center Study funded by: Cooperative Research Centre for Asthma, which was funded by the Australian Federal Government and by industry, including AstraZeneca, Aventis Pharma, GlaxoSmithKline, Merck Sharp and Dohme and the New South Wales State Department of Health. These partners all contributed to the design of the present study protocol, but Merck Sharp and Dohme withdrew from involvement in the study prior to its commencement. H. Reddel is supported by the Asthma Foundation of New South Wales, Australia.	Intervention: Drug 1 Baseline: ML Drug 1 Endpoint: ML Drug 2 Baseline: eFM Drug 2 Endpint: eFM Drug 3 Baseline: FP Drug 3 Endpoint: FP Number in group (n): Drug 1- endpoint: 53 Drug 2- endpoint: 53 Drug 3- endpoint: 53	Rescue med use during 24 hour period: Drug 1- baseline: run-in = 0 Drug 1-endpoint: rescue free days (%) = 30 Drug 2-baseline: run-in = 0 Drug 2-endpoint: 40 Drug 3 - baseline: run-in = 0 Drug 3- endpoint: 37 P values: M vs EF 0.008; M vs FP 0.03; EF vs FP 0.3 Rescue med use day: Drug 1- baseline: run-in = 3 Drug 1 -endpoint: 0 Drug 2 - baseline: run-in = 3 Drug 2 - endpoint: 0 Drug 3 - baseline: run-in = 3 Drug 3 - endpoint: 0 P value: M vs EF 0.01; M vs FP 0.05; EF vs FP 0.1 Rescue med use at night: Drug 1- baseline: run-in = 2 Drug 1 - endpoint: 0.3 Drug 2 - baseline: run-in = 2 Drug 2 - endpoint: 0 Drug 3- baseline: run-in = 2 Drug 3 - endpoint: 0 P value: M vs EF <0.0001; M vs FP 0.02; EF vs FP 0.04 Asthma exacerbations: D1 baseD1 end: severe asthma exacerbations = 3 D2 baseD2 end: 1 (plus 1 after eformoterol washout) D3 baseD3 endP Symptom control during 24 hour period: D1 base: run-in = 0 D1 end: symptom-free days (%) = 0 D2 base: run-in = 0 D2 end: 23 D3 base: run-in = 0 D3 end: 26

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Jenkins et al.{Jenkins, 2005 #204} 2005 Australia, research center Study funded by: Cooperative Research Centre for Asthma, which was funded by the Australian Federal Government and by industry, including AstraZeneca, Aventis Pharma, GlaxoSmithKline, Merck Sharp and Dohme and the New South Wales State Department of Health. These partners all contributed to the design of the present study protocol, but Merck Sharp and Dohme withdrew from involvement in the study prior to its commencement. H. Reddel is supported by the Asthma Foundation of New South Wales, Australia.	Oral candidiasis- thrush (%): Drug 1: 2 Drug 3: 2 Drug 3: 2 Hoarseness (%): Drug 2: 14 Drug 3: 12	Adherence Compliance with study medications was 98% for ML and 95% for fluticasone. Adherence was assessed covertly, using a capsule count for ML and Accuhaler counter for fluticasone, however no measure of eFM adherence was available.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
110	Jenkins et al.{Jenkins, 2006 #110} 2006 54 centers, 6 countries AstraZeneca	Study design: RCT Double-blind Double-dummy Other: patients were randomized to the 12-week treatment (two inhalations BUD) with one of the following: BUD/FM 320/9 µg (Symbicort® Turbuhaler®;AstraZeneca, Lund, Sweden); corresponding doses of BUD 400 µg plus FM 9 µg via separate inhalers; or a corresponding dose of BUD 400 µg. The doses of budesonide in each treatment group were comparable; differences areexplained by labelling changes for new inhaled drugs, which require the delivered dose rather than metereddose to be reported. At week 13, patients in the BUD/FM and BUD plus FM groups continued their treatment for the remaining12 weeks of the study; patients receiving BUD alone were switched to receive one of the other twotreatments for the remaining 12 weeks of the study. Duration: 12wk, 24wk; see other in RCT design details. Main outcome assessment appears to be at 12wk. N=456 Enrolled: 489 enrolled, NR, 456 randomized ITT Analysis: Yes	Age: >/= 12 FEV1 expressed as a percent of the predicted value: 40-85% Reversability of FEV1: >=15%, for patients aged 18 years, an increase in baseline FEV1 of 200 mL 15¨C30 min post bronchodilator was required at study entry (visit 1). Previous use of corticosteroids: >=4mo and also at a constant daily dose of >=750mcg for at least 4wk prior to study entry Duration of condition: >=6mo Other: total asthma symptom score was >1 on a scaleof 0-6 for at least 4 of the last 7 days of run-in. The total asthma symptom score was the sum of daytime and night-time asthma symptom scores, each measured on a scale of 0-3 (where 0 = no symptoms and 3 = unable to perform usual activities (or to sleep) because of asthma). Asthma Severity: Mild Moderate Not or poorly controlled Other: asthma severity not explicity stated in article but based on runin dosages

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Jenkins et al.{Jenkins, 2006 #110} 2006 54 centers, 6 countries AstraZeneca	Terbutaline 0.5mg prn	Other: if asthma deteriorated, resulting in a change in asthma therapy	Yes: 2 wk runin where patients continued does of >=750mcg/d

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Jenkins et al.{Jenkins, 2006 #110} 2006 54 centers, 6 countries AstraZeneca	Intervention: Drug 1: BUD/FM (same inhaler) Drug 2: BUD+FM (separate inhalers) Drug 3: BUD Total daily dose: Drug 1: 1280/36 Drug 2: 1600/36 Drug 3: 1600 Steroid dosing range (Low, medium or high): Drug 1: high Drug 2: high Drug 3: high Delivery device: Drug 1: MDI Drug 2: MDI Drug 3: MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 226 Drug 2: 115 Drug 3: 115 Mean age (years): Drug 1: 46 Drug 2: 47 Drug 3: 46 Sex (% female): Drug 1: 64 Drug 2: 60 Drug 3: 57 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Optional - Disease duration (years): Drug 1: 8 Drug 2: 10 Drug 3: 8 Optional - % of rescue free days: Drug 1: 30 Drug 2: 28 Drug 3: 25 Other: Drug 1: mean ICS dose at entry 1033 Drug 2: 1036 Drug 3: 1052 Other: Drug 1: asthma control days, % 10 Drug 2: 9	Number (%) withdrawn: Drug 1: 30 (13.3) Drug 2: 11 (10) Drug 3: 16 (13.9) Overall: 57 (12.5) Adverse events caused withdrawal (%): Drug 1: 4.0 Drug 2: 5.2 Drug 3: 5.2 Optional - Lost to follow-up (%): Drug 1: 0 Drug 2: 0 Drug 3: 0.8 Optional - Other reasons for withdrawal (%): Drug 1: 9.3 Drug 2: 4.3 Drug 3: 7.8

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Jenkins et al.{Jenkins, 2006 #110} 2006 54 centers, 6 countries AstraZeneca	Intervention: Drug 1 Baseline: BUD/FM (same inhaler) Drug 1 Endpoint: BUD/FM (same inhaler) Drug 2 Baseline: BUD+FM (separate inhalers) Drug 2 Endpoint: BUD+FM (separate inhalers) Drug 3 Baseline: BUD Drug 3 Endpoint: BUD P-values (Define comparison): BUD/FM vs BUD, BUD+FM vs BUD, BUD/FM vs BUD+FM Number in group (n): Drug 1- baseline: 226 Drug 1- endpoint: 226 Drug 2- baseline: 115 Drug 2-endpoint: 114 Drug 3- baseline: 115 Drug 3- endpoint: 115	Rescue med use during 24 hour period: Drug 1- baseline: reliever-free days, %=30 Drug 1-endpoint: 36.1 Drug 2-baseline: 28 Drug 2-endpoint: 38.6 Drug 3 - baseline: 25 Drug 3- endpoint: 17.2 P values: <0.001, <0.001, NS Symptom control during 24 hour period: D1 base: symptom-free days, % = NR D1 end: 31.2 D2 base: NR D2 end: 32.2 D3 base: NR D3 end: 15.6 P: <0.001, <0.001, NS Other: D1 base: total asthma symptom score = NR D1 end : -0.62 D2 base: NR D2 end: -0.66 D3 base: NR D3 end: -0.36 P: <0.01, <0.01, NS Other: D1 base: asthma control days, % = 10 D1 end : 32.4 D2 base: 9 D2 end: 32.2 D3 base: 7 D3 end: 16.3 P: <0.001. <0.001. NS Other Relevant Health Outcome Results: The time to first mild exacerbation was significantly longer in patients receiving BUD/FM compared with those in the BUD group. The instantaneous risk of a mild

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Jenkins et al.{Jenkins, 2006 #110} 2006 54 centers, 6 countries AstraZeneca	Overall adverse events reported (%): Drug 1: 30, 51 Drug 2: 27, 55 Drug 3: 23, (50, 52) Serious adverse events (%): Drug 1: 2, 4 Drug 2: 0, 3 Drug 3: 2, (7, 2) Respiratory infection (%): Drug 1: 7, 13 Drug 2: 10, 15 Drug 3: 5, (17, 16) Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: Mean levels of morning p-cortisol declined over the duration of the study to a similar extent in all treatment groups; changes from baseline to weeks 12 and 24 were not statistically significant for any of the treatment groups Morning p-cortisol shifted from concentrations within the defined reference limit at baseline to concentrations below the limit at week 24 in 19–24% of patients in all treatment groups. However, no significant between-group differences occurred and no new safety concerns were identified. The ACTH stimulation test was performed in a subgroup of patients from the BUD/FM (n = 75), BUD plus FM (n = 38) and BUD (n = 38 (n = 20 in the BUD/BUD plus FM group; n = 18 in the BUD/BUD/FM groups. No significant differences: Week 12 Adjusted change from baseline‡ (nmol/L) BUD 0.75; BUD/I Week 24 Adjusted change from baseline‡ (nmol/L) BUD NA ; BUD/E	Adherence Self-reported adherence to study medication was high (mean > 98%) in the three treatment groups.	Good: randomization, masking, ITT all adequate; few withdrawals Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4736	Jick et al.{Jick, 2001 #4736} 2001 United Kingdom Database - General Practitioners (GPRD) GlaxoSmithKline	Study design: Observational Cohort Case-control restrospective cohort and nested case-control study Duration: NR N=201,816 (103,289 ICS cohort; 98,527 non-exposed cohort) N=3,581 Case-control study (1,194 cataract cases; 2,387 matched controls) Enrolled: NR, NR, 201, 816 ITT Analysis: Not applicable	: All subjects in UK General Practice Research Database (GPRD), inhaled corticosteroid users and patients without previous steroid use who were younger than 90 years of age. Inhaled corticosteroid users included all subjects in the database who had received at least one prescription for inhaled BDP, BUD, or fluticasone, and who had a diagnosis of asthma or chronic obstructive pulmonary disease (COPD) recorded on the computer. Asthma Severity: NR
5083	Johannes et al.{Johannes, 2005 #5083} 2005 USA GlaxoSmithKline	Study design: Nested case control Duration: Jan 1997 to June 2001 N= 1722 cases 17220 controls	Age: at least 40 years and enrolled in a health plan for at least 12 continuous months from January 1, 1997, through June 30, 2001, and with at least two claims for a physician visit in an outpatient setting or one claim in an inpatient setting with (ICD-9) codes for asthma (493), or COPD (chronic bronchitis [491], emphysema [492], or chronic airway obstruction, not elsewhere classified [496]).

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Jick et al.{Jick, 2001 #4736} 2001 United Kingdom Database - General Practitioners (GPRD) GlaxoSmithKline	NR	Subjects with prescriptions for other steroids (including intranasal, but not topical); any subject who had diagnosis of cataract before entry into study.	No
Johannes et al.{Johannes, 2005 #5083} 2005 USA GlaxoSmithKline	NA	NA	NA

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Jick et al.{Jick, 2001 #4736} 2001 United Kingdom Database - General Practitioners (GPRD) GlaxoSmithKline	Intervention: Drug 1: ICS cohort (BDP, BUD, FP) Drug 2: Non-exposed cohort Total daily dose: Drug 1: NR Drug 2: NA Steroid dosing range (Low, medium or high): Drug 1: NR Drug 2: NA Delivery device: Drug 1: NR Drug 2: NA	# in group (n): Drug 1: 103,289 Drug 2: 98,527 Mean age (years): Drug 1: Male (%): <40 = 71.3; 40-69 = 20.8; >/=70 = 7.9; Female (%): <40 = 69.3; 40-69 = 22.5; >/=70 = 8.2 ;case-control = 73.1 Drug 2: Male (%): <40 = 86.7; 40-69 = 10.6; >/=70 = 2.8; Female (%): <40 = 82.2; 40-69 = 13.5; >/=70 = 4.4 ;case-conrol = 73.1 Sex (% female): Drug 1: 50.1 Drug 2: 47.3 Current smokers (%): Drug 1: 50.1 Drug 2: 47.3	Number (%) withdrawn: Drug 1: NA Drug 2: NA Adverse events caused withdrawal (%): Drug 1: NA Drug 2: NA
Johannes et al.{Johannes, 2005 #5083} 2005 USA GlaxoSmithKline	ICS vs.. Control (no ICS)	Female %: case 70.6% vs. control 58.9% Age: 76% 40 to 59 years 14% 60 to 64 years old, 10% at least 65 years old	NA

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Jick et al.{Jick, 2001 #4736} 2001 United Kingdom Database - General Practitioners (GPRD) GlaxoSmithKline	Intervention: Drug 1: ICS cohort (BDP, BUD, FP) Drug 2: Non-exposed cohort # in group (n): Drug 1: 103,289 Drug 2: 98,527	See adverse events
Johannes et al.{Johannes, 2005 #5083} 2005 USA GlaxoSmithKline	Intervention: ICS - cases Non-ICS - controls Number in group (n): 1722 17220	No ICS-related increase in the risk of nonvertebral fracture over 1 year for the total group of subjects or for either of the separate respiratory disease categories (asthma or COPD)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Jick et al.{Jick, 2001 #4736} 2001 United Kingdom Database - General Practitioners (GPRD) GlaxoSmithKline	Additional adverse events and comments: RR 1.3 (95% CI: 1.1 to 1.5) for incidence of cataract in ICS users as compared to non-exposed cohort based on cohort analysis and same RR estimate found in case-control analysis ; In case-control analysis, RR estimates increased with increasing numbers of ICS prescriptions (RR 2.5 (95% CI: 1.7 to 3.6) for > 40 prescriptions) ; In case-control analysis, age-stratified RR estimates show no increased risk of cataract among ICS users less than 40 years old, regardless of the number of prescriptions; Analysis of individual ICS showed similar increased risk for all drugs	NR	
Johannes et al.{Johannes, 2005 #5083} 2005 USA GlaxoSmithKline	See outcomes.	NA	NA Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
5081	Johansson et al.{Johansson, 2001 #5081} 2001 Multicenter Multinational (six countries--Canada, Greece, Israel, Italy, S Africa, and Sweden)) Glaxo Wellcome Research and Development	Study design: RCT double-blind, double-dummy, parallel-group study Duration: 12 weeks N=349 ITT Analysis: Yes	Age: Male and female pts. 12 years or older, documented history of reversible airways obstruction. Reversibility=increase in FEV1 of at least 15% (at clinic visit one or two), an average morning PEF [over the last 7 evaluable days of the run-in period] at or below 85%, or a documented history of reversibility (up to 3 months before clinic visit one) after inhalation of a short-acting β2-agonist. Pts. had previously received up to 500 µg/day of BDP or BUD for at least 4 weeks. Pts. with mild-to-moderate asthma FEV1 or PEF between 65% and 85% predicted during run-in on pre-study medication) were included. Pts required to be symptomatic, which was determined either by use of rescue SM (on more than two occasions per 24-hour period) or symptoms (total day and night diary card symptom score of ≥2) on at least 4 of the last 7 days of the run-in period. Asthma Severity: mild-to-moderate (uncontrolled on existing therapy)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Johansson et al.{Johansson, 2001 #5081} 2001 Multicenter Multinational (six countries--Canada, Greece, Israel, Italy, S Africa, and Sweden)) Glaxo Wellcome Research and Development		if they had changed their regular asthma medication or received any longacting or slow-release bronchodilators within the previous 2 weeks, had a lower respiratory tract infection within the previous 4 weeks, or were smokers with a history of 10 pack years or more. Pts. were also excluded if in the previous 4 weeks they had had an asthma exacerbation requiring hospitalisation and/or treatment with oral, parenteral or depot corticosteroids. Pts. with serious uncontrolled disease likely to interfere with study or showed evidence of alcohol or drug abuse were also excluded. Females were excluded if they were prego, lactating or likely to become prego.	2-week run-in period: During the run-in period, patients continued to take their usual inhaled corticosteroid therapy (table II) and rescue salbutamol; any other asthma treatment was stopped.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Johansson et al.{Johansson, 2001 #5081} 2001 Multicenter Multinational (six countries--Canada, Greece, Israel, Italy, S Africa, and Sweden)) Glaxo Wellcome Research and Development	Intervention: Drug 1: SM/FP Drug 2: BUD Total daily dose: Drug 1: 100/200µg Drug 2: 800µg Steroid dosing range: Drug 1: low Drug 2: medium Delivery device: Drug 1: Diskus (DPI) Drug 2: Turbuhaler (DPI) Is dosing comparable between treatment groups? LABA + low ICS vs medium ICS	# in group (n): Drug 1: 176 Drug 2: 173 Mean age (years): Drug 1: 36 ± 16 Drug 2: 36 ± 17 Sex (% female): Drug 1: 62% Drug 2: 52%	Number (%) withdrawn: Drug 1: 23 (13) Drug 2: 15 (8.7) Optional - Withdrew due to lack of efficacy (%): Drug 1: n=0 Drug 2: n=1 Optional - Withdrew due to asthma exacerbations (%): Drug 1: n=3 Drug 2: n=0 Adverse events caused withdrawal (%): Drug 1: n=1 Drug 2: n=1 Optional - Failure to return (%): Drug 1: n=5 Drug 2: n=7 Optional - Failure to to fulfil entry criteria (%): Drug 1: n=1 Drug 2: n=3

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Johansson et al.{Johansson, 2001 #5081} 2001 Multicenter Multinational (six countries--Canada, Greece, Israel, Italy, S Africa, and Sweden)) Glaxo Wellcome Research and Development	Intervention: Drug 1: SM/FP Drug 2: BUD Number in group (n): Drug 1: 176 Drug 2: 173	Days when symptom score <2 (% ± SD): Drug 1: 79 ± 30 Drug 2: 79 ± 27, P=NS Symptom-free days (% ± SD): Drug 1: 53 ± 38 Drug 2: 55 ± 38, P=NS Nights when symptom score <2 (% ± SD): Drug 1: 91 ± 18 Drug 2: 92 ± 18, P=NS Symptom-free nights (% ± SD): Drug 1: 68 ± 36 Drug 2: 72 ± 33, P=NS Salbutamol-free days (% ± SD): Drug 1: 64± 37 Drug 2: 63 ± 38, P=NS Salbutamol-free nights (% ± SD): Drug 1: 78 ± 30 Drug 2: 79 ± 29, P=NS Patients with no Exacerbations (%): Drug 1: 86% Drug 2: 86%, P=NR One or more exacerbation of asthma (%): Drug 1: 14% Drug 2: 14% P-value= NR The number of times salbutamol was used during the day and night was also recorded. Daytime and night-time symptom scores were recorded every morning and evening, on the patients' DRCs. FEV1 (the best of three measurements) was measured at each clinic visit. Patients withheld salbutamol for at least 6 hours before, and did not take their study medication on the morning of each clinic visit. Patients recorded asthma exacerbations on their DRCs. The occurrence and severity of any exacerbation was assessed by the physician at scheduled clinic visits based on the need for treatment interventions as recorded in (inhaled and/or oral) and/or permitted

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Johansson et al.{Johansson, 2001 #5081} 2001 Multicenter Multinational (six countries--Canada, Greece, Israel, Italy, S Africa, and Sweden)) Glaxo Wellcome Research and Development	Overall adverse events reported (n): Drug 1: 67 (12 considered drug related) Drug 2: 65 (11 considered drug related) Serious adverse events (n): Drug 1: 3 (one with acute asthma, one with exacerbation of asthma and one with cough and sputum production who was withdrawn from the study as a result) Headache (n): (drug related) Drug 1: 7 Drug 2: 10 Exacerbation of asthma (n): Drug 1: 7 Drug 2: 10	NR	Good Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
838	Kannisto et al.{Kannisto , 2000 #838} 2000 Finland tertiary center, University clinic Finnish Foundation for Pediatric Research	Study design: RCT : open label, presumably Duration: 6 months for lab outcomes, 12 months for growth outcome N=75 Enrolled: NR/NR/75 ITT Analysis: Unable to determine	Age: 5-15 Asthma Severity: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Kannisto et al.{Kannisto , 2000 #838} 2000 Finland tertiary center, University clinic Finnish Foundation for Pediatric Research	new onset of asthma	Prior treatment with: any steroid prior 12 months Current treatment with: any steroid prior 12 months	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Kannisto et al.{Kannisto , 2000 #838} 2000 Finland tertiary center, University clinic Finnish Foundation for Pediatric Research	Intervention: Drug 1: BUD Drug 2: FP Drug 3: Cromone (non-ICS control) Total daily dose: Drug 1: 800 ug/day during the first 2 monthsand 400 ug/day thereafter. At 4 months, a subgroup of these then had their ICS stopped (and were switched to cromones). Drug 2: 500 ug/day during the first 2 months and 200 ug/day thereafter. At 4 months, a subgroup of these then had their ICS stopped (and were switched to cromones). Steroid dosing range (Low, medium or high): Drug 1: medium, low Drug 2: medium, low Delivery device: Drug 1: DPI Drug 2: DPI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 30 Drug 2: 30 Drug 3: 15 Mean age (years): Drug 1: 9.3 Drug 2: 10.1 Drug 3: 8.7 Sex (% female): Drug 1: 57 Drug 2: 37 Drug 3: 73 Current smokers (%): Drug 1: na Drug 2: na Drug 3: na Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0	Number (%) withdrawn: Drug 1: NR Drug 2: NR Adverse events caused withdrawal (%): Drug 1: NR Drug 2: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Kannisto et al.{Kannisto , 2000 #838} 2000 Finland tertiary center, University clinic Finnish Foundation for Pediatric Research	Intervention: Drug 1 Baseline: BUD unstimulated cortisol baseline= 247 (204–291) Drug 1 Endpoint: BUD cortisol at 2 months = 205(166–244)(NS); at 4 months =211 (180–241)(p<.01) ; at 6 months 207 (116-298)(NS). p values given for change from baseline but not for drug-drug comparison. Drug 2 Baseline: FP baseline cortisol 271 (223–320). Drug 2 Endpoint: FP cortisol at 2 months= 231(197–265)(NS); at 4 months= 284 (238–330)(p<.05 compared w/ 2 mo values); at 6 months= 249 (201–297)(NS) . p values given for change from baseline or from precious value, P values fordrug-drug comparisons were NR. Drug 3 Baseline: CROM (control) Drug 3 Endpoint: CROM (control) P-values (Define comparison): P values given for change from baseline but not for drug-drug comparison. Number in group (n): Drug 1- baseline: 30 Drug 1- endpoint: 30 Drug 2- baseline: 30 Drug 2- endpoint: 30 Drug 3- baseline: 15	Other: D1 base: BUD post-ACTH stim cortisol at 0 months = 247 (204–291) D1 end : BUD post-ACTH stim cortisol at 2 months =429(377–480)(P , 0.001 compared with the values of the same treatment group at 0 months). At 4 months= 406a,b (363–449)(a P<0.001 compared with the values of the same treatment group at 0 months, b P<0.05 compared to the CROM group at 4 months.)At 6 months= 362 (261–463)d (d P<0.01 compared to the children who switched to cromones from BUD group at 4 months.) D2 base: 0 months= 528 D2 end: at 2 months= 407a (373–441) at 4 months= 443a(399–487) at 6 months 455 (363–547)f (a P<0.001 compared with the values of the same treatment group at 0 months. D3 baseD3 endP: d P<0.01 compared to the children who switched to cromones from BUD group at 4 months.) Other: D1 base: BUD height sd score at baseline = D1 end : At 4 months: the height sd score decreased during the 4-month treatmentperiod in the BUD group (P<0.01), but not in the FPand CROM groups (Fig. 2, does nto give actual numbers). At 12 months: The mean decrease in height sd score was 0.23 in the BUD group, 0.03 in the FP group, and 0.09 in the C D2 baseD2 endD3 baseD3 endP Other Relevant Health Outcome Results: FLUP treated children had significantly less growth reduction than BUD treated chil

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Kannisto et al.{Kannisto , 2000 #838} 2000 Finland tertiary center, University clinic Finnish Foundation for Pediatric Research	Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: More BUD-treated children than FP treated children had an abnormal test (30% vs. 18%; P < 0.05)* (n=9 vs n=5); Overall ACTH tests were abnormal in 23% of children;		Fair: n/a Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
805	Kavuru et al.{Kavuru, 2000 #805} 2000 USA Multicenter GlaxoWellcome Inc., RTP, NC	Study design: RCT Double-blind Duration: 12 weeks N=356 Enrolled: 527/NR/356 ITT Analysis: No another type of analysis was used (define)	: Male and female patients; at least 12 years old and had a medical history of asthma of at least 6 months duration that required pharmacotherapy for 6 months; FEV1 between 40% to 85% of the predicted value; greater than or equal to a 15% increase in FEV1 30 minutes after 2 puffs (180 µg) of inhaled albuterol. Stratified into 2 groups according to type of asthma therapy used at enrollment. Group 1 ICSs for at least 3 months; using SM with ICSs were eligible to participate if they could replace salmeterol with as-needed β2-agonists at least 1 week before the screening visit. Patients taking inhaled corticosteroids must have been treated with a dose of 6 to 10 puffs per day of BDP (252-420 µg/d) or TAA (600-1000 µg/d), 4 puffs per day of FLUN (1000 µg/d), or 4 puffs per day of FP 44 µg per puff (176 µg/d) for at least 1 month before screening with no change in regimen. Group 2 patients must have been using SM at least 1 week before screening. Patients treated with SM must have demonstrated a screening FEV1 ≤85% of predicted normal after 2 puffs of albuterol and should not hav Asthma Severity: Moderate Controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Kavuru et al.{Kavuru, 2000 #805} 2000 USA Multicenter GlaxoWellcome Inc., RTP, NC	albuterol	Other: negative pregnancy tests; surgically sterile, postmenopausal for at least 1 year, or using acceptable birth control for at least 1 month; history of life-threatening asthma; hypersensitivity reaction to sympathomimetic drugs or corticosteroids; smoking within the previous year or a history of >10 pack years; use of oral, inhaled, or injectable corticosteroid therapy within the previous month; use of intranasal corticosteroids except for Flonase; use of daily oral corticosteroid treatment within the previous 6 months; use of any other prescription or over-the-counter medication that mayaffect the course of asthma or interact with sympathomimetic amines; abnormal chest x-ray films; clinically significant abnormal 12-lead ECGs (ECG); or history of significant concurrent disease (eg, glaucoma, diabetes, hypertension)	Yes: 14 day, single-blind placebo screening period to evaluate eligibility, assess compliance with therapy, obtain baseline data, and confirm asthma stability

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Kavuru et al.{Kavuru, 2000 #805} 2000 USA Multicenter GlaxoWellcome Inc., RTP, NC	Intervention: Drug 1: Placebo Drug 2: Combo Drug 3: SM Drug 4: FP Total daily dose: Drug 1: NA Drug 2: 100/50 Drug 3: 50 Drug 4: 100 Delivery device: Drug 1: Diskus Inhaler Drug 2: Diskus Inhaler Drug 3: Diskus Inhaler Drug 4: Diskus Inhaler Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 82 Drug 2: 92 Drug 3: 92 Drug 4: 90 Mean age (years): Drug 1: 35 Drug 2: 38 Drug 3: 37 Drug 4: 39 Sex (% female): Drug 1: 49 Drug 2: 41 Drug 3: 49 Drug 4: 48 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Drug 4: 0 Current use of ICS at baseline (%): Drug 1: 67 Drug 2: 72 Drug 3: 72 Drug 4: 70 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 51 (66) Drug 2: 15 (17) Drug 3: 38 (44) Drug 4: 22 (26) Adverse events caused withdrawal (%): Drug 1: 1 Drug 2: 0 Drug 3: 2 Drug 4: 1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Kavuru et al.{Kavuru, 2000 #805} 2000 USA Multicenter GlaxoWellcome Inc., RTP, NC	Intervention: Drug 1 Baseline: Placebo Drug 1 Endpoint: Placebo Drug 2 Baseline: Combo Drug 2 Endpoint: Combo Drug 3 Baseline: SM or FP Drug 3 Endpoint: SM or FP Number in group (n): Drug 1- baseline: 82 Drug 1- endpoint: 77 Drug 2- baseline: 92 Drug 2- endpoint: 87 Drug 3- baseline: 92 or 90 Drug 3- endpoint: 86 or 85	Rescue med use during 24 hour period: Drug 1- baseline: 3.2 Drug 1-endpoint: Mean change 1.7 Drug 2-baseline: 3.1 Drug 2-endpoint: -1.9 (0.26) ((P</= 0 .013 versus placebo; P</=0.023 versus salmeterol; P</=0.025 versus FP 100) Drug 3 - baseline: 3.3 or 3.1 Drug 3- endpoint: -0.3 (SM); -0.4 (0.21) (FP); P</=0.013 for each vs. placebo Symptom control during 24 hour period: D1 base: asthma symptom score: 1.8 D1 end: mean change from baseline: 0.4 D2 base: 1.5 D2 end: -0.7 (-0.11) (P</=0.013 versus placebo; P</=0.023 versus SM; P</=0.025 versus FP) D3 base: 1.8 or 1.6 D3 end: -0.1 (SM), -0.2 (0.09) (FP); (for both, P</=0.013 versus placebo) Nocturnal awakenings: D1 base: nights w/out 89.9 D1 end: mean change -16.5 D2 base: 91.7 D2 end: 4.6 (1.73) (P</=0.013 versus placebo; P</=0.023 versus SM) D3 base: 91.6 or 91.3 D3 end: -5.3 (SM), 2.4 (2.34) (FP); (for both P</=0.013 versus placebo) Other Relevant Health Outcome Results: Percent of days with no astyma symptoms (mean change): placebo: -3.8; combo: 22.6 (P</=0.013 vs. placebo; P</=0.23 vs. SM; P</=0.025 vs. FP); SM: 8.0 (P</=0.013 vs. placebo); FP: 7.24 (P=NR)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Kavuru et al.{Kavuru, 2000 #805} 2000 USA Multicenter GlaxoWellcome Inc., RTP, NC	Oral candidiasis- thrush (%): Drug 1: 0 Drug 2: 1 Drug 3: 0 Drug 4: 2 Sore throat (%): Drug 1: 1 Drug 2: 4 Drug 3: 1 Drug 4: 2 Headache (%): Drug 1: 0 Drug 2: 2 Drug 3: 0 Drug 4: 0 Hoarseness (%): Drug 1: 0 Drug 2: 3 Drug 3: 1 Drug 4: 1 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: NR	Adherence Mean adherence to treatment ranged from 93% to 100% across treatment groups.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
852	Kelsen et al.{Kelsen, 1999 #852} 1999 United States 34 outpatient clinical sites Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 24 weeks N=483 Enrolled: 639 screened, 483 randomized ITT Analysis: Yes	: Non-smokers, non-pregnant, 18 years and older with symptomatic asthma despite the use of 168mcg of inhaled beclomethasone twice daily. (Symptomatic asthma was defined as >/= 3 days or nights with daytime or nighttime symptoms, or >/3 days with albuterol used as a relief medicine occurring during the 7 days prior to randomization). Baseline FEV1 45 to 80% of predicted value and to demonstrate an increase in FEV1 of >/=12% after albuterol. Must have been using an ICS on a regular basis for at least 3 months prior to enrollment and taken either 336mcg of beclomethasone daily or 800mcg of TAA daily during the 14 days prior to enrollment. Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Kelsen et al.{Kelsen, 1999 #852} 1999 United States 34 outpatient clinical sites Glaxo Wellcome	albuterol as needed for relief, stable doses of theophylline, and those drugs prescribed for an asthma exacerbation.	Smoking - current or former: nonsmokers Other: Not specifically reported	Yes: 2 week run-in all patients took beclomethasone 168mcg twice daily and as needed albuterol. At the end of the run-in, patients emeting the criteria for "symptomatic asthma" (as previously described in inclusion criteria), were randomised.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Kelsen et al.{Kelsen, 1999 #852} 1999 United States 34 outpatient clinical sites Glaxo Wellcome	Intervention: Drug 1: BDP/SM Drug 2: BDP Total daily dose: Drug 1: 336mcg/84 Drug 2: 672mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: high Delivery device: Drug 1: MDI Drug 2: MDI Is dosing comparable between treatment groups? NA: looking at ICS plus LABA versus higher dose ICS	# in group (n): Drug 1: 239 Drug 2: 244 Mean age (years): Drug 1: 42.4 Drug 2: 42 Sex (% female): Drug 1: 57 Drug 2: 65 Current smokers (%): Drug 1: 0 Drug 2: 0 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Optional - Current methylxanthine (i.e. theophylline) use (%): Drug 1: 22 Drug 2: 22 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 48 (20%) Drug 2: 49 (20%) Overall: 97 (20%) Adverse events caused withdrawal (%): Drug 1: 7% Drug 2: 7% Overall: 7%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Kelsen et al.{Kelsen, 1999 #852} 1999 United States 34 outpatient clinical sites Glaxo Wellcome	Intervention: Drug 1 Baseline: BDP/ SM Drug 1 Endpoint: BDP/ SM Drug 2 Baseline: BDP Drug 2 Endpoint: BDP Number in group (n): Drug 1- baseline: 239 Drug 2- baseline: 244	Rescue med use during 24 hour period: Drug 1- baseline: % of days with no albuterol use: Drug 1-endpoint: % of days with no albuterol use = NR Drug 2-endpoint: NR P </= 0.011 for BDP/SM versus BDP Rescue med use day: Drug 1- baseline: mean puffs/day Drug 1 -endpoint: NR P </= 0.011 for BDP/SM versus BDP Rescue med use at night: Drug 1- baseline: puffs/night: 0.89 Drug 1 - endpoint: -0.52 (0.06) Drug 2 - baseline: 1.04 Drug 2 - endpoint: -0.44 (0.08) P </= 0.05 for BDP/SM versus BDP Asthma exacerbations: D1 end: 38 patients (16%) reported 52 exacerbations D2 end: 44 patients (18%) reported 58 exacerbations P = NS Symptom control during 24 hour period: D1 base: Asthma Symptom Score for wheezing, shortness of breath, and chest tightness. cough D1 end: Asthma Symptom Score (mean change from baseline) for wheezing -0.35, shortness of breath -0.48, and chest tightness -0.45. cough NR D2 end: -0.22, -0.28, -0.26. cough NR P </= 0.05 for BDP/Sal versus BDP; cough NR, NS Night time symptom control: D1 - base: % nights with no awakenings: 67 D1 - end: % nights with no awakenings (mean change from baseline) = 18.8 D2 - base: 68 D2 - end: 13.4 P </= 0.05 for BdP/Sal versus BDP Nocturnal awakenings:

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Kelsen et al.{Kelsen, 1999 #852} 1999 United States 34 outpatient clinical sites Glaxo Wellcome	Overall adverse events reported (%): Drug 1: 11 Drug 2: 14 P = NS Oral candidiasis- thrush (%): Drug 1: 2 Drug 2: 6 P = 0.059 Cough (%): Drug 1: 7 Drug 2: 4 Sore throat (%): Drug 1: 7 Drug 2: 8 Headache (%): Drug 1: 8 Drug 2: 7 Headache (%): Drug 1: 8 Drug 2: 7 Respiratory infection (%): Drug 1: 28 Drug 2: 29 Other (%): Drug 1: sinusitis = 10 Drug 2: 11 Other (%): Drug 1: bronchitis = 6 ; nausea and vomiting 3; disturbance of temperature regulation 4 Drug 2: 5 ; 5 ; <1 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: Abnormal baseline cortioctrophin stimulation was similar between groups (BDP/SM 0 versus BDP 1). After 24 weeks, the number with abnormal response to stimulation was not statistically different between groups (BDP/SM 1 versus BDP 1).	NR	Fair: attrition Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1053	Kemp et al.{Kemp, 1998 #1053} 1998 USA Multicenter Glaxo Wellcome, Inc	Study design: RCT double-blind parallel-group study Duration: 12 weeks N=506 ITT Analysis:	Male or female patients (>12 years of age) met the criteria for asthma as defined by the American Thoracic Society, had an average daytime or night time symptom score of 1 on a 0 to 3 point scale over a 2-week screening period, used a short-acting bronchodilator on a daily basis, and used a fixed dose of ICS that was within package insert guidelines

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Kemp et al.{Kemp, 1998 #1053} 1998 USA Multicenter Glaxo Wellcome, Inc		tobacco use, oral corticosteroid therapy, immunotherapy requiring dosage change, inability to withdraw asthma/allergy medications before pulmonary function testing at screening; cystic fibrosis, chronic obstructive pulmonary disease, any significant uncontrolled disease state other than asthma, any other significant illness, pregnancy or lactation, contraindication to study medications, or inability to complete baseline QOL assessment. Patients also had to have stable asthma that did not require excess albuterol use, required hospitalization for asthma within 3 months, mechanical ventilation during an asthma exacerbation within 2 years, or more than 2 albuterol (or equivalent) inhalers per month within 3 months of screening.	None

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Kemp et al.{Kemp, 1998 #1053} 1998 USA Multicenter Glaxo Wellcome, Inc	Intervention: Drug 1: Placebo Drug 2: SM Total daily dose: Drug 1: NA Drug 2: 42µg Steroid dosing range: NA Delivery device: Drug 1: Aerolizer Drug 2: Diskus Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 254 Drug 2: 252 Mean age (years): Drug 1: 41.6 Drug 2: 42.0 Sex (% female): Drug 1: 52 Drug 2: 55	Number (%) withdrawn: Drug 1: 19 Drug 2: 10 Adverse events caused withdrawal (%): Drug 1: 2 Drug 2: 3

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Kemp et al.{Kemp, 1998 #1053} 1998 USA Multicenter Glaxo Wellcome, Inc	Intervention: Drug 1: Placebo Drug 2: SM # in group (n): Drug 1: 254 Drug 2: 252	Symptoms: ICS+SM > ICS+placebo [Daytime symptom score, mean change from baseline (SEM): -0.55 (0.03) vs. -0.30 (0.03); P<0.001; Nighttime symptom score): -0.65 (0.04) vs. -0.26 (0.04); P<0.001] Rescue med use: ICS+SM > ICS+ placebo [Puffs/day, mean change from baseline (SEM): -2.73 (0.16) vs. -1.06 (0.12), P<0.001; Puffs/night, mean change from baseline (SEM): -0.75 (0.07) vs. -0.18 (0.07), P<0.001; % rescue-free days, mean change: 38.1 (2.3) vs. 13.6 (1.8), P<0.001; % rescue-free nights, mean change: 29.2 (2.4) vs. 9.5 (1.8), P<0.001] Quality of life: No difference, trend toward ICS+SM > ICS + placebo [AQLQ global score: baseline mean (SEM): 4.30 (0.06) vs. 4.27 (0.06); mean change from baseline (SEM): 1.08 (0.08) vs. 0.61 (0.07), P=0.47; AQLQ activity limitation: 4.64 (0.07) vs. 4.57 (0.07); mean change: 0.91 (0.07) vs. 0.54 (0.07), P=0.37; AQLQ asthma symptoms: 4.07 (0.07) vs. 4.05 (0.06); mean change: 1.28 (0.08) vs. 0.71 (0.08), P=0.57; AQLQ emotional function: 3.96 (0.09) vs. 4.02 (0.09); mean change 1.17 (0.10) vs. 0.65 (0.09), P=0.52; AQLQ environmental exposure: 4.50 (0.09) vs. 4.45 (0.09); mean change: 0.84 (0.09) vs. 0.47 (0.08), P= Asthma exacerbations: Drug 1: 59 (n); 22% Drug 2: 53 (n), 20%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Kemp et al.{Kemp, 1998 #1053} 1998 USA Multicenter Glaxo Wellcome, Inc	Overall adverse events reported (%): Drug 1: 51% Drug 2: 53%	No	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
343	Kemp{Kemp, 2004 #343} 2004 USA, Multicenter GlaxoSmithKline	Study design: RCT Double-blind Duration: 2 years N= 160 Enrolled: 190/160/160	Men aged 18-50 y; women aged 18-40 y (not pregnant, nonlactating, premenopausal, and, if of child-bearing age, using defined contraception) Asthma history: at least a 6-mo history of stable and relatively mild asthma Hypothalamic- Normal stimulated cortisol response, defined pituitary-adrenal as morning plasma cortisol of ≥5 µg/dL, axis increase from baseline of ≥7 µg/dL, and peak of ≥18 µg/dL, was required; during the study, a more conservative limit (≥35 µg/dL) was also evaluated but was not exclusionary for study entry Bone mineral Normal BMD on screening; On screening, absence of glaucoma, posterior examination subcapsular cataracts, or blindness FEV1 On screening, FEV1 of 50%-100% predicted Prior corticosteroid None (any type) for 1 mo before screening

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Kemp{Kemp, 2004 #343} 2004 USA, Multicenter GlaxoSmithKline	As needed theophylline, β-adrenergic agonists, cromolyn sodium, or nedocromil. Two courses (maximum) of 1 to 10 days of oral prednisone were allowed each year.	Clinically meaningful diseases, glucocorticoid therapy, anticholinergic medications/ drugs, anticonvulsants, digitalis, ketoconazole, supplements fluoride, calcitonin, nondietary vitamin D supplements, rifampicin, methylphenidate, meprobamate, hormone replacement therapy, medroxyprogesterone acetate; Reversal of normal nocturnal sleeping hours; criteria alterations in body weight: anorexia, morbid obesity, or recent unexplained weight loss of >25%; substance abuse, including drug and alcohol abuse	21 day placebo run-in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Kemp{Kemp, 2004 #343} 2004 USA, Multicenter GlaxoSmithKline	Intervention: Drug 1: Placebo BID Drug 2: FP 88 µg BID Drug 3: FP 440 µg BID	% female: Drug 1: Placebo BID 41 Drug 2: FP 88 µg BID 40 Drug 3: FP 440 µg BID 41 Mean age: Drug 1: Placebo BID 28.4 Drug 2: FP 88 µg BID 31.6 Drug 3: FP 440 µg BID 29.0 White/Black/Other %: Drug 1: Placebo BID 89/6/6 Drug 2: FP 88 µg BID 82/5/13 Drug 3: FP 440 µg BID 90/0/10 No current smokers Former smokers %: Drug 1: Placebo BID 15 Drug 2: FP 88 µg BID 18 Drug 3: FP 440 µg BID 10	Overall withdrawals n(%): Drug 1: Placebo BID 14/54 Drug 2: FP 88 µg BID 23/55 Drug 3: FP 440 µg BID 25/51 Withdrawal due to adverse events Drug 1: Placebo BID 1/54 Drug 2: FP 88 µg BID 1/55 Drug 3: FP 440 µg BID 5/51

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Kemp{Kemp, 2004 #343} 2004 USA, Multicenter GlaxoSmithKline	Intervention: Drug 1: Placebo BID Drug 2: FP 88 µg BID Drug 3: FP 440 µg BID Number in group (n): Drug 1: 54 Drug 2: 55 Drug 3: 51	Among the 3 groups, no significant differences were observed in BMD at week 104 (at any anatomical site). Mean percent change from baseline in the lumbar spine was less than 1% for all 3 groups. Change from baseline- Lumbar spine (SE) Placebo BID -0.001(0.005) FP 88 ug BID 0.000(0.006) FP 440 ug BID -0.004(0.006) Proximal femur Placebo BID -0.004(0.006) FP 88 ug BID -0.007(0.007) FP 440 ug BID -0.012(0.006) Total body Placebo BID 0.008(0.004) FP 88 ug BID 0.010(0.005) FP 440 ug BID 0.002 (0.003)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Kemp{Kemp, 2004 #343} 2004 USA, Multicenter GlaxoSmithKline	See outcomes.	No	NA Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
5068	Kim et al.{Kim, 2000 #5068} 2000 United States Multicenter GlaxoSmithKline	Study design: RCT Double-blind Double-dummy Duration: 6 weeks N= 437 Enrolled: 563, 437, 437 ITT Analysis: Yes	: Male and female patients>= 12 years of age with a diagnosis of asthma were eligible for the study if they met the following criteria: had an FEV1 of 60% to 85% of predicted values, had an increase in FEV1 of >=12% from baseline after inhalation of 180 µg of albuterol, used albuterol on a scheduled or as-needed basis, used low doses of ICSs for at least 8 weeks, and used a fixed dose of inhaled BDP (168 to 336 µg /day) or TAA (400 to 800 µg /day) for at least 4 weeks immediately before screening and during the l-week run-in period. The dose ranges of BDP and TAA used were defined as low-dose based on current asthma treatmentl guidelines. Asthma severity: Mild Moderate Controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Kim et al.{Kim, 2000 #5068} 2000 United States Multicenter GlaxoSmithKline	Albuterol for rescue.	Other: Patients were not allowed ~,: to have received montelukast, zaflrrlukast, or zileuton within 1 week or !9 systemic corticosteroids within 6l,',! weeks of screening. Patients who had a history of life-threatening asthma or t .'had1 rece~ved m~rde th~th°ne burst ofora corticosterOl s WI in 6 months were excluded. Other exclusion critei"ria included' use of tobacco prQducts within the previous year or a smoking history of > 10 pack-years; respiratory infection within 2 weeks of screening or during the run-in period; current evidence of significant respiratory disordersother than asthma; or other significantuncontrolled disease states. Concurrent use of medications that might affect the course of asthma (eg, salmeterol, theophylline) or interact with zafirlukast were prohibited.	Yes: During the run-in period, each patient's dose of BDP or TAA was maintained, and all patients used rescue albuterol to relieve breakthroughsymptoms of asthma (Ventolin Inhalation Aerosol, Glaxo Wellcome Inc, Research Triangle Park, NC). The purpose of the I-week run-in period was to monitor the stability of the patients'asthma, confirm each patient's eligibility for the study, obtain baseline diary card assessments of asthma symptom scores and rescue albuterol use, and to assess patient compliance in completing diary cards. Following run-in, - the patients had to meet the following asthma stability criteria: (1) a FEV1 between 60% to 85% of predicted'normal, (2) an average of ~4 puffs/day of rescue albuterol over the 7 days prior to randomization, and (3)~ I night with an awakening due to asthma over the 7 days prior to randomization.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Kim et al.{Kim, 2000 #5068} 2000 United States Multicenter GlaxoSmithKline	Intervention: Drug 1: FP Drug 2: Zafirlukast Total daily dose: Drug 1: 176mcg/day Drug 2: 40mg/day Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: NA Is dosing comparable between treatment groups? NA: ICS vs LTRA	# in group (n): Drug 1: 221 Drug 2: 216 Mean age (years): Drug 1: 35.5 Drug 2: 32.9 Sex (% female): Drug 1: 61 Drug 2: 59 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100	Number (%) withdrawn: Drug 1: 19 (9%) Drug 2: 46 (21%) Overall: 65 (15%) Optional - Withdrew due to lack of efficacy (%) Drug 1: 2 Drug 2: 14 Overall: p = 0.001 Adverse events caused withdrawal (%): Drug 1: 3 Drug 2: 4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Kim et al.{Kim, 2000 #5068} 2000 United States Multicenter GlaxoSmithKline	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: Zafirlukast Drug 2 Endpoint: Zafirlukast Number in group (n): Drug 1- baseline: 221 Drug 1- endpoint: 221 Drug 2- baseline: 216 Drug 2- endpoint: 216	Rescue med use during 24 hour period: Drug 1- baseline: mean puffs/day (SE): 1.96 (0.10) Drug 1-endpoint: -0.66 (0.11) Drug 2-baseline: 1.88 (0.11) Drug 2-endpoint: 0.27 (0.13 P <0.001 at endpoint Rescue med use day: Drug 1- baseline: % rescue free days, mean baseline (SE) = 34 (2.6) Drug 1 -endpoint: 57.1 (2.7) Drug 2 - baseline: 35.9 (2.6) Drug 2 - endpoint: 45 (2.8) P <0.001 increase in % rescue-free days at endpoint (mean change in % rescue-free days: FP 23.4 (2.5) vs Zaf 9.3 (2.4) Asthma exacerbations: exacerbation requiring treatment with oral or iv steroids D1 end: 5 D2 end: 14 P =: 0.035 Day time symptom control: D1 - base: % symptom free days, mean baseline (SE) = 30.9 (2.4) D1 - end: 16.2 (+/- 2.4) D2 - base: 30 (2.3) D2 - end: 7.1 (+/- 2.9) P = 0.007 at endpoint Night time symptom control: D1 - base: mean % awakening free nights (SE) = 97.3 (0.5) D1 - end: 96 D2 - base: 96.8 (0.5) D2 - end: 88 P <0.001 at endpoint Other Relevant Health Outcome Results: Mean asthma symptom scores were low at baseline for each of the four asthma symptoms evaluated (wheeze, shortness of breath, chest tightness, and cough) and AQLQ: Treatment with FP resulted in an increase from baseline in AQLQ scores, a

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Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Kim et al.{Kim, 2000 #5068} 2000 United States Multicenter GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 3at least one AE thought to be related to drug 30 (14%) Drug 2: 15 (7%) P = 0.027 Dysphonia (%): Drug 1: 1 Drug 2: 0 Sore throat (%): Drug 1: <1 Drug 2: 2 Headache (%): Drug 1: 5 Drug 2: 3 Other (%): Drug 1: nausea = 2 Drug 2: <1 Other (%): Drug 1: diarrhea = 2 Drug 2: 0 Other (%): Drug 1: fatigue = 1 Drug 2: 0	Compliance patient self reported at 88% for both groups	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
829	Kips et al.{Kips, 2000 #829} 2000 Multinational (Canada, UK and Belgium) Multicenter (3 University clinics) Astra Draco	Study design: RCT Double-blind Duration: 1 year N: 60 Enrolled: NR/NR/70 ITT? Unable to determine	Established diagnosis of asthma for at least 6 mo; between 18 and 70 yr of age, treated with ICS for at least 3 mo. The dose of ICS had to be constant for at least 1 mo. Baseline FEV 1 had to be at least 50% of the predicted value. The increase in FEV1 in response to an inhalation of 1 mg of terbutaline was at least 15% from baseline or 9% of the predicted value. Patients were randomized only if they had taken between 75% and 125% of the recommended number of doses of BUD and if their asthma had been stable for the last 10 days fo the run-in period Asthma Severity: Controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Kips et al.{Kips, 2000 #829} 2000 Multinational (Canada, UK and Belgium) Multicenter (3 University clinics) Astra Draco	rescue terbutaline	treated daily with more than 2,000 mg of BDP, more than 1,600 mg of BUD via pressurized metered dose inhaler, more than 800 mg of BUD via Turbuhaler or more than 800 mg of FP. Patients who had needed at least three courses of oral steroids or who had been hospitalized owing to asthma in past 6 mo	Yes- 1 month on BUD in addition to terbutaline as needed

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Kips et al.{Kips, 2000 #829} 2000 Multinational (Canada, UK and Belgium) Multicenter (3 University clinics) Astra Draco	Intervention: Drug 1: BUD + FM Drug 2: BUD Total daily dose: Drug 1: 200+24 Drug 2: 800 Steroid dosing range: Drug 1: low Drug 2: medium Delivery device: Drug 1: Turbuhaler Drug 2: Turbuhaler Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 29 Drug 2: 31 Mean age (years): Drug 1: 34.7 Drug 2: 37.6 Sex (% female): Drug 1: 59 Drug 2: 61 Current smokers (%): Drug 1: NR Drug 2: NR Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: NR Drug 2: NR Adverse events caused withdrawal (%): Drug 1: NR Drug 2: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Kips et al.{Kips, 2000 #829} 2000 Multinational (Canada, UK and Belgium) Multicenter (3 University clinics) Astra Draco	Intervention: Drug 1 Baseline: BDU+FM Drug 1 Endpoint: BUD + FM Drug 2 Baseline: BUD Drug 2 Endpoint: BUD Number in group (n): Drug 1- endpoint: 29 Drug 2- endpoint: 31	Severe exacerbations, n (rate = n/pt/yr) Drug 1 - endpoint: 8 (0.29) Drug 2 - endpoint: 12 (0.47) P = NS Asthma exacerbations: Mild exacerbations, n (rate = n/pt/yr) D1 end: 339 (18.3) D2 end: 348 (14.6) P = NS Symptom control during 24 hour period: D1 base: Episode free days % D1 end: 41.3 (7.0) D2 end: 30.4 (6.0) P = NS Other Relevant Health Outcome Results: Both morning and evening symptom scores were consistently lower in the BUD+FM group. The difference was not significant and no significant changes occurred during the treatment period. The use of rescue inhalers and nocturnal awakenings did not differ between treatment groups.

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Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Kips et al.{Kips, 2000 #829} 2000 Multinational (Canada, UK and Belgium) Multicenter (3 University clinics) Astra Draco	NA	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
127	Koopmans et al.{Koopmans, 2006 #127} 2006 The Netherlands Outpatient, Academic Medical Center GlaxoSmithKline	Study design: RCT Double-blind Duration: 1 year N=54 Enrolled: 60 agreed to participate/54 randomized ITT? Unable to determine	mild-mod persistent allergic asthma; From online appendix: 1. sensitization to housedust mite (Dermatophagoides pteronyssinus) and/or cat dander and/or grass pollen, asdetermined by Radio-Allergo-Sorbent-Test (RAST) and skin prick test; 2. age between 18 and60 years; 3. FEV1 70 % of the predicted value after maximal bronchodilation; 4. bronchialhyperresponsiveness to histamine, PC20histamine 8.0 mg/ml at the end of the run-in period;5. clinically stable disease, no exacerbations of asthma within 3 months prior to inclusionrequiring oral steroids and/or antibiotics; 6. no changes to regular asthma medication during 4weeks before entry; 7. able to correctly inhale via a Diskus inhaler; 8. able to performreproducible lung function tests Asthma Severity: Mild Moderate Other: mild-moderate persistent allergic asthma

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Koopmans et al.{Koopmans, 2006 #127} 2006 The Netherlands Outpatient, Academic Medical Center GlaxoSmithKline	salbutamol PRN	Smoking - current or former: non-specific exclusion Other: from online appendix: 1. comorbidity likely to interfere with the study; 2.lower respiratory tract infection during 4 weeks before entry; 3. use of theophyline, sodiumcromoglycate, nedocromil sodium or antileukotrienes during the study or antibiotics 4 weeksprior to the study; 4. current smoking, regularly smoking within 6 months before entry or asmoking history of more than 10 pack years; 5. pregnant or lactating females; 6. unable tofollow the therapy instructions; 7. participation in another clinical trial within 4 weeks prior tothe study.	Yes- 2wk steroid washout followed by a 4wk run-in with FP 250mcg BID and baseline bronchial allergen challenge.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Koopmans et al.{Koopmans, 2006 #127} 2006 The Netherlands Outpatient, Academic Medical Center GlaxoSmithKline	Intervention: Drug 1: FP Drug 2: FP/SM Total daily dose: Drug 1: 500mcg Drug 2: 500/100mcg Steroid dosing range: Drug 1: medium Drug 2: medium Delivery device: Drug 1: DPI Drug 2: DPI Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 27 Drug 2: 27 Mean age (years): Drug 1: 32 Drug 2: 32 Sex (% female): Drug 1: 70 Drug 2: 63 Current smokers (%): Drug 1: 0 Drug 2: 0 Optional - Rescue medication use (puffs per day): Drug 1: 1.4 Drug 2: 1.0 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Other: Drug 1: total IgE (IU/mL) 127 Drug 2: 172 Other: Drug 1: Sx score (scale 0-4) AM, PM 0.2, 0.6 Drug 2: 0.3, 0.6 Groups similar at baseline? No - FP	Number (%) withdrawn: Drug 1: 4 (14.8) Drug 2: 0 Overall: 4 (14.8) Optional - Withdrew due to asthma exacerbations (%): Drug 1: 3.7 Optional - Other reasons for withdrawal (%): Drug 1: "personal reasons" 7.4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Koopmans et al.{Koopmans, 2006 #127} 2006 The Netherlands Outpatient, Academic Medical Center GlaxoSmithKline	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: FP/SM Drug 2 Endpoint: FP/SM P-values (Define comparison): Mean difference between groups FP/S minus FP alone, (SE), (p-value) Number in group (n): Drug 1- baseline: 27 Drug 1- endpoint: 23 Drug 2- baseline: 27 Drug 2- endpoint: 27	Rescue med use during 24 hour period: P values: -0.9 (0.3), (<0.001) Day time symptom control: D1 - base: Sx score, AM (0-4 scale) D3 - endP: -0.1 (0.1), (0.02) Night time symptom control: D1 - base: Sx score, PM (0-5 scale) D3 - endP: -0.2 (0.1), (0.01)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Koopmans et al.{Koopmans, 2006 #127} 2006 The Netherlands Outpatient, Academic Medical Center GlaxoSmithKline	NR	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4864 Combo	Kuna and Price {Price, 2007 #4789} 2007 How do you want ID# 4864 cited? -Rachael Multinational (16 countries) Multicenter (235 centers) Astrazeneca	Study design: RCT Double-blind Double-dummy Duration: 6 months N=3335 Enrolled: 4399/3467/3335 ITT Analysis: Yes	Outpatients aged at least 12 years with a diagnosis of asthma for at least 6 months 6 months and using ICS for 3 months or more; FEV1 at least 50% predicted normal with at least 12% reversibility following terbutaline 1 mg and 1 or more asthma exacerbation in the previous 1–12 months. Patients using reliever medication on at least 5 of the last 7 days of the 2-week run-in Asthma severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Kuna and Price {Price, 2007 #4789} 2007 How do you want ID# 4864 cited? -Rachael Multinational (16 countries) Multicenter (235 centers) Astrazeneca	Terbutaline for relief	More than 10 as-needed inhalations in any day of run-in and patients whoexperienced an asthma exacerbation during run-in; systemic corticosteroidsor with respiratory infections affecting asthma control within 30 days	Yes- elucidate....: 2 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Kuna and Price {Price, 2007 #4789} 2007 How do you want ID# 4864 cited? -Rachael Multinational (16 countries) Multicenter (235 centers) Astrazeneca	Intervention: Drug 1: FP/SM Drug 2: BUD/FM Drug 3: BUD/FM SMART Total daily dose: Drug 1: 500/100 Drug 2: 640/18 Drug 3: 320/9 + prn Steroid dosing range (Low, medium or high): Drug 1: Med Drug 2: Med Drug 3: low plus prn amount Delivery device: Drug 1: DPI Drug 2: pMDI Drug 3: pMDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 1123 Drug 2: 1105 Drug 3: 1107 Mean age (years): Drug 1: 38 Drug 2: 38 Drug 3: 38 Sex (% female): Drug 1: 57 Drug 2: 59 Drug 3: 57 Current smokers (%): Drug 1: 5 Drug 2: 7 Drug 3: 5 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100	Number (%) withdrawn: Drug 1: 45 (4%) Drug 2: 53 (5) Drug 3: 51 (5%) Adverse events caused withdrawal (%): Drug 1: 1% Drug 2: 1% Drug 3: 1%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Kuna and Price {Price, 2007 #4789} 2007 How do you want ID# 4864 cited? -Rachael Multinational (16 countries) Multicenter (235 centers) Astrazeneca	Intervention: Drug 1 Baseline: FP/SM Drug 1 Endpoint: FP/SM Drug 2 Baseline: BUD/FM Drug 2 Endpint: BUD/FM Drug 3 Baseline: BUD/FM SMART Drug 3 Endpoint: BUD/FM SMART P-values (Define comparison): BUD/FM vs. FP/SM, SMART vs. BUD/FM, SMART vs. FP/SM Number in group (n): Drug 1- baseline: 1123 Drug 1- endpoint: 1123 Drug 2- baseline: 1105 Drug 2-endpoint: 1105 Drug 3- baseline: 1107 Drug 3- endpoint: 1107	Rescue med use during 24 hour period: Drug 1- baseline: total # inhalations/day: 2.33 Drug 1-endpoint: 0.96 Drug 2-baseline: 2.31 Drug 2-endpoint: 1.05 Drug 3 - baseline: 2.29 Drug 3- endpoint: Mean difference(95% CI): 0.10 (0.01 to 0.19) P < 0.05 ; -0.03(-0.12 to 0.06) P = NS ; 0.07 (-0.02 to 0.16) P = NS Asthma exacerbations: Severe exacerbations: # of patients (%) having at least one/rate per 100 patients/6 mos D1 end: 138 (12%)/19 D2 end: 126 (11%)/16 D3 end: 94 (9%)/12 0.91 (0.72 to 1.16); P = 0.45/ 0.85 (0.69 to 1.04); P = 0.1; 0.74 (0.56 to 0.9 P = 0.026 / 0.72 (0.57 to 0.90) P =0.0048; 0.67 (0.52 to 0.87) P = 0.003 / 0.61 (0.49 to 0.76) P < 0.001 Symptom control during 24 hour period: D1 base: total symptom score (0-6): 1.93 D1 end: 1.03 D2 base: 1.93 D2 end: 1.07 D3 base: 1.91 D3 end: 1.06 Mean difference(95% CI): 0.04 (-0.02 to 0.11)/ 0.00 (-0.07 to 0.06) / 0.04 (-0.03 to 0.10) for all P = NS Day time symptom control: D1 - base: Symtom free days (%) 8.6 D1 - end: 46.0 D2 - base: 8.8 D2 - end: 44.6 D3 - base: 9.3 D3 - end: 44.2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Kuna and Price {Price, 2007 #4789}	Serious adverse events (%): Drug 1: 3%	Adherence	Good Fair
2007 How do you want ID# 4864 cited? -Rachael	Drug 2: 4% Drug 3: 3%	99% of all patients were 81% adherent	No
Multinational (16 countries) Multicenter (235 centers)	Death (%): Drug 1: 1 person from cardiac arrest Drug 2: 0 Drug 3: 1 RESPIRATORY FAILURE		
Astrazeneca	Additional adverse events and comments: "All three treatments were well tolerated and there were no notable between-group differences in the number or severity of adverse events."		

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
100	Kuna et al.{Kuna, 2006 #100} 2006 61 centers in 8 countries AstraZeneca	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=617 Enrolled: 658 enrolled --> 617 randomized to treatment ITT? Yes	Age: >=18yr FEV 1 expressed as a percent of the predicted value: 60-90 Reversability of FEV1: 12% s/p terbutaline 1mg or salbutamol 0.4mg Other: asthma diagnosis >=6mo that was not optimally controlled despite adaily ICS dose of 200–500 mg for at least 30 days before study entry. Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Kuna et al.{Kuna, 2006 #100} 2006 61 centers in 8 countries AstraZeneca	Patients were given terbutaline sulfate (Bricanyls Turbuhalers) or another preferred shortacting b2-agonist for as-needed reliever medication. The same reliever was used throughout the study. No other concomitant asthma medication was allowed during the study.	Pregnant or lactating: women of child-bearing potential who were pregnant or failed to use effective contraception Prior treatment with: OCS within 30 days of study entry Concommitant diseases: seasonal asthma (defined as asthma exacerbatedby seasonal increases in aeroallergens); a respiratory infection in the 4 weeks before studyentry; a severe cardiovascular disorder or anyother significant disease Current treatment: b-blocker therapy (including eye drops) Smoking - current or former: >=10PY Other: unable touse a peak flow meter or who did not complete thedaily diary card during 7 or more of the last 10 daysof the run-in period were not permitted to enterthe randomized treatment period	Yes- 2wk where patients received BUD 100mcg BID

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Kuna et al.{Kuna, 2006 #100} 2006 61 centers in 8 countries AstraZeneca	Intervention: Drug 1: BUD+FM daily Drug 2: BUD+FM BID Drug 3: BUD daily Total daily dose: Drug 1: 160/9mcg Drug 2: 160/9mcg Drug 3: 200mcg Steroid dosing range: Drug 1: low Drug 2: low Drug 3: low Delivery device: Drug 1: Turbuhaler Drug 2: Turbuhaler Delivery device: Drug 1: Turbuhaler Drug 2: Turbuhaler Drug 3: Turbuhaler Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 202 Drug 2: 207 Drug 3: 207 Mean age (years): Drug 1: 45.8 Drug 2: 43.9 Drug 3: 45.1 Sex (% female): Drug 1: 60 Drug 2: 62 Drug 3: 56 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Optional - Disease duration (years): Drug 1: 11.5 Drug 2: 12.2 Drug 3: 10.6 Optional - % of rescue free days: Drug 1: symptom-free days 38 Drug 2: 36 Drug 3: 38 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100	Number (%) withdrawn: Drug 1: 21 (10.4) Drug 2: 16 (7.7) Drug 3: 24(11.6) Overall: 61(10) Adverse events caused withdrawal (%): Drug 1: 2.5 Drug 2: 1.4 Drug 3: 1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Kuna et al.{Kuna, 2006 #100} 2006 61 centers in 8 countries AstraZeneca	Intervention: Drug 1 Baseline: BUD+FM daily Drug 1 Endpoint: BUD+FM daily Drug 2 Baseline: BUD+FM BID Drug 2 Endpoint: BUD+FM BID Drug 3 Baseline: BUD daily Drug 3 Endpoint: BUD daily Number in group (n): Drug 1- baseline: 202 Drug 1- endpoint: 202 Drug 2- baseline: 207 Drug 2-endpoint: 206 Drug 3- baseline: 207 Drug 3- endpoint: 207	Rescue med use during 24 hour period: Drug 1- baseline: releiver-free days, treatment mean % (95%CI) Drug 1-endpoint: 61.8, (58.1, 65.4) Drug 2-endpoint: 66.3 (62.7, 69.9) Drug 3- endpoint: 55.5 (52.0, 59.1) Endpoint drug1 vs drug3 P < 0.05; endpoint drug2 vs drug3 endpoint P < 0.001 Symptom control during 24 hour period: D1 base: treatment mean %, (95%CI) = 37.8 D1 end: 50.0 (46.0, 54.0) D2 base: 36.1 D2 end: 50.3 (46.3, 54.3) D3 base: 38 D3 end: 43.4 (39.4, 47.3) Endpoints for both drug1 and drug2 vs drug3, P < 0.05 Nocturnal awakenings: D1 base: treatment mean % (95%CI) = 15.8 D1 end: 11.3 (9.0, 13,6) D2 base: 14.6 D2 end: 9.9 (7.7, 12.2) D3 base: 17.9 D3 end: 12.0 (9.8, 14.3) P: NS Asthma Control Score: D1 base: asthma control days, treatment mean % (95%CI)= 33.9 D1 end: 47.3 (43.4, 51.3) D2 base: 32.5 D2 end: 47.3 (43.3, 51.1) D3 base: 35.1 D3 end: 40.0 (36.2, 43.9) Endpoints for both drug1 and drug2 vs drug3 P < 0.01

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Kuna et al.{Kuna, 2006 #100} 2006 61 centers in 8 countries AstraZeneca	Overall adverse events reported (%): Drug 1: 38 Drug 2: 38 Drug 3: 36 Serious adverse events (%): Drug 1: 1 Drug 2: <1 Drug 3: 2 Sore throat (%): Drug 1: 2.0 Drug 2: 3.4 Drug 3: 2.4 Headache (%): Drug 1: 2.0 Drug 2: 1.9 Drug 3: 1.0 Respiratory infection (%): Drug 1: 11.4 Drug 2: 15.5 Drug 3: 12.1 Rhinitis (%): Drug 1: 2.0 Drug 2: 1.9 Drug 3: 1.9 Death (%): Drug 1: pharynx disorder 2.0 Drug 2: 1.0 Drug 3: 0.5 Other (%): Drug 1: asrhma aggravated 5.9 Drug 2: 2.9 Drug 3: 4.8 Other (%): Drug 1: viral infection 3.0 Drug 2: 3.4 Drug 3: 2.4 Other (%): Drug 1: bronchitis 1.0 Drug 2: 2.9 Drug 3: 1.4	Adherence Self reported adherence to study medication was high, with a mean medcication use of >97% in all treatment arms	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
452	Lalloo et al.{Lalloo, 2003 #452} 2003 Multinational (51 centers: Czech Republic, Hungary, Norway, Poland, South Africa, United Kingdom) University hospitals AstraZeneca	Study design: RCT Double-blind Duration: 12 weeks N=467 Enrolled: 494 screened; 467 randomised ITT? Yes	Male and female, aged >/= 18, with a diagnosis of asthma for a minimum of 6 months, FEV1 of 60 to 90% of predicted, and >/= 12% reversibility of FEV1 within 15 min of inhalation of albuterol, all used inhaled corticosteroid at a constant dose 200 to 500 mcg per day for at least 1 month prior to study entry. Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Lalloo et al.{Lalloo, 2003 #452} 2003 Multinational (51 centers: Czech Republic, Hungary, Norway, Poland, South Africa, United Kingdom) University hospitals AstraZeneca	Inhaled terbutaline or salbutoaml depeing on patient preference for rescue throughout study. Meds NOT permitted included: systemic antihistamines, beta blockers or other antiasthma products.	Other: Use of oral, parenteral, or rectal steroids within 30 days of study, any respiratory infection affecting disease control within the previous 4 weeks and known hypersensitivity to study medication or inhaled lactose. Severe cardiovascular disorders or significant concomitant diseases, and current and previous smokers with a history of smoking for >/= 10 pack years. Females were required to be postmenopausal, surgically sterile, or using adequate contraceptive methods during study.	Yes- BUD 100mcg BID for 2 week run-in.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Lalloo et al.{Lalloo, 2003 #452} 2003 Multinational (51 centers: Czech Republic, Hungary, Norway, Poland, South Africa, United Kingdom) University hospitals AstraZeneca	Intervention: Drug 1: BUD/FM 80/4.5 BID Drug 2: BUD 200 BID Total daily dose: Drug 1: 160mcg Drug 2: 400mcg Steroid dosing range: Drug 1: low Drug 2: low Delivery device: Drug 1: DPI Drug 2: DPI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 230 Drug 2: 237 Overall: 467 Mean age (years): Drug 1: 42 Drug 2: 40 Sex (% female): Drug 1: 56 Drug 2: 59 Current smokers (%): Drug 1: NR Drug 2: NR Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 15 (7) Drug 2: 22 (9) Overall: 37 (8) Adverse events caused withdrawal (%): Drug 1: 1 Drug 2: 1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Lalloo et al.{Lalloo, 2003 #452} 2003 Multinational (51 centers: Czech Republic, Hungary, Norway, Poland, South Africa, United Kingdom) University hospitals AstraZeneca	Intervention: Drug 1 : BUD/FM Drug 2: BUD Number in group (n): Drug 1: 230 Drug 2: 237	Rescue med use during 24 hour period: Drug 1: baseline: 1.3; mean change from baseline: -0.33 Drug 2: 1.2; -0.1 P = 0.025 for comparison of change from baseline btwn groups. Asthma exacerbations: D1 at least one mild asthma exacerbation = 110 (48%); proportion of patients with severe exacerbations = 7% D2: 136 (57%); severe exacerbations = 7% Symptom control during 24 hour period: D1 : improvement in proportion of symptom free days = +16% D2: +10% Estimated between group difference was 6% (95% CI 2 to 11%); p=0.007 Night time symptom control: D1 - base: repeated nighttime awakeneings = 75 D2: 105 P = NR Nocturnal awakenings: D1: Reduction from run-in baseline: 23% D2: 14% P = NR Asthma Control Test: D1 : change in proportion of asthma control days = +17% D2: +10% Estimated between group difference 8% (95% CI 3 to 13%); P = 0.002 Other: D1 : Reduction from baseline for asthma symtpom score: 24% D2 : 6% P = NR Other Relevant Health Outcome Results: Reductions from baseline asthma symptom scores and nighttime awakenings were observed in both treatment groups. Significanly greater reduction in reliever n

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Lalloo et al.{Lalloo, 2003 #452} 2003 Multinational (51 centers: Czech Republic, Hungary, Norway, Poland, South Africa, United Kingdom) University hospitals AstraZeneca	Overall adverse events reported (%): Drug 1: 58 Drug 2: 54 Drug 5: NR Serious adverse events (%): Drug 1: 2 Drug 2: 1 Drug 5: NR Respiratory infection (%): Drug 1: 16 Drug 2: 17 Drug 5: NR Rhinitis (%): Drug 1: 3 Drug 2: 3 Drug 5: NR Other (%): Drug 1: Pharyngitis = 4 Drug 2: 4 Drug 5: NR Other (%): Drug 1: aggravated asthma = 3 Drug 2: 3 Drug 5: NR Other (%): Drug 1: viral infection = 3 Drug 2: 2 Drug 5: NR	Adherence Adherence to therapy was assessed by reviewing patinent diary cards. Self reported adherence to study medication was high in both treatment groups (>97%).	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
855	Laviolette et al.{Laviolette, 1999 #855} 1999 Multinational - 18 countries including North America, Europe, Africa, Australia, and Asia Multicenter - 70 centers Merck	Study design: RCT Double-blind Double-dummy Duration: 16 weeks N = 642 Number screened: NR, NR, NR ITT Analysis: Unable to determine	: Healthy, nonsmoking, male and female patients (age 15 yr and older), with a history of at least 1 yr of intermittent or persistent asthma symptoms treated with ICS for at least 6 wk before the prestudy visit were eligible for participation (the dose of ICS 1 wk before the prestudy visit was either equal or comparable to 400 to 500 mcg of BDP). After run-in, to be eligible for Period 2, patients were required to demonstrate, on at least two of the four visits in Period 1, an FEV1 between 50 and 85% of the predicted value after withholding inhaledb -agonist and antihistamine for at least 6 and 48 h, respectively, and to show at least a 15% increase in FEV 1 (absolute value) 20 to 30 min after inhaled b -agonist administration. In addition, patients were required to haveat least a minimum total daytime asthma symptom score (64 out of a possible 336 score) and daily average b -agonist use (as needed) of at least 1 puff during the last 2 wk of Period 1. Asthma Severity: Not or poorly controlled Other: not controlled on ICS

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Laviolette et al.{Laviolette, 1999 #855} 1999 Multinational - 18 countries including North America, Europe, Africa, Australia, and Asia Multicenter - 70 centers Merck	Antihistamines, except terfenadine (within 2 wk) and astemizole (within 3 mo), were permitted as needed during the study; immunotherapy was allowed at a constant monthly dose if initiated at least 6 mo before the prestudy visit. Patients used short-acting, inhaled b -agonist on an “as needed” basis (via metered-dose inhalers of albuterol/salbutamol, 100 mcg/actuation).	Other: Patients were excluded if they had respiratory disorders other than asthma or had signs and symptoms of an upper respiratory infection within 3 wk of the prestudy visit. Female patients had a negative pregnancy test at the prestudy visit. Antiasthma medications excluded before the prestudy visit wereoral and parenteral corticosteroids within 1 mo; cromolyn and nedocromilwithin 2 wk; theophylline (oral and intravenous), b-agonists (oral or long-acting inhaled), and anticholinergic agents within 1 wk.	Yes: During the run-in period (Period 1) patients were dispensed two inhalers (morning and evening), in a blind manner, containing BDP 50mcg/actuation) and a bottle of placebo tablets. Patients were instructed to take 4 puffs (200 mcg twice daily) and a tablet once daily at bedtime. Inhaled study medication was administered with an AeroChamber spacer device throughout the study.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Laviolette et al.{Laviolette, 1999 #855} 1999 Multinational - 18 countries including North America, Europe, Africa, Australia, and Asia Multicenter - 70 centers Merck	Intervention: Drug 1: Placebo Drug 2: ML Drug 3: BDP Drug 4: BDP + ML Total daily dose: Drug 1: NA Drug 2: NA Drug 3: 400mcg Drug 4: 400mcg Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: NA Drug 3: medium Drug 4: medium Delivery device: Drug 1: placebo MDI and placebo pill Drug 2: pill and placebo MDI Drug 3: MDI and placebo pill Drug 4: MDI and pill Is dosing comparable between treatment groups? NA: Placebo versus LTRA versus ICS versus LTRA plus ICS - steroids comparable	# in group (n): Drug 1: 48 Drug 2: 201 Drug 3: 200 Drug 4: 193 Mean age (years): Drug 1: 41 Drug 2: 38 Drug 3: 39 Drug 4: 40 Sex (% female): Drug 1: 60 Drug 2: 51 Drug 3: 48 Drug 4: 44 Optional - Race (% white): Drug 1: 83.3 Drug 2: 94 Drug 3: 92 Drug 4: 91.7 Current smokers (%): 0 Optional - Rescue medication use (puffs per day): Drug 1: 4.2 Drug 2: 3.5 Drug 3: 3.5 Drug 4: 3.4 Current use of ICS at baseline (%): 100 Other: Drug 1: history of allergic rhinitis (%) = 90 Drug 2: 74 Drug 3: 74 Drug 4: 76 Other: Drug 1: history of exercise-induced asthma (%) = 77 Drug 2: 89 Drug 3: 83 Drug 4: 88	Number (%) withdrawn: Drug 1: 11 (23%) Drug 2: 42 (21%) Drug 3: 22 (11%) Drug 4: 16 (8%) Overall: 14% Optional - Withdrew due to lack of efficacy (%): Drug 1: worsening asthma = 15 Drug 2: 11 Drug 3: 4 Drug 4: 1 Adverse events caused withdrawal (%): NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Laviolette et al.{Laviolette, 1999 #855} 1999 Multinational - 18 countries including North America, Europe, Africa, Australia, and Asia Multicenter - 70 centers Merck	Intervention: Drug 1: Placebo Drug 2: ML Drug 3: BDP Drug 4: BDP + ML Number in group (n): Drug 1: 48 Drug 2: 201 Drug 3: 200 Drug 4: 193	Rescue med use during 24 hour period: Total daily B agonist use, % Drug 3: 6.04 Drug 4: -5.51 P = 0.08 for BDP versus BDP + ML Asthma exacerbations: % days = D3: 17.92 D4: 13.37 P = 0.041 for BDP versus BDP + ML Symptom control during 24 hour period: asthma attacks (% of patients) = D3: 12 D4: 6.2 P = 0.055 for BDP versus BDP + ML Day time symptom control: base: daytime asthma symptom score (change from baseline) = D3: -0.02 D4: -0.13 P = 0.041 for BDP versus BDP + ML Nocturnal awakenings: nights/week (includes nocturnal asthmatic patients only = BDP 74, BdP + mont 85) = D3: -0.45 D4: -1.04 P = 0.010 for BDP versus BDP + ML Other: daytime symptom score, mean change: D3: 0.27 (0.17, 0.38) D4 -0.09 (-0.20, 0.002)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Laviolette et al.{Laviolette, 1999 #855} 1999 Multinational - 18 countries including North America, Europe, Africa, Australia, and Asia Multicenter - 70 centers Merck	Cough (%): Drug 1: 6.3 Drug 2: 5.5 Drug 3: 2.5 Drug 4: 4.1 Sore throat (%): Drug 1: bronchitis = 8.3 Drug 2: 3.5 Drug 3: 2 Drug 4: 2.6 Headache (%): Drug 1: 12.5 Drug 2: 25.9 Drug 3: 21 Drug 4: 25.9 Upper respiratory tract infection (%): Drug 1: 39.6 Drug 2: 35.8 Drug 3: 39.5 Drug 4: 36.3 Respiratory infection (%): Drug 1: influenza = 6.3 Drug 2: 7.5 Drug 3: 5.5 Drug 4: 5.7 Rhinitis (%): Drug 1: sinusitis = 4.2 Drug 2: 6 Drug 3: 4.5 Drug 4: 4.1 Hoarseness (%): Drug 1: pharyngitis = 4.2 Drug 2: 6 Drug 3: 8 Drug 4: 5.2 Other (%): Drug 1: asthenia/fatigue = 6.3 Drug 2: 1 Drug 3: 0.5 Drug 4: 1.6 Other (%): Drug 1: Nausea = 0 ; rash = 6.3 Drug 2: 6 ; 3.5 Drug 3: 5.5 ; 1.5 Drug 4: 2.6 ; 0.5 Other (%): Drug 1: worsening asthma = 41.7 Drug 2: 37.3 Drug 3: 20 Drug 4: 11.9 Additional adverse events and comments: Laboratory adverse experiences occurred with similar frequency across the four treatment groups. There were no patients who discontinued because of a laboratory abnormality. The incidence of	Compliance The compliance (mean 6 SD) with the inhaled study medication over the 16-wk treatment period was 96.5, 94.0, 92.4, and 94.6% for the placebo, ML, beclomethasone, and additivity groups, respectively. The compliance with oral medication was 99.0, 98.7, 98.7, and 98.6% for the placebo, ML, BDP, and additivity groups, respectively.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
30	Lazarus et al.{Lazarus, 2007 #30} 2007 SMOG Study USA Multicenter NHLBI	Study design: RCT Double-blind Double-dummy Duration: 8 wks then 6 wk wash out then 8 weeks N = 83 randomized Number screened: 182/146/83 ITT Analysis: Yes	Age: 18-50 FEV 1 expressed as a percent of the predicted value: 70-90 Reversability of FEV1: at least 12% Previous use of corticosteroids: Steroid-naive Other: Nonsmokers were required to have a total lifetime smoking history of less than2 pack-years, and no smoking for at least 1 year. Subjects were enrolledas smokers if they were currently smoking 10 to 40 cigarettes/day, had a 2 to 15 pack-year smoking history, and a diffusing capacity of carbonmonoxide (DlCO) of 80% of predicted or greater. Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Lazarus et al.{Lazarus, 2007 #30} 2007 SMOG Study USA Multicenter NHLBI	NR	Smoking - current or former: smoking history of greater than 15 pack-years, active smoking of more than 40 cigarettes/day Other: DlCO less than 80% of predicted.	Yes: After a 2-week run-in period, to establish eligibility and adherence to study protocol and forms, subjects entered an 8-week single-blind placebo treatment period.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Lazarus et al.{Lazarus, 2007 #30} 2007 SMOG Study USA Multicenter NHLBI	Intervention: Drug 1: Non-smokers: ML vs BDP Drug 2: Smokers: ML vs BDP Total daily dose: Drug 1: 10mg ; 320mcg Drug 2: 10mg ; 320mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Delivery device: Drug 1: tablet ; MDI or DPI Drug 2: tablet ; MDI or DPI Is dosing comparable between treatment groups? NA: ICS vs LTRA in smokers vs nonsmokers	# in group (n): Drug 1: 44 Drug 2: 39 Mean age (years): Drug 1: 28.98 Drug 2: 29.06 Sex (% female): Drug 1: NR Drug 2: NR Current smokers (%): Drug 1: 0 Drug 2: 100 Optional - Disease duration (years): Drug 1: 17.15 Drug 2: 14.96 Current use of ICS at baseline (%): Drug 1: NR Drug 2: NR Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: NR Drug 2: NR Adverse events caused withdrawal (%): Drug 1: NR Drug 2: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Lazarus et al.{Lazarus, 2007 #30} 2007 SMOG Study USA Multicenter NHLBI	Intervention: Drug 1: Non-smokers: ML vs BDP Drug 2: Smokers: ML vs BDP Number in group (n): Drug 1: 44 Drug 2: 39	Other Relevant Health Outcome Results: Change in AQOL average score: ML/Non smoker 0.23 (0.04, 0.42 ; p=0.02); /smoker 0.07 (-0.19, 0.32; p = NS) ; Beclomethasone/Non smoker 0.13 (-0.06, 0.32; p = NS); /Smoker 0.12 (-0.13, 0.37; p = NS) and overall, "In general, the changes in the physiologic outcomes in the smokers were in the same direction as in the nonsmokers, but were of smaller magnitude"

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Lazarus et al.{Lazarus, 2007 #30} 2007 SMOG Study USA Multicenter NHLBI	NR	Adherence Pill bottles were fitted with an electronic Drug Exposure Monitor (eDEM) and metered-dose inhalers were fitted with a Doser device to record opening of the pill container and actuation of the metered-dose inhaler, respectively. Analysis of the Doser devices, eDEM monitors, and diary cards demonstrated that adherence to inhaled and oral medication regimens was 77 to 92% and was not significantly different between smokers and nonsmokers (p = 0.13), and that concordance among the three methods of assessing adherence was good.	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
694	Lazarus, S et al.; Deykin, A et al. 2001; 2005 SOCS Trial North America Multicenter NHLBI	Study design: RCT Double-dummy Other: triple blind (patients, clinic center personnel, and data analysts) Duration: 16 weeks N=164 Enrolled: 422 enrolled, 361 completed run-in, 339 eligible for randomization, 164 eligible for randomization to SOCS (other 175 with poorly controlled asthma entered SLIC trial, SM + ICS ITT Analysis: Yes	: Age 12 through 65 years; for patients not already receiving an ICS: FEV1 >80% of predicted value; and Documentation of >/=12% increase in FEV1 after aerosolized albuterol treatment; for patients already receiving an ICS: FEV1 >40% of predicted value If FEV1 is 40%-80% of predicted value, patient must demonstrate >/=12% increase in FEV1 after aerosolized albuterol treatmentIf FEV1 is >80% of predicted value, patient must demonstrate a 20% reductionin FEV1 in response to a concentration of inhaled methacholine </=8 mg/mL (PC20FEV1 </=8 mg/mL); Nonsmoker (total lifetime smoking history ,10 pack-years; no smoking for at least 1 year); No regular use of other medications except oral contraceptives and nasal BDP; No respiratory tract infection or asthma exacerbation within 6 weeks of run-in period; No serious medical illness other than asthma After 6-Week Run-in Period: FEV1 .80% of predicted value; and average peak expiratory flow (PEF) variability </=20%, calculated as [(PM PEF − AM PEF)/(PM PEF + AM PEF)/2] x 100, during the final 2 weeks of the run-in period; andability of the Asthma Severity: Moderate Controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Lazarus, S et al.; Deykin, A et al. 2001; 2005 SOCS Trial North America Multicenter NHLBI	Albuterol as needed	Other: NR	Yes: 6-week run-in phase during which all patients received 400 ìg (4 puffs) twice per day of open-label TAA. Patients whose asthma was well controlled, defined objectively (Box 1), following the 6-week run-in period were entered into the SOCS study

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Lazarus, S et al.; Deykin, A et al. 2001; 2005 SOCS Trial North America Multicenter NHLBI	Intervention: Drug 1: placebo Drug 2: SM Drug 3: TAA Total daily dose: Drug 1: NA Drug 2: 84mcg Drug 3: 800mcg Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: NA Drug 3: medium Delivery device: Drug 1: MDI Drug 2: MDI Drug 3: MDI Is dosing comparable between treatment groups? NA: ICS versus LABA	# in group (n): Drug 1: 56 Drug 2: 54 Drug 3: 54 Overall: 164 Mean age (years): Drug 1: 31% age less than 18 = 9 Drug 2: 31; % age less than 18 = 9 Drug 3: 31; % age less than 18 = 11 Sex (% female): Drug 1: 68 Drug 2: 61 Drug 3: 67 Optional - Race (% white): Drug 1: 68 Drug 2: 76 Drug 3: 67 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Optional - Rescue medication use (puffs per day): Drug 1: 0.4 Drug 2: 1 Drug 3: 0.8 Optional - Previous ICS use (%): Drug 1: 93 Drug 2: 98 Drug 3: 100 Current use of ICS at baseline (%): Drug 1: 100	Number (%) withdrawn: Drug 1: for 16 week comparison: 5 (9); including the additonal 6 wk placebo run-out period = 7 (12.5) Drug 2: 6 (11); 13 (24) Drug 3: 1 (1.9); 14 (26) Overall: 34 (21) Adverse events caused withdrawal (%): Drug 1: 0 Drug 2: 2 Drug 3: 0 Optional - Lost to follow-up (%): Drug 1: 0 Drug 2: 0 Drug 3: 2 Optional - Consent withdrawn (%): Drug 1: 9 Drug 2: 9 Drug 3: 2 Optional - Other reasons for withdrawal (%): Drug 1: run-ou failure = 3.5; 0 Drug 2: 11; physician initiated = 2 Drug 3: 18; 4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Lazarus, S et al.; Deykin, A et al. 2001; 2005 SOCS Trial North America Multicenter NHLBI	Intervention: Drug 1: placebo Drug 2: SM Drug 3: TAA Number in group (n): Drug 1: 56 Drug 2: 54 Drug 3: 54	Rescue med use during 24 hour period: P values: NS Asthma exacerbations: D1 base: 16 (29%) D1 end: 11(20%) D2 base: 4 (7%) P: significantly lower in the TAA group compared with the SM p=0.04 and placebo p=0.003 AQLQ - overall: P: P<0.001 for SM and TAA versus placebo Other: D1 base: treatment failure rate = 20 patients (36%) D1 end : 13 (24%) D2 base: 3 (6%) P: TAA group significantly lower than placebo p<0.001 and SM p=0.004; NS between placebo and SM (p=0.18) Other: D1 base: number of asthma deteriorations = 21 D1 end : 13 D2 base: 5 P: p=0.13 SM versus placebo; p<0.05 TAA versus SM; p<0.001 TAA versus placebo Other Relevant Health Outcome Results: Treatment Failure defined by any of the following: 1) >=1 course of prednisone for an exacerbation; 2) more than 1 ED or urgent care visit for treatment of an exacerbation; 3) hospitalization for an exacerbation; 4) physician clinical judgment for safety.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Lazarus, S et al.; Deykin, A et al. 2001; 2005 SOCS Trial North America Multicenter NHLBI	NR	NR	Good No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1120	Lorentzen et al.{Lorentzen, 1996 #1120} 1996 Multinational Multicenter (20 outpatient clinics) GlaxoSmithKline NR: Corresponding author works for GSK	Study design: RCT Double-blind : parallel group Duration: 12 months N=213 Enrolled: NR/NR/213 ITT Analysis: Yes	Age: 18-77 : established clinical history of severe chronic asthma, requiring and responding to B2-agonist therapy and treatment with high doses of ICSs; were receiving between 1000 mcg and 2000 mcg BDP and had no change to regular asthma medication for at least 1 month; already stable on 1500-2000 mcg/day ICS or were mildly symptomatic on 1000-1500 mcg/day ICS Asthma Severity: Controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Lorentzen et al.{Lorentzen, 1996 #1120} 1996 Multinational Multicenter (20 outpatient clinics) GlaxoSmithKline NR: Corresponding author works for GSK	oral prednisolone if necessary	Pregnant or lactating Prior treatment: Patients were excluded from the study if any of the following applied: serious uncontrolled systemic disease; recent admission to hospital with asthma; infection of the upper or lower respiratory tract within the previous month; treatment with systemic corticosteroids during the last month or on at least three occasions during the last 6 months; hypersensitivity to ICSs; treatment with other investigational drugs during the previous month; lactation, pregnancy or inadequate contraceptive precautions in women of child-bearing potential; evidence of alcohol abuse; inability to use a pressurizedmetered dose inhaler correctly; or inability or refusal to comply with any of the trial procedures.	Yes: 2 week run-in period during which patients receiving more than 1500 mcg/day of an inhaled steroid were required to demonstrate that their asthma was stable.Stability was assessed from the results of lung function tests, daily PEF data and a clinical examination. Patients receiving less than 1500 mcg/day of aninhaled steroid had either: (1) to exhibit asthma symptoms (with a score of at least 1) on no less than 4 of the last 14 days of the run-in period; or (2) to demonstrate at least 15% reversibility in FEV1 15 min after inhaling 200 mcg salbutamol from a metered dose inhaler or 400 mcg salbutamol from a Diskhaler. At the start of the 2-week run-in period, all prestudy bronchodilator therapy was replaced by inhaled salbutamol administered via MDI to be used as required. All inhaled steroid medication was stopped at the end of the run-in period and replaced with the randomized study medication.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Lorentzen et al.{Lorentzen, 1996 #1120} 1996 Multinational Multicenter (20 outpatient clinics) GlaxoSmithKline NR: Corresponding author works for GSK	Intervention: Drug 1: FP Drug 2: BDP Total daily dose: Drug 1: 1000 mcg Drug 2: 2000 mcg Steroid dosing range (Low, medium or high): Drug 1: high Drug 2: high Delivery device: Drug 1: MDI Drug 2: MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 159 Drug 2: 54 Mean age (years): Drug 1: 51 Drug 2: 54 Sex (% female): Drug 1: 53 Drug 2: 46 Optional - Race (% white): Drug 1: 97 Drug 2: 100 Current smokers (%): Drug 1: 18 Drug 2: 22 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100	Number (%) withdrawn: Drug 1: 27 (17) Drug 2: 9 (17) Optional - Withdrew due to lack of efficacy (%): Drug 1: 1 Drug 2: 6 Adverse events caused withdrawal (%): Drug 1: 13 Drug 2: 9

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Lorentzen et al.{Lorentzen, 1996 #1120} 1996 Multinational Multicenter (20 outpatient clinics) GlaxoSmithKline NR: Corresponding author works for GSK	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: BDP Drug 2 Endpoint: FP	Other Relevant Health Outcome Results: Sixty-one percent of patients on FP and 52% of patients on BDP remained free of exacerbations throughout the study period; 22% of FP patients vs. 20% of BDP patients experienced 1 exacerbation, 10% of FP patients vs. 19% of BDP patients experienced 2 exacerbations. There was no statistical difference between the two treatment groups in frequency of asthma exacerbations. The rate of occurrence of exacerbations remained fairly constant over the 12-month period. NOTE: asthma exacerbations were defined as asthma or related adverse events.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Lorentzen et al.{Lorentzen, 1996 #1120} 1996 Multinational Multicenter (20 outpatient clinics) GlaxoSmithKline NR: Corresponding author works for GSK	Overall adverse events reported (%): Drug 1: 72 Drug 2: 72 P = NR Serious adverse events (%): Drug 1: 7 Drug 2: 6 Oral candidiasis- thrush (%): Drug 1: 4 Drug 2: 4 Cough (%): Drug 1: 7 Drug 2: 2 Sore throat (%): Drug 1: 4 Drug 2: 7 P = NR Headache (%): Drug 1: <1 Drug 2: 7 P = 0.03 Respiratory infection (%): Drug 1: 6 Drug 2: 9 Rhinitis (%): Drug 1: 10 Drug 2: 1 P = NR Hoarseness (%): Drug 1: 6 Drug 2: 7 P = NR Other (%): Drug 1: asthma & related events: 35 Drug 2: 46 P = NR Other (%): Drug 1: influenza: 5	Compliance Compliance to treatment was not assessed formally but inspection of returned medication revealed only a small percentage of 'non-compliant' patients	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1247	Lundback et al.{Lundback, 1993 #1247} 1993 Multinational Multicenter Funding?	Study design: RCT Double-blind Duration: 6 weeks plus 46 weeks N=585 Enrolled: NR/NR/NR ITT? NR	Previous use of corticosteroids: all were ICS users Other: moderate asthma, currently receiving 400-1000 micrograms day-1 of an inhaled corticosteroid, asthma symptoms on 4 of 14 run in days, reversability of FEV1 of at least 15%for patients on ICS 400-600 day and those on 600-1000 had to be stable Asthma Severity: Moderate Controlled Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Lundback et al.{Lundback, 1993 #1247} 1993 Multinational Multicenter Funding?	Rescue med use of salbutamol	Other: Systemic ccs w/in last month or 3 or more times in previous 6 months; serious disease; pregnancy/ lactation or other investigational within last 4 weeksalso excluded were those cho changed their ICS dose in month prior to study or were admitted to a hosp for asthma.	Yes- 2 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Lundback et al.{Lundback, 1993 #1247} 1993 Multinational Multicenter Funding?	Intervention: Drug 1: FP PI Drug 2: FP DH Drug 3: BDP Total daily dose: Drug 1: 500 Drug 2: 500 Drug 3: 1000 Delivery device: Drug 1: Pressurized Inhaler Drug 2: Diskhaler Drug 3: Pressurized inhaler Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 193 Drug 2: 198 Drug 3: 194 Mean age (years): Drug 1: 46 Drug 2: 45 Drug 3: 46 Sex (% female): Drug 1: 48 Drug 2: 45 Drug 3: 49 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: by investigagtors 18 (9.3) Drug 2: 17 (8.6) Drug 3: 20 (10.3) Adverse events caused withdrawal (%): Drug 1: 3.6 Drug 2: 4.0 Drug 3: 2.6

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Lundback et al.{Lundback, 1993 #1247} 1993 Multinational Multicenter Funding?	Intervention: Drug 1: FP PI Drug 2: FP DH Drug 3: BDP Number in group (n): Drug 1- endpoint: 164-183 Drug 2-endpoint: 167-187 Drug 3- endpoint: 169-184	Rescue med use day: % pts w/ same or reduced rescue meds - day Drug 1: 83 Drug 2: 83 Drug 3: 88 P value: NR Rescue med use at night: % pts w/ same or reduced rescue meds - nite Drug 1: 77 Drug 2: 83 Drug 3t: 82 P value: NR Day time symptom control: % patients w/ no change improvement in daytime symptoms D1: 88 D2: 90 D3: 92 P: NR Night time symptom control: % patients w/ no change improvement in nitetime symptoms D1: 92 D2: 89 D3: 90 P: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Lundback et al.{Lundback, 1993 #1247} 1993 Multinational Multicenter Funding?	Oral candidiasis- thrush (%): Drug 1: 2 Drug 2: 2 Drug 3: 4 Drug 4: 2/3 Sore throat (%): Drug 1: 5 Drug 2: 2 Drug 3: 1 Drug 4: NR Headache (%): Drug 1: 5 Drug 2: 7 Drug 3: 7 Drug 4: NR Upper respiratory tract infection (%): Drug 1: 6 Drug 2: 9 Drug 3: 7 Drug 4: 44/19 Rhinitis (%): Drug 1: 2 Drug 2: 5 Drug 3: 2 Hoarseness (%): Drug 1: 2 Drug 2: 2 Drug 3: <1 Drug 4: 2/1 Other (%): Drug 1: Asthma and related events 2 Drug 2: 5 Drug 3: 2	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
168	Lundback et al.{Lundback, 2006 #168} 2006 Sweden; patients were recruited from approximately 4000 individuals with asthma who had particpated in large epidemiologic studies of the general population in N. Sweden. GlaxoSmithKline	Study design: RCT Double-blind Duration: 12 weeks N=322 recruited; 282 randomized Enrolled: 322 recruited; 282 randomized ITT Analysis: Yes	Age: 18-70 Reversability of FEV1: AHR, demonstrated by methacholinechallenge with PC20o8 mg/ml (the oncentration required to provoke a 20% reduction in forced expiratory volume in one second [FEV1]); OR a reversible increase of X15% in FEV1 or PEF after salbutamol inhalation (0.8 mg). Other: mild to moderate asthma, with sx at least twice per week; diurnal variability in peak expiratory flow (PEF) of X20% on> 3 days during the last 14 days of the run-in; OR a 30% difference between the highest and second lowest PEF reading during any 7 days in the run-in period; Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Lundback et al.{Lundback, 2006 #168} 2006 Sweden; patients were recruited from approximately 4000 individuals with asthma who had particpated in large epidemiologic studies of the general population in N. Sweden. GlaxoSmithKline	previous ics permitted if daily doses <1200 ug	Pregnant or lactating Current treatment: daily doses of ICS > 1200 mg Other: one or more lifethreateningexacerbation requiring hospitalisationduring the previous 12 months OR were hypersensitiveto beta-agonists or ICS OR had a respiratory tract infection during the 4 weeks prior to run-in	Yes: a 1-month pre-run-in period on previoustherapy, and a 1-month run-in period, during whichthe dose of ICS was reduced (in subjects using ICS) to a maximum of BUD 400 mg per day orequivalent,

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Lundback et al.{Lundback, 2006 #168} 2006 Sweden; patients were recruited from approximately 4000 individuals with asthma who had particpated in large epidemiologic studies of the general population in N. Sweden. GlaxoSmithKline	Intervention: Drug 1: SFC=Combined SM (S)/ FP (FP) (50 µg/250 µg) twice daily Drug 2: FP (250 µg) twice daily Drug 3: SM (50 µg) twice daily Total daily dose: Drug 1: 100 µg S/ 500 µg FP Drug 2: 500µg Drug 3: 100 µg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Drug 3: n/a Delivery device: Drug 1: Diskus Drug 2: Diskus Drug 3: Diskus Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 95 Drug 2: 92 Drug 3: 95 Mean age (years): Drug 1: 39.9 Drug 2: 39.1 Drug 3: 40.7 Sex (% female): Drug 1: 66 Drug 2: 58 Drug 3: 63 Current smokers (%): Drug 1: 14 Drug 2: 12 Drug 3: 17 Optional - Disease duration (years): Drug 1: percent w/ ashtma for > 10 years 58% Drug 2: 58% Drug 3: 71% Optional - Previous ICS use (%): Drug 1: 73 Drug 2: 62 Drug 3: 66 Optional - Current use of LABA (%): Drug 1: ("previous" use) 20 Drug 2: 22 Drug 3: 28 Other: Drug 1: FEV1% predicted (%) 92.1 Drug 2: 93	Number (%) withdrawn: Drug 1: 9 (9.5) Drug 2: 5 (5.4) Drug 3: 5 (5.3) Optional - Withdrew due to lack of efficacy (%): Drug 1: 1 Drug 2: 0 Drug 3: 1 Adverse events caused withdrawal (%): Drug 1: 2 Drug 2: 2 Drug 3: 1 Optional - Lost to follow-up (%): Drug 1: 1 Optional - Protocol violation (%): Drug 1: 1 Drug 2: 2 Drug 3: 2 Optional - Consent withdrawn (%): Drug 1: 1 Drug 2: 0 Drug 3: 1 Optional - Other reasons for withdrawal (%): Drug 1: 3 Drug 2: 1 Drug 3: 1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Lundback et al.{Lundback, 2006 #168} 2006 Sweden; patients were recruited from approximately 4000 individuals with asthma who had particpated in large epidemiologic studies of the general population in N. Sweden. GlaxoSmithKline	Intervention: Drug 1:FP/SM Drug 2: FP Drug 3t: SM Number in group (n): Drug 1- endpoint: 95 Drug 2- endpoint: 92 Drug 3- endpoint: 95	Rescue med use day: Drug 1 -endpoint: median proportion of rescue medication-free days 85.7% Drug 2 - endpoint: 85.7% Drug 3 - endpoint: 60% P < 0.05 for Sal vs either group Rescue med use at night: Drug 1 - endpoint: median proportion of patients withrescue medication-free nights was 100% for allthree-treatment groups. 100% Drug 2 - endpoint: 100% Drug 3 - endpoint: 100% Asthma exacerbations: D1 end: percentage of patients experiencing >=2 exacerbations during the 12-month treatment 4.2% D2 end: 17.4% D3 end: 40.0% P <0.01 SFR vs FP; p < 0.001 SFC vs SM and FP vs SM Day time symptom control: D1 - end: median proportion of symptom-free days 66.7% D2 - end: 67.9% D3 - end: 44.5% P <.05 for Sal vs either group; NR for other comparisons Night time symptom control: D1 - end: median symptom-free nights 100% D2 - end: 100% D3 - end: 92.3% P < 0.001 for Sal vs either group Other: D1 end : number and Proportion (%) requiring medication adjustment 10 (10.5%) D2 end: 32 (34.8%) D3 end: 58 (61.1%) P < 0.001 for all 3 combinations of comparisons

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Lundback et al.{Lundback, 2006 #168} 2006 Sweden; patients were recruited from approximately 4000 individuals with asthma who had particpated in large epidemiologic studies of the general population in N. Sweden. GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 92 patients (97 Drug 2: 88 (96) Drug 3: 90 (95) Oral candidiasis- thrush (%): Drug 1: 6 Drug 2: 0 Drug 3: 1 Dysphonia (%): Drug 1: 11% Drug 2: 9% Drug 3: 2% Cough (%): Drug 1: 2% Drug 2: 3% Drug 3: 7% Headache (%): Drug 1: 2% Drug 2: 7% Drug 3: 8% Respiratory infection (%): Drug 1: 74% Drug 2: 78% Drug 3: 55% Hoarseness (%): Drug 1: included in dysphonia numbers Other (%): Drug 1: gastroenterities: 12 Drug 2: 5 Drug 3: 5	Compliance	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
954	Malmstrom et al.{Malmstrom, 1999 #954} 1999 Williams et al.{Williams, 2001 #682} 2001 Multicenter/funding?	Study design: RCT Double-blind Double-dummy Duration: 12wk, plus a 3wk placebo washout period where patients were switched from treatment to placebo. (Double-blind extension phase =37 weeks) N = 895 (Extension: n=436) Number screened: 2253/895 ITT Analysis: No another type of analysis was used (define): LOCF, with exclusion if no data past baseline	Age: >= 15yr FEV 1 expressed as a percent of the predicted value: 50-85% Reversability of FEV1: 15% on 2 of 3 visits during the 2wk run-in Duration of condition: >= 1yr Other: non-smoker, daytime asthma symptom score >=64 (max 336), daily use of short-acting beta-agonist. (All ML and BDP patients completing study were eligible to enter extension period.) Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Malmstrom et al.{Malmstrom, 1999 #954} 1999 Williams et al.{Williams, 2001 #682} 2001 Multicenter/funding?	Intermittent use of short-acting antihistamines was allowed, and immunotherapy was permitted if it had been started at least 6 months before the initial study evaluation and if the monthly dose remained constant. Short-acting beta-agonist PRN. Patients with worsening episodes of asthma that required additional therapy were treated with oral corticosteroids according to a standard protocol. Patients who had more than two worsening episodes of asthma requiring corticosteroid therapy were dropped from the study.	Prior treatment with: inhaled and oral corticosteroids, cromolyn, ornedocromil within 4 weeks before the initial evaluation;had used long-acting b-agonists, antimuscarinics,and newly instituted theophylline within 2 weeks before the initial evaluation; or had usedlong-acting antihistamines (for example, they couldnot have used astemizole within 3 months of theinitial evaluation, and they could not have usedterfenadine or loratadine within 2 weeks of the initialevaluation) Smoking - current or former: current smokers excluded	Yes: 2wk placebo-only run-in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Malmstrom et al.{Malmstrom, 1999 #954} 1999 Williams et al.{Williams, 2001 #682} 2001 Multicenter/funding?	Intervention: Drug 1: ML Drug 2: BDP Drug 3: placebo Drug 4: Extension ML/BDP Total daily dose: Drug 1: 10mg Drug 2: 400mcg Drug 3: NA Drug 4: 10 mg/400 mcg Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: medium Drug 3: NA Drug 4: NA/medium Delivery device: Drug 1: tablet Drug 2: inhaler Drug 3: tablet & inhaler Drug 4: tablet/inhaler with spacer Is dosing comparable between treatment groups? NA: only one group has ICS	# in group (n): Drug 1: 387 Drug 2: 251 Drug 3: 257 Drug 4: 269/167 Mean age (years): Drug 1: 35 Drug 2: 35 Drug 3: 36 Sex (% female): Drug 1: 60 Drug 2: 65 Drug 3: 57 Optional - Race (% white): Drug 1: 54 Drug 2: 47 Drug 3: 53 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Optional - Disease duration (years): Drug 1: 17 Drug 2: 18 Drug 3: 18 Optional - Rescue medication use (puffs per day): Drug 1: 5.8 Drug 2: 5.5 Drug 3: 5.8 Optional - Current methylxanthine (i.e. theophylline) use (%):	Number (%) withdrawn: Drug 1: all withdrawal numbers include 12wk treatment period and 3wk placebo washout period 41 (10.6) Drug 2: 24 (9.6) Drug 3: 47 (18,3) Drug 4: 32 (12%)/23 (14%) Optional - Withdrew due to asthma exacerbations (%): Drug 1: 4 (1.0) Drug 2: 1 (0.4) Drug 3: 8 (3.1) Adverse events caused withdrawal (%): Drug 1: includes asthma exacerbation 8 (2) Drug 2: 5 (2) Drug 3: 11 (4) Drug 4: 4%/4% Optional - Lost to follow-up (%): Drug 1: 4 (1) Drug 2: 4 (2) Drug 3: 9 (4) Optional - Protocol violation (%): Drug 1: 16 (4) Drug 2: 10 (4) Drug 3: 16 (6) Optional - Consent withdrawn (%): Drug 1: 11 (3) Drug 2: 4 (2) Drug 3: 10 (4) Optional - Other reasons for withdrawal (%):

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Malmstrom et al.{Malmstrom, 1999 #954} 1999 Williams et al.{Williams, 2001 #682} 2001 Multicenter/funding?	Intervention: Drug 1 Baseline: ML Drug 1 Endpoint: ML Drug 2 Baseline: BDP inh Drug 2 Endpint: BDP inh Drug 3 Baseline: placebo Drug 3 Endpoint: placebo P-values (Define comparison): ML & BDP vs placebo Number in group (n): Drug 1- baseline: 387 Drug 1- endpoint: 354 or 346, unclear Drug 2- baseline: 251 Drug 2-endpoint: 233 or 227 Drug 3- baseline: 257 Drug 3- endpoint: 215 or 210 P-Values	Rescue med use during 24 hour period: Drug 1- baseline: 5.4 Drug 1-endpoint: % change from baseline -23.9 Drug 2-baseline: 5.5 Drug 2-endpoint: -40.0 Drug 3 - baseline: 5.8 Drug 3- endpoint: 0 Asthma exacerbations: % decrease vs placebo D1 end: 15.2, 42 D2 end: 9.7, 63 D3 end: 26.1, NA P: <0.05 Symptom control during 24 hour period: % change from placebo D1 end: 33 D2 end: 43 P: <0.001, <0.05 favoring BDP between BDP and ML Day time symptom contro Daytime symptom score, avg change from baseline D1 - end: -0.41 D2 - end: -0.62 D3 - end: -0.17 P: <0.001 for either vs plac; <0.01 ML vs BDP Nocturnal awakenings: D1 base: 5.5 D1 end: change from baseline -1.7 D2 base: 5.3 D2 end: -2.4 D3 base: 5.6 D3 end: -0.5 P: <0.001 AQLQ - overall: D1 end: mean improvement from baseline: 0.62

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Malmstrom et al.{Malmstrom, 1999 #954} 1999 Williams et al.{Williams, 2001 #682} 2001 Multicenter/funding?	Headache (%): Drug 1: 18 Drug 2: 19 Drug 3: 16 Upper respiratory tract infection (%): Drug 1: 12 Drug 2: 13 Drug 3: 11 Other (%): Drug 1: influenza 7 Drug 2: 7 Drug 3: 4 Other (%): Drug 1: pharyngitis 7 Drug 2: 6 Drug 3: 4 Other (%): Drug 1: worsening asthma 25 Drug 2: 19 Drug 3: 39 Additional adverse events and comments: only reported if in >=6% of patients	Compliance Mean compliance (6SD) with the inhaled study medication during the treatment period was 89.6% +- 36.3% in the placebo group, 87.6% +- 30.9% in the ML group, and 88.6% +- 34.8% in the beclomethasone group. Mean compliance with the oral study medication during the treatment period was 99.6% +- 2.6% in the placebo group, 99.8% +- 0.9% in the ML group, and 99.3% +- 3.4% in the beclomethasone group.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
904	Malo et al.{Malo, 1999 #904} 1999 Canada Multicenter GlaxoSmithKline Partially supported by the Centre d'excellence en santeÂ respiratoire, FRSQ-Bureau d'affaires du QueÂbec	Study design: RCT Double-blind : crossover Duration: 16 weeks for each randomization treatment group N=69 Enrolled: ~200 screened, 100 eligible, 69 enrolled ITT Analysis: Yes	: >18 yrs old asthmatic subjects who fulfilled the criteria for asthma, taking ICS at a dose equivalent to 1 mg/day of BDP. All participants demonstrateda >15% improvement in FEV1 either spontaneously or after treatment in the 2 yrs preceding their entry into the study. Asthma had to be moderate-to-severe, but had to have been stable for at least 3 months prior to the study. Subjects should not have taken oral steroids on a continuous basis for >1 yr in the previous 5 yrs. They couldbe included if they had only required short courses of oral steroids, but not if they had taken more than three courses per year, and not if they had taken any in the 3 months preceding the study. Asthma Severity: : NR, asthma as defined by ATS

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Malo et al.{Malo, 1999 #904} 1999 Canada Multicenter GlaxoSmithKline Partially supported by the Centre d'excellence en santeÂ respiratoire, FRSQ-Bureau d'affaires du QueÂbec	salbutamol as needed for rescue	Smoking - current or former : Patients who reported bleeding disorders, or took aspirin or nonsteroidal anti-inflammatory drugs or anticoagulants were excluded. Patients were excluded if they were current smokers or if they had used tobacco products within the preceding year.	Yes: Patients continued to take their usual ICS therapy during the run-in period of 2 weeks. On entry into the study treatment period, patients discontinued their usual inhaled ICS therapy and took only the ICS provided in the study treatment packs.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Malo et al.{Malo, 1999 #904} 1999 Canada Multicenter GlaxoSmithKline Partially supported by the Centre d'excellence en santeÂ respiratoire, FRSQ-Bureau d'affaires du QueÂbec	Intervention: Drug 1: FP Drug 2: BDP Total daily dose: Drug 1: 400mcg to 1000mcg Drug 2: 800mcg to 2000mcg Steroid dosing range (Low, medium or high): Drug 1: medium - high Drug 2: medium - really high Delivery device: Drug 1: MDI Drug 2: MDI Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 34 Drug 2: 33 Mean age (years): Drug 1: NR Drug 2: NR Overall: 48.4 Sex (% female): Drug 1: NR Drug 2: NR Overall: 57 Current smokers (%): Drug 1: 0 Drug 2: 0 Overall: 0 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100	Number (%) withdrawn: Drug 1: NR Drug 2: NR Overall: 2 (3%) Adverse events caused withdrawal (%): Drug 1: NR Drug 2: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Malo et al.{Malo, 1999 #904} 1999 Canada Multicenter GlaxoSmithKline Partially supported by the Centre d'excellence en santeÂ respiratoire, FRSQ-Bureau d'affaires du QueÂbec	Intervention: Drug 1: FP Drug 2: BDP Number in group (n): Drug 1: 34 Drug 2: 33	See adverse events

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Malo et al.{Malo, 1999 #904} 1999 Canada Multicenter GlaxoSmithKline Partially supported by the Centre d'excellence en santeÂ respiratoire, FRSQ-Bureau d'affaires du QueÂbec	Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: Skin bruising was not significantly different in terms of the number of subjects affected, its severity and frequency, as well as the number of bruises on direct examination were significantly greater in subjects taking BDP (mean 1.64 lesions on BDP and 1.24 lesions on FP). Although 24-h urinary cortisol and baseline plasma cortisol were not significantly different, post-Cortrosyn cortisol values were lower when subjects were on BDP, and the difference between the pre-Cortrosyn and postcortrosyn values was significantly different by a mean of 95 mmol/dL-1 in the BDP and the FP periods. In addition, osteocalcin was significantly lower when subjects were on BDP than when they were on FP. Table 4 shows that the increase in cortisol after Cortrosyn and the difference in osteocalcin levels were significantly more pronounced when the order of administration of treatment was BDP followed by FP, whereas the difference in the number of skin bruising events was greater when the order of administration of treatment was FP foll between each of the three outcomes, i.e. the increase in cortisol after	NR	Fair: not an efficacy/effectiveness study; this is a KQ2 study; not conducted for these outcomes Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
190	Malone et al.{Malone, 2005 #190} 2005 United States and Canada outpatients, multicenter (66 sites US/ 13 sites Canada) GlaxoSmithKline	Study design: RCT Double-blind Duration: 12 weeks N=203 Enrolled: 421 screened, 203 randomised ITT? Yes	boys and girls 4 to 11 years, with asthma for at least 2 months and were receiving ICS therapy at a consistent dose for at least 1 month before screening. Screening visit, those 6-11 were required to have a FEV1 of 50 to 95%, aged 4-5 were required to have morning PEFR 50% to 95%. Had to demonstrate an increase in FEV1 (age 6-11) or morning PEFR (age 4-5) of 12% or more within 30 min of inhalation of 2-4 actuations of albuterol or documentation of such. During run-in: 70% or greater compliance with study procedures and diary card completion, daytime asthma symptom score of at least 1 (scale 0-5) on 3 or more days or albuterol use on 3 or more days during the 7 days before randomization Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Malone et al.{Malone, 2005 #190} 2005 United States and Canada outpatients, multicenter (66 sites US/ 13 sites Canada) GlaxoSmithKline		Other: history of life-threatening asthma, hospitalization due to ashtma twice or more in the previous year; a significant concurrent disease; recent upper or lower respiratory tract infection; current chickenpox or recent exposure; severe milk protein allergy; hypersensitivity to beta agonist, sympathomimetic, or corticosteroids; clinically significant abnormal lab test results; a history or present use of tobacco; history or current presence of glaucoma or cataracts; no use of parenteral or oral corticosteroids for at least 1 month before screening; cromolyn or nedocromil for at least 1 week, long acting beta agonist within 48 hours and throughout study. Use of medications that could affect the course of asthma or interact with study medications were prohibited.	Yes- 2 week run-in period during which their baseline ICS therapy was continued.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Malone et al.{Malone, 2005 #190} 2005 United States and Canada outpatients, multicenter (66 sites US/ 13 sites Canada) GlaxoSmithKline	Intervention: Drug 1: FP/SAL Drug 2: FP Total daily dose: Drug 1: 200mcg/100 Drug 2: 200mcg Steroid dosing range: Drug 1: low Drug 2: low Delivery device: Drug 1: Diskus Drug 2: Diskus Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 101 Drug 2: 102 Mean age (years): Drug 1: 8 Drug 2: 8.1 Sex (% female): Drug 1: 32 Drug 2: 41 Optional - Race (% white): Drug 1: 67 Drug 2: 72 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Disease duration (years): Drug 1: 5.3 Drug 2: 5.1 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: NR Drug 2: NR Optional - Withdrew due to asthma exacerbations (%): Drug 1: 2 Drug 2: 5 Adverse events caused withdrawal (%): Drug 1: 3 Drug 2: 0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Malone et al.{Malone, 2005 #190} 2005 United States and Canada outpatients, multicenter (66 sites US/ 13 sites Canada) GlaxoSmithKline	Intervention: Drug 1: FP/SAL Drug 2: FP # in group (n): Drug 1: 101 Drug 2: 102	Asthma exacerbations: D1 end: 3% D2 end: 8% D3 end: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Malone et al.{Malone, 2005 #190} 2005 United States and Canada outpatients, multicenter (66 sites US/ 13 sites Canada) GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 59 (58%) Drug 2: 57 (56%) Oral candidiasis- thrush (%): Drug 1: 4 Drug 2: 0 Cough (%): Drug 1: 2 Drug 2: 3 Sore throat (%): Drug 1: 8 Drug 2: 7 Headache (%): Drug 1: 20 Drug 2: 20 Upper respiratory tract infection (%): Drug 1: 10 Drug 2: 17 Respiratory infection (%): Drug 1: viral = 0 Drug 2: 3 Bruising (%): Drug 1: 0 Drug 2: 3 Other (%): Drug 1: ear, nose, throat infection = 4 Drug 2: 0 Other (%): Drug 1: GI discomfort and pain = 7 Drug 2: 5	Compliance - Mean overall comliance with study medication was 93% for FP/SAL and 89% for FP group.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4739	Medici et al.{Medici, 2000 #4739} 2000 Switzerland Multicenter (7 outpatient sites) GlaxoSmithKline Research and Development, UK	Study design: RCT Double-blind Duration: 12 months N=69 Enrolled: NR/NR/69 ITT Analysis: Yes	: Patients with mild to moderate asthma; age limit was 20–55 years for men and 20–45 years for women (premenopausal). For the six months preceding the start of the study patients had been receiving regular treatment with ICSs in doses ranging from 400 to 1600 mcg/day. Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Medici et al.{Medici, 2000 #4739} 2000 Switzerland Multicenter (7 outpatient sites) GlaxoSmithKline Research and Development, UK	Salbutamol MDI was used as required to relieve symptoms and most patients also used long acting B2 agonists.	a change in regular asthma medication (other than inhaled corticosteroids), treatment with antibiotics for infections of the upper or lower respiratory tract, admission to hospital during the previous four weeks; treatment with systemic corticosteroids during the previous eight weeks; more than three short courses of oral steroids or depot corticosteroids in the previous 12 months; excessively overweight or underweight; immobilisation; fractures occurring within the six months preceding the start of the study; disordersof bone metabolism such as osteoporosis or Paget's disease; pregnancy, lactation, inadequate contraceptive precautions, amenorrhoea or a history of irregular menstrual cycles during the 12 months preceding the start of thestudy; treatment with any medication likely to influence bone metabolism.	Yes: four week run in period during which their regular ICS therapy wasstandardised to either BDP 800 mcg/day or 1500 mcg/day, depending on the dose of their ICS prior to entry and at the discretion of the investigator.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Medici et al.{Medici, 2000 #4739} 2000 Switzerland Multicenter (7 outpatient sites) GlaxoSmithKline Research and Development, UK	Intervention: Drug 1: FP Drug 2: FP Drug 3: BDP Drug 4: BDP Total daily dose: Drug 1: 400 mcg Drug 2: 750 mcg Drug 3: 800 mcg Drug 4: 1500 mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: high Drug 3: medium Drug 4: high Delivery device: Drug 1: MDI Drug 2: MDI Drug 3: MDI Drug 4: MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 22 Drug 2: 13 Drug 3: 21 Drug 4: 13 Mean age (years): Drug 1: 39 Drug 2: 38 Drug 3: 38 Drug 4: 40 Overall: 39 Sex (% female): Drug 1: 23 Drug 2: 31 Drug 3: 38 Drug 4: 46 Overall: 33 Current smokers (%): Drug 1: 14 Drug 2: 23 Drug 3: 5 Drug 4: 23 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Drug 4: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Drug 4: 100	Number (%) withdrawn: Drug 1: 1 (4.5) Drug 2: 1 (7.7) Drug 3: 1 (4.8) Drug 4: 1 (7.7) Adverse events caused withdrawal (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Drug 4: 7.7

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Medici et al.{Medici, 2000 #4739} 2000 Switzerland Multicenter (7 outpatient sites) GlaxoSmithKline Research and Development, UK	Intervention: Drug 1 Baseline: FP 400/FP 750 Drug 1 Endpoint: BDP 800/BDP 1500 Number in group (n): Drug 1- baseline: 22/13 Drug 1- endpoint: 21/13	Other Relevant Health Outcome Results: Overall, pQCT measurements showed no loss of trabecular or integral bone in the radius or tibia in any patients over 12 months. While some negative changes were recorded in the median bone density of compact bone of the radius (FP 750 patients) and tibia (BDP 800 patients and FP 750 patients), none of these changes exceeded –2% which suggests that the results were not clinically significant. BDP 800 mcg/d group showed some loss in BMD of the lumbar spine at 12 months; difference significant relative to FP 400 mcg/day group (P=0.02). With the exception of urine phosphate, all markers (10 measured) of bone resorption and formation were within clinically normal values. A statistically significant difference in osteocalcin at 12 months suggested lower bone formation in BDP 800 patients than FP 400 patients (P=0.047). A statistically significant difference in ICTP at 6 months suggested greater bone resorption in FP 750 patients than BDP 1500 patients (P=0.031).

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Medici et al.{Medici, 2000 #4739} 2000 Switzerland Multicenter (7 outpatient sites) GlaxoSmithKline Research and Development, UK	Reduction in bone mineral density (%): Drug 1: see above Drug 2: see above Additional adverse events and comments: Adverse events were reported by a similar number of patients in both treatment groups. Overall, the adverse event profile was highly comparable between the two treatment groups and the events themselves were not unexpected in this group of patients. The most common events were infections of the upper respiratory tract and rhinitis. There were no reports of serious adverse events and the only withdrawal was due to pregnancy (one patient taking BDP 1500 mcg/day). The only predictable adverse event was hoarseness/dysphonia reported by three patients (one in each of the FP400, BDP800, and FP750 groups). There were no reports of allergic skin reactions, oral candidiasis, or rash/skin eruptions.	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
573	Meltzer et al.{Meltzer, 2002 #573} 2002 US Multicenter Glaxo Wellcome Inc., RTP, NC	Study design: RCT Double-blind Double-dummy Duration: 24 weeks N = 522 Number screened: 1346/NR/522 ITT Analysis: Yes	: Healthy, nonsmoking male and female patients aged 15 years or older were enrolled in the study if they demonstrated the following at their screening visit: (1) a diagnosis of asthma as defined by the American Thoracic Society for at least 6 months before screening; (2) use of an inhaled or oral short-acting B2-agonist on a regular or as-needed basis during the preceding 3 months; (3) a predose FEV1 of 50% to 80% of predicted normal; and (4) reversibility of airway obstruction, demonstrated by an increase in FEV1 of at least 15% after inhalation of 180 mcg of albuterol. Patients were eligible for randomization if they demonstrated that additional asthma controller therapy was warranted using the following criteria at the end of the run-in period: (1) an unmedicated FEV1 value of 50% to 80% of predicted normal that was within 15% of the FEV1 value obtained at screening; (2) use of albuterol to relieve asthma symptoms on at least 6 of the 7 days before randomization; and (3) an asthma symptom score of 2 or more (based on a 0- to 5-point scale) on at least 4 of the 7 days before randomi Asthma Severity: Mild Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Meltzer et al.{Meltzer, 2002 #573} 2002 US Multicenter Glaxo Wellcome Inc., RTP, NC	The use of antihistamines, nasal decongestants, and other intranasal medications (including corticosteroids) for the treatment of rhinitis was allowed.	Other: history of life-threatening or unstable asthma or other severe and uncontrolled diseases, known hypersensitivity to study medications, respiratory tract infections within 4 weeks of screening, pregnancy, and use of tobacco products within the previous year or a smoking history of more than 10 pack-years. Excluded medications included inhaled or systemic corticosteroids, inhaled cromolyn or nedocromil, LM, anticholinergics, and theophylline products. The use of other medications that might affect the course of asthma or interact with study medications was not allowed.	Yes: 8- to 14-day run-in period (see inclusion criteria for additional info)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Meltzer et al.{Meltzer, 2002 #573} 2002 US Multicenter Glaxo Wellcome Inc., RTP, NC	Intervention: Drug 1: FP Drug 2: ML Total daily dose: Drug 1: 176 mcg Drug 2: 10 mg Steroid dosing range (Low, medium or high): Drug 1: Low Drug 2: NA Delivery device: Drug 1: MDI Drug 2: tablet Is dosing comparable between treatment groups? NA: ICS vs LTRA	# in group (n): Drug 1: 258 Drug 2: 264 Mean age (years): Drug 1: 36.2 Drug 2: 35.4 Sex (% female): Drug 1: 58 Drug 2: 49 Optional - Race (% white): Drug 1: 79 Drug 2: 83 Current smokers (%): Drug 1: 0 Drug 2: 0 Current use of ICS at baseline (%): Drug 1: NR Drug 2: NR Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 60 (23) Drug 2: 67 (25) Adverse events caused withdrawal (%): Drug 1: 2 Drug 2: 2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Meltzer et al.{Meltzer, 2002 #573} 2002 US Multicenter Glaxo Wellcome Inc., RTP, NC	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: ML Drug 2 Endpoint: ML Number in group (n): Drug 1- baseline: 258 Drug 1- endpoint: 258 Drug 2- baseline: 264 Drug 2-endpoint: 264	Rescue med use during 24 hour period: Drug 1- baseline: Albuterol use (absolute change): 5.05 Drug 1-endpoint: -3.21 Drug 2-baseline: 5.25 Drug 2-endpoint: -2.25 P < 0.001 Symptom control during 24 hour period: Asthma symptom score (absolute change): D1 end: -0.91 D2 end: -0.57 P < 0.001 AQLQ - overall: D1 end: 1.3 (0.1) D2 end: 1.0 (0.1) P < 0.001 AQLQ - symptoms: D1 end: 1.4 (0.1) D2 end: 1.0 (0.1) P < 0.001 AQLQ - environment: D1 end: 1.2 (0.1) D2 end: 0.9 (0.1) P = 0.01 AQLQ - emotions: D1 end: 1.3 (0.1) D2 end: 0.9 (0.1) P < 0.001 AQLQ - activities: D1 end: 1.3 (0.1) D2 end: 1.0 (0.1) P = 0.004 Other:

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Meltzer et al.{Meltzer, 2002 #573} 2002 US Multicenter Glaxo Wellcome Inc., RTP, NC	Overall adverse events reported (%): Drug 1: NR Drug 2: NR P >/=0.99 Serious adverse events (%): Drug 1: <1 Drug 2: 1.1 Oral candidiasis- thrush (%): Drug 1: 3 Drug 2: 0 P = 0.008 Sore throat (%): Drug 1: 1 Drug 2: <1 P = 0.37 Headache (%): Drug 1: 2 Drug 2: 2 P > 0.99 Hoarseness (%): Drug 1: 3 Drug 2: 0 P = 0.002 Other (%): Drug 1: Insomnia: 1 Drug 2: 0 P = 0.12 Additional adverse events and comments: Compared with ML-treated patients, a greater proportion of FP-treated patients experienced hoarseness or oral pharyngeal candidiasis that was considered to be related to study medication (P<0.05).	Compliance Mean patient-reported compliance with the MDI and oral capsules was 92.0% or more and 93.3% or more, respectively.	Fair: Attrition on the high side Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
674 504 5106	Milgrom et al. Lemanske et al. 2001 + unpublished data (FDA) US Multicenter Genetech, Inc and Novartis Pharmaceuticals Corporation	Study design: RCT Duration: 28 wks (16 wk stable steroid phase followed by 12 wk steroid reduction phase) N = 334	Patients age 6-12; moderate to severe allergic asthma of at least 1 yr duration that was well controlled with ICSs equivalent to 168-420 mcg/d BDP; positive SPT; total serum IgE level between 30 and 1300 IU/mL; body weight < 90 kg; no significant change in asthma meds and no acute exacerbation requiring corticosteroid rescue at least 4 weeks before enrollment Asthma Severity: moderate to severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Milgrom et al. Lemanske et al. 2001 + unpublished data (FDA) US Multicenter Genetech, Inc and Novartis Pharmaceuticals Corporation	Albuterol 2 puffs as needed (maximum 8 puffs/d) allowed as rescue medication for symptoms of bronchospasm. Except for treatment of asthma exacerbation, all other asthma medications, including B-adrenergic agonists other than albuterol, were prohibited.	Previous OM treatment; known hypersensitivity to any study drug; a history of acute infectious sinusitis or respiratory tract infection or active lung disease other than allergic asthma within 1 month or any other significant systemic disease within 3 months of visit 1; clinically significant abnormalities in ECG, chest radiograph, or laboratory values, or elevated serum IgE levels for reasons other than atopy.	Yes-4-6 wks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Milgrom et al. Lemanske et al. 2001 + unpublished data (FDA) US Multicenter Genetech, Inc and Novartis Pharmaceuticals Corporation	Drug 1: OM 0.016 mg/kg IgE IU/mL per 4 weeks SQ n=225 Drug 2: Placebo NA n=109	Age: Drug 1: OM 9.4 Drug 2: Placebo 9.5 Sex (% female): Drug 1: OM 29.8 Drug 2: Placebo 33 Race (% white): Drug 1: OM 74.7 Drug 2: Placebo 78.9 Current smokers (%) NR ICS (%): Drug 1: OM 100 Drug 2: Placebo 100	Withdrawals: Drug 1: OM 16 (7.1%) Drug 2: PL 12 (11.0%) Withdrawals due to Aes: Drug 1: OM 1 (<1%) Drug 2: PL 1 (<1%)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Milgrom et al. Lemanske et al. 2001 + unpublished data (FDA) US Multicenter Genetech, Inc and Novartis Pharmaceuticals Corporation	Intervention: Drug 1: OM Drog 2: Placebo Number in group (n): Drug 1: 225 Drug 2: 109	• Symptoms: “Little change” in asthma symptom scores during either phase; “minimal difference” between treatment groups (data NR) • Night symptoms: Median nocturnal asthma symptom score: lower in OM group but no significant differences between groups during stable steroid phase • Exacerbations: Incidence of exacerbations lower in OM group in both phases; statistical difference in steroid reduction phase % patients with exacerbations: stable phase 15.6% vs. 22.9% (P = 0.95); reduction phase: 18.2% vs. 38.5% (P < 0.001). Mean number of episodes/patient: stable phase 0.3 vs. 0.4 (P = 0.093); reduction phase: 0.42 vs. 0.72 (P < 0.001) • Nocturnal awakenings/exacerbations requiring rescue meds on 2 or 3 consecutive nights: 11.6% vs. 21.1%; P = 0.002 • Rescue med use: # of puffs/day of albuterol consistently lower than baseline during both phases in OM group. At week 28, median puffs/day was 0 vs. 0.46 (P = 0.004) • QoL: Both groups had modest improvement in PAQLQ scores from baseline throughout study. OM showed larger improvement over placebo in all domains at end of stable phase but difference was not statistically significant. At study end, OM • PAQLQ overall score > 0.5 point increase at week 16: 36.8% vs. 38.5%; at week 2 • Overall score increase > 1.5 points end of stable phase: 9.5% vs. 6.6% (ns); end o • PAQLQ overall change (0.3 vs. 0.2) at 16 weeks, P = NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Milgrom et al. Lemanske et al. 2001 + unpublished data (FDA) US Multicenter Genetech, Inc and Novartis Pharmaceuticals Corporation	Overall OM 89.3 Placebo 87.2 Injection site reaction: OM 37.5 Placebo 36.6		

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
423	Mitchell et al.{Mitchell, 2003 #423} 2003 Multicenter (16 in Australia) outpatients Novartis Pharmaceutical Australia	Study design: RCT Double-blind Duration: 12 weeks N=203 randomised Enrolled: 274 screened; 203 randomised ITT Analysis: No another type of analysis was used (define)	: Outpatients aged 18 years or more who suffered from moderate-to-severe asthma. FEV1 was >/=50% of predicted and increased by 15% or more within 30 min after a β2-agonist. If there was historical evidence of asthma determined by a reversibility test carried out within one year, this test was not repeated. Patients had to have received treatment with ICS (delivered by a MDI) at a constant daily dose of 1000 mg BDP or 800 mg BUD for at least one month before the screening visit. The presence of at least two of the following on at least 2 of the last 7 days of the run-in period was required: waking at least once a night caused by asthma, asthma interfering with daily activities on at least one day, at least 4 puffs of salbutamol rescue medication a day required, or diurnal variation in PEF of at least 15%. Asthma Severity: Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Mitchell et al.{Mitchell, 2003 #423} 2003 Multicenter (16 in Australia) outpatients Novartis Pharmaceutical Australia	Rescue use of inhaled salbutamol was allowed during the entire treatment period. Short courses of oral corticosteroids (up to 10 days) and/or nebulised b2-adrenoceptor agonists were allowed for acute asthma exacerbations.	Other: Patients who had undergone any change in daily dose of ICS in the previous month, patients who had used a LABA or had received a course of oral corticosteroid in the month before the screening visit, and patients who had experienced problems using the Aerolizer despite proper instruction. Oral b2-adrenoceptor agonists, anticholinergic drugs, xanthine derivatives and ICS other than trial medication were not allowed.	Yes: Run-in period of 2–4 weeks, during which baseline measurements were performed and the patients were treated with BDP 500 mg twice daily. Rescue medication with inhaled salbutamol via a MDI

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Mitchell et al.{Mitchell, 2003 #423} 2003 Multicenter (16 in Australia) outpatients Novartis Pharmaceutical Australia	Intervention: Drug 1: FM plus BDP Drug 2: BDP Total daily dose: Drug 1: 24mcg + 1000mcg Drug 2: 2000mcg Steroid dosing range (Low, medium or high): Drug 1: high Drug 2: high Delivery device: Drug 1: Aerolizer, MDI Drug 2: MDI Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 102 Drug 2: 101 Mean age (years): Drug 1: 44 Drug 2: 44 Sex (% female): Drug 1: 55 Drug 2: 56 Current smokers (%): Drug 1: 8 Drug 2: 10 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Optional - Current use of LABA (%): Drug 1: 0 Drug 2: 0 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 7 (7%) Drug 2: 12 (12%) Overall: 19 (9%) Adverse events caused withdrawal (%): Drug 1: 2 Drug 2: 4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Mitchell et al.{Mitchell, 2003 #423} 2003 Multicenter (16 in Australia) outpatients Novartis Pharmaceutical Australia	Intervention: Drug 1 Baseline: FM plus BDP Drug 1 Endpoint: FM plus BDP Drug 2 Baseline: BDP Drug 2 Endpoint: BDP Number in group (n): Drug 1- baseline: 102 Drug 1- endpoint: 100 Drug 2- baseline: 101 Drug 2-endpoint: 101	Rescue med use day: Drug 1 -endpoint: mean # of inhalations reported at visit 3 = 0.97; reported at visit 4 = 0.90; reported at visit 5 = 0.93 (1.38) Drug 2 - endpoint: reported at visit 3 = 2.62; reported at visit 4 = 2.47; reported at visit 5 = 2.43 (2.43) P value: p=0.001 for all three for BDP plus FM versus BDP Rescue med use at night (SD): Drug 1 - endpoint: mean # of inhalations reported at visit 3 = 0.76; reported at visit 4 = 0.69; reported at visit 5 = 0.69 (1.27) Drug 2 - endpoint: reported at visit 3 = 1.63; reported at visit 4 = 1.36; reported at visit 5 = 1.43 (1.56) P value: all p = 0.001 Asthma exacerbations: D1 end: total = 34% D2 end: total = 51% P: NR Day time symptom control (SD): D1 - end: mean daytime symptom score reported at visit 3 = 0.58; reported at visit 4 = 0.50; reported at visit 5 = 0.49 (0.71) D2 - end: reported at visit 3 = 1.07; reported at visit 4 = 1.00; reported at visit 5 = 0.99 (0.76) P =0.001 for all three for BDP plus formoterol versus BDP Night time symptom control (SD): D1 - end: mean night time symptom score reported at visit 3 = 0.32; reported at vis D2 - end: reported at visit 3 = 0.49; reported at visit 4 = 0.46; reported at visit 5 = 0 p = 0.022 for visit 3; p = 0.018 for visit 4; p = 0.001 for visit 5 Other Relevant Health Outcome Results: visit 5 was the 12 week visit (visit 3 at 4wks, visit 4 at 8wks).

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Mitchell et al.{Mitchell, 2003 #423} 2003 Multicenter (16 in Australia) outpatients Novartis Pharmaceutical Australia	Overall adverse events reported (%): Drug 1: 68 Drug 2: 70 Serious adverse events (%): Drug 1: 1% Drug 2: 1% Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: The mean urinary cortisol/creatinine ratio at baseline, when all patients were using the same dose of beclomethasone, was similar in the two treatment groups. At visit 5, there was a statistically significant lower ratio in the P/BDP group than in the FM/BDP group (p = 0:001): The mean change in the ratio from baseline to visit 5 was also statistically significantly different between the two groups (p = 0:001); with the patients on FM/BDP1000 showing an increase of 3.48 nmol/mmol and the patients on P/BDP2000 showing a reduction of 13.38 nmol/mmol. Summary of urinary cortisol/creatinine ratios at baseline and at the end of the treatment period (visit 5) Ratio (nmol/mmol) Baseline Visit 5 Change from baseline FM/BDP P/BDP FM/BDP P/BDP FM/BDP P/BDP Mean 50.47 50.02 53.23 37.55 3.48 -13.38 SD 32.84 27.18 28.52 22.53 38.2 29.91 p value 0.38 0.001 0.001	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
225	Molimard et al.{Molimard, 2005 #225} 2005 France Specialty care - 69 pulmonologists Laboratoires IVAX, France	Study design: RCT : open label, parallel group with stratification for long-acting beta agoinst use (yes/no) 2:1 Duration: 12 weeks N=460 (Safety Set = all randomized and received one dose); 446 (ITT = all randomized and received one dose and one assessment for main endpoint); 353 (Per Protocol = all eligible for ITT after exclusion of those presenting with major protocol violations) Enrolled: NR ITT Analysis: No another type of analysis was used (define): excluded those who did not take at least one dose of medication and had one endpoint value	: Either sex, aged 18–60 years, presenting with moderate to severe asthma, not controlled with a regimen of inhaled corticosteroids: FPp 500 mg/day or BUD p 800 mg/day, corresponding to p 1000 mg/ day CFC-BDP with or without longacting b2-mimetics (LAb2). Poor control was definedby at least one nocturnal discomfort during the last 5 days and/or asthma requiring on average 2 puffs per day of short-acting β2-agonists (SAb2) p.r.n. during the last 7 days and/or asthma responsible for exercise dyspnea. Asthma Severity: Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Molimard et al.{Molimard, 2005 #225} 2005 France Specialty care - 69 pulmonologists Laboratoires IVAX, France	NR	NR	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Molimard et al.{Molimard, 2005 #225} 2005 France Specialty care - 69 pulmonologists Laboratoires IVAX, France	Intervention: Drug 1: BDP Drug 2: BUD Drug 3: FP Total daily dose: Drug 1: 800 mcg Drug 2: 1600 mcg Drug 3: 1000 mcg Steroid dosing range (Low, medium or high): Drug 1: high Drug 2: high Drug 3: high Delivery device: Drug 1: Qvar Autohaler Drug 2: Turbuhaler Drug 3: Diskus Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 149 Drug 2: 162 Drug 3: 149 Overall: 460 Mean age (years): Drug 1: 42 Drug 2: 43 Drug 3: 42 Sex (% female): Drug 1: 46 Drug 2: 54 Drug 3: 50 Optional - Disease duration (years): Drug 1: 18 Drug 2: 17 Drug 3: 16 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Optional - Current use of LABA (%): Drug 1: 64 Drug 2: 64 Drug 3: 65 Other: Drug 1: baseline juniper score = 2 Drug 2: 2 Drug 3: 2	Adverse events caused withdrawal (%): Drug 1: #1 Drug 2: #1 Drug 3: #2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Molimard et al.{Molimard, 2005 #225} 2005 France Specialty care - 69 pulmonologists Laboratoires IVAX, France	Intervention: Drug 1: BDP Drug 2: BUD Drug 3: FP Number in group (n): Drug 1: 149 Drug 2: 162 Drug 3: 149	Other: D1: mean change from baseline: Juniper Score = -1; each component of Juniper Score: nocturnal awakening -1; morning discomfort ; limitation of activity ; dyspnea ; wheezing ; consumption of rescue . D2 : -0.8; each component of Juniper Score: nocturnal awakening -0.7; morning discomfort ; limitation of activity ; dyspnea ; wheezing ; consumption of rescue . D3: -0.8; each component of Juniper Score: nocturnal awakening -0.8; morning discomfort ; limitation of activity ; dyspnea ; wheezing ; consumption of rescue . P: NS for Qvar versus FP (CI = -0.30 to 0.07)or BUD (CI = -0.29 to 0.08) for overall score; all individual components also NS except Qvar vs BUD for nocturnal awakenings CI = -0.43 to -0.05 (p=0.045) Other Relevant Health Outcome Results: Asthma control: improved in all groups, with no difference between groups. Subgroups: For patients treated with LAb2 (n = 286) a significantly greater improvement of the ACQ score was obtained with Qvar Autohaler versus fluticasone (1.0+/-1.0 vs. 0.6+/-0.9; P = 0:019), but not versus BUD (0.9+/-0.9; NS).

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Molimard et al.{Molimard, 2005 #225} 2005 France Specialty care - 69 pulmonologists Laboratoires IVAX, France	Overall adverse events reported (%): Drug 1: 38 Drug 2: 35 Drug 3: 37 P = 0.791 between all Dysphonia (%): Drug 1: 13 Drug 2: 16 Drug 3: 20 Respiratory infection (%): Drug 1: 19 Drug 2: 14 Drug 3: 16 Other (%): Drug 1: moniliasis = 3 Drug 2: 3 Drug 3: 4 Other (%): Drug 1: Central and peripheral nervous system disorders = 18 Drug 2: 19 Drug 3: 20 Additional adverse events and comments: This was stated by article - may decrease reliability of AE in this article as well = (the discrepancy with the local safety results is linked to the differences in assessment of safety data by the physician and the patient)	Compliance Compliance was assessed at the end of the study by weighing the bottles of Qvar Autohaler and BUD (to calculate the number of remaining doses) and counting the remaining doses of fluticasone. The percentage of compliance was calculated as (number of actual intakes/number of theoretic intakes) x 100. Descriptive statistics indicate that treatment compliance was similar in the BUD and FPgroups (81729% and 80718%, respectively) and higher compared to the Qvar Autohaler group (68725%). Due to the differences in compliance assessment between groups (weighing vs. counting), no statistical comparison was performed.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4857 Combo	Morice et al.{Morice, 2007 #4857} 2007 Multinational (8 countries) Multicenter (62 centers) AstraZeneca	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=680 (679 ITT) Enrolled: nr/nr/892 ITT Analysis: Yes	Adult and adolescent outpatients (12 years or more) with asthma for at least 6 months, who were inadequately controlled on ICS alone; FEV1 between 50% and 90% of predicted normal (prebronchodilator), reversibility of at least 12% FEV1 after inhalation of terbutaline 1 mg and a history of daily ICS use (stable dose of 500–1600 mcg/day within 30 days prior to enrolment) for at least 3 months. Asthma severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Morice et al.{Morice, 2007 #4857} 2007 Multinational (8 countries) Multicenter (62 centers) AstraZeneca	Terbutaline 0.5 mg/inhalation or equivalent for symptom relief	NR	Yes- elucidate....: 2 week on usual ICS medication; LABA therapy discontinued 3 days prior to run-in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Morice et al.{Morice, 2007 #4857} 2007 Multinational (8 countries) Multicenter (62 centers) AstraZeneca	Intervention: Drug 1: BUD Drug 2: BUD/FM Drug 3: BUD/FM Total daily dose: Drug 1: 800 Drug 2: 640/18 Drug 3: 640/18 Delivery device: Drug 1: pMDI Drug 2: DPI Drug 3: pMDI Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 217 Drug 2: 229 Drug 3: 234 Mean age (years): Drug 1: 40 Drug 2: 39 Drug 3: 40 Sex (% female): Drug 1: 69 Drug 2: 61 Drug 3: 60 Current smokers (%): Drug 1: 6 Drug 2: 5 Drug 3: 6 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 29 (13%) Drug 2: 23 (10%) Drug 3: 27 (12%) Adverse events caused withdrawal (%): Drug 1: 7 Drug 2: 2 Drug 3: 5

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Morice et al.{Morice, 2007 #4857} 2007 Multinational (8 countries) Multicenter (62 centers) AstraZeneca	Intervention: Drug 1 Baseline: BUD Drug 1 Endpoint: BUD Drug 2 Baseline: BUD/FM DPI Drug 2 Endpint: BUD/FM DPI Drug 3 Baseline: BUD/FM pMDI Drug 3 Endpoint: BUD/FM pMDI Number in group (n): Drug 1: 217 Drug 2: 229 Drug 3: 233	Rescue med use during 24 hour period: Drug 1-endpoint: -0.35 Drug 2-endpoint: -0.92* Drug 3- endpoint: -0.94* Day time symptom control: Symptom free days D1 - end: 19.1 D2 - end: 34.2* *** D3 - end: 28.0** Nocturnal awakenings: % mean change D1 end: -9.7 D2 end: -15.5** D3 end: -16.5* AQLQ - overall: AQLQ(S) adjusted mean change D1 end: +0.37 D2 end: +0.76 D3 end: +0.65 P < 0.001 BUD/FM DPI vs. BUD; P=0.002 vs. BUD/FM pMDI vs. BUD Other: Total Asthma symptom score 0-6 D1 end : -0.44 D2 end: -0.84* D3 end: -0.7 Other: Asthma control days D1 end : 18.3 D2 end: 33.1* *** D3 end: 26.5** Other Relevant Health Outcome Results: *p < 0.001, **p < 0.01 vs. budesonide pMDI; ***p < 0.05 budesonide/formoterol DPI vs. budesonide/formoterol pMDI. For the overall AQLQ(S) score, 52% and 56% of budesonide/formoterol pMDI-treated and budesonide/formoterol DPI-treated patients, respectively, had a clinically relevant increase of >/= 0.5 units

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Morice et al.{Morice, 2007 #4857} 2007 Multinational (8 countries) Multicenter (62 centers) AstraZeneca	Overall adverse events reported (%): Drug 1: 38 Drug 2: 29 Drug 3: 30 Oral candidiasis- thrush (%): Drug 1: 1 Drug 2: 2 Drug 3: 1 Cough (%): Drug 1: 2 Drug 2: 1 Drug 3: 1 Sore throat (%): Drug 1: 3 Drug 2: 3 Drug 3: 2 Headache (%): Drug 1: 2 Drug 2: 2 Drug 3: 2 Upper respiratory tract infection (%): Drug 1: 4 Drug 2: 4 Drug 3: 3 Respiratory infection (%): Drug 1: lower 3 Drug 2: 2 Drug 3: 1 Other (%): Drug 1: Nasopharyngitis 8 Drug 2: 3 Drug 3: 2 Other (%): Drug 1: Influenza 2 Drug 2: 1 Drug 3: 2	Adherence > 98% across groups	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
5111	Morice et al.{Morice, 2007 #5111} 2007 Multinational (8 countries) Multicenter (53 centers) AstraZeneca	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=622 Enrolled: nr/nr/812 ITT Analysis: Yes	Paediatric outpatients (aged 6–11 years) with asthma [10] for>=6 months and PEF >=50% of predicted normal (prebronchodilator), all patients had to have a history of daily ICS use (stable dose of 375-1000 mg/day within the 30 days prior to enrolment) and clinically important exercise-induced bronchoconstriction (X1 episode/week) for >=3 months before enrolment. Patients also had to demonstrate the ability to use a DPI, pMDI and peak flow meter and total asthma symptom score >=1 on >=4 of the last 7 days of run in and and a mean morning PEF 50–85% of their post-bronchodilatory PEF

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Morice et al.{Morice, 2007 #5111} 2007 Multinational (8 countries) Multicenter (53 centers) AstraZeneca	inhaled shortacting b2-agonist, terbutaline 0.5 mg/inhalation, for symptom relief. If the subject preferred another short-acting b2-agonist that was regarded as being equivalent in clinical practice, e.g. salbutamol, it was prescribed by the investigator.	NR	Yes, 10- to 14-day run-in, during which they continued their pre-study ICS medication

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Morice et al.{Morice, 2007 #5111} 2007 Multinational (8 countries) Multicenter (53 centers) AstraZeneca	Intervention: Drug 1: Bud Drug 1: Bud + Fm DPI Drug 2: Bud + Fm pMDI Total daily dose: Drug 1: 200 ug Drug 2: 160 + 9 Drug 3: 160 + 9 Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: med Delivery device: Drug 1: pMDI Drug 2: DPI Drug 3: pMDI Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 207 Drug 2: 212 Drug 3: 203 Mean age (years): Drug 1: 9 Drug 2: 8 Drug 3: 8 Sex (% female): Drug 1: 34 Drug 2: 33 Drug 3: 35 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 14 (6) Drug 2: 13 (6) Drug 3: 12 (6) Adverse events caused withdrawal (%): Drug 1: 1 Drug 2: <1 Drug 3: <1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Morice et al.{Morice, 2007 #5111} 2007 Multinational (8 countries) Multicenter (53 centers) AstraZeneca	Intervention: Drug 1: Bud Drug 1: Bud + Fm DPI Drug 2: Bud + Fm pMDI # in group (n): Drug 1: 207 Drug 2: 212 Drug 3: 203	All are adjusted mean change from baseline Rescue drug use during 24 hr period Drug 1: -0.42 Drug 2: -0.54 Drug 3: -0.50 Total asthma symptom score (0-6) Drug 1: -0.69 Drug 2: -0.77 Drug 3: -0.68 Nights w/awakenings Drug 1: -7.5 Drug 2: -8.2 Drug 3: -7.9 Symptom free days Drug 1: 35.2 Drug 2: 37.4 Drug 3: 34.9 Asthma control days Drug 1: 35.8 Drug 2: 37.6 Drug 3: 35.2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Morice et al.{Morice, 2007 #5111} 2007 Multinational (8 countries) Multicenter (53 centers) AstraZeneca	Bud vs. Bud/FM DPI vs. Bud/FM pMDI n(%) Patients with at least 1 event 81 (39) vs. 100 (47) vs. 92 (45) Nasopharyngitis 16 (8) vs. 18 (8) vs. 17 (8) Pharyngitis 10 (5) vs. 12 (6) vs. 13 (6) Upper respiratory tract 7 (3) vs. 11 (5) vs. 12 (6) infection Asthma aggravated 13 (6) vs. 7 (3) vs. 7 (3) Pyrexia 10 (5) vs. 4 (2) vs. 4 (2) Acute bronchitis 5 (2) vs. 4 (2) vs. 7 (3) Rhinitis 1 < (0.5) vs. 8 (4) vs. 6 (3) Influenza 4 (2)vs. 5 (2) vs. 5 (2) Cough 4 (2) vs. 3 (1) vs. 7 (3) Vomiting 5 (2) vs. 4 (2) vs. 4 (2)	Overall 98% adhered	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
913	Murray et al.{Murray, 1999 #913} 1999 USA Multicenter (35) Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 24 weeks N=514 Enrolled: NR/NR/514 ITT Analysis: Yes	: 18 yrs or more; FEV 45-80%; increase of at least 12% following albuterol and symptomatic on BDP 336 µg or Tri 800µg. During screening period must be symptomatic at least 3 out of 7 days (using relief medication, night time awakenings or daytime symptoms) Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Murray et al.{Murray, 1999 #913} 1999 USA Multicenter (35) Glaxo Wellcome	Immunotherapy or maintainenece theophylline	Other: Pregnant	Yes: 14 day screening period

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Murray et al.{Murray, 1999 #913} 1999 USA Multicenter (35) Glaxo Wellcome	Intervention: Drug 1: BDP + SM Drug 2: BDP Total daily dose: Drug 1: 336+84 Drug 2: 672 Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: med Delivery device: Drug 1: MDI Drug 2: MDI Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 260 Drug 2: 254 Mean age (years): Drug 1: 42.2 Drug 2: 41.9 Sex (% female): Drug 1: 59 Drug 2: 55 Optional - Race (% white): Drug 1: 86 Drug 2: 85 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 50 (19) Drug 2: 57 (22) Optional - Withdrew due to lack of efficacy (%): Drug 1: 2 Drug 2: 2 Adverse events caused withdrawal (%): Drug 1: 3 Drug 2: 2 Optional - Lost to follow-up (%): Drug 1: Failure to return 3 Drug 2: 4 Optional - Other reasons for withdrawal (%): Drug 1: 11 Drug 2: 15

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Murray et al.{Murray, 1999 #913} 1999 USA Multicenter (35) Glaxo Wellcome	Intervention: Drug 1 Baseline: BDP + SM Drug 1 Endpoint: BDP + SM Drug 2 Baseline: BDP Drug 2 Endpoint: BDP Number in group (n): Drug 1- baseline: 260 Drug 2- baseline: 254	Rescue med use during 24 hour period: Drug 1- baseline: see below Rescue med use day: Drug 1- baseline: see below Rescue med use at night: Drug 1- baseline: see below P value: P =< 0.05 in favor of combo Asthma exacerbations: # (%) of patients: D1 end: 43 (17%) D2 end: 45 (18%) P: P= NR Other Relevant Health Outcome Results: Actual data NR for much of the following (data shown in figures), only p values reported: symptom scores significantly greater improvements after BDP + SM in ratings of wheeze, SOB, and chest tightness (mean decreases from baseline at week 24 of 0.49, 0.71, and 0.62 compared to decreases of 0.27, 0.25, and 0.33; p<=0.05); reduction in mean combined symptom scores and increase in mean % symptom free-days were significantly (p<=0.05) improved at all weekly intervals after BDP + SM vos higher dose BDP.; greater decrease (p<=0.05) in mean daytime use of albuterol and a greateer increase in % of days with no rescue albuterol during BDP + SM; greater decrease in mena night time use of albuterol with combined therapy, but NS at end of 24 week therapy; % of nights in which no rescue albuterol was req

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Murray et al.{Murray, 1999 #913}	Oral candidiasis- thrush (%):		Fair
1999	Drug 1: 3		Fair
	Drug 2: 6		No
USA			
Multicenter (35)	Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels:		
Glaxo Wellcome	After 24 weeks # patients with abnormal results was not significantly different between groups. One patient in combo therapy and 2 in BDP group had an abnormal response to corticotropin stimulation; no differences in vital signs or PE results, no unfavorable ECG changes from baseline in combined group, 1 patient had NS TW abnormality and prolonged QT interval at week 24.		

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
273	Murray et al.{Murray, 2004 #273} 2004 USA Multicenter (33 sites) GlaxoSmithKline	Study design: RCT Double-blind Duration: 12 weeks N=267 Enrolled: 555 screened 267 randomized ITT Analysis: Yes	: 12 years and older with persistent asthma who were symptomatic while taking as-needed, short-acting β2-agonists alone; FEV1 between 40-85% and increase of at least 15% within 30 minutes of 2 puffs of albueterol Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Murray et al.{Murray, 2004 #273} 2004 USA Multicenter (33 sites) GlaxoSmithKline	Rescue med	Other: Pregnancy or lactation, life threatening asthma, hospitalization due to asthma 2x or more in last yr; current or past smoker >10 pack/yrs; significant concurrent disease; inhaled, oral or parenteral corticosteroids; theophylline, or other meds that could confound study med	Yes: 2 week single bind placebo run-in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Murray et al.{Murray, 2004 #273} 2004 USA Multicenter (33 sites) GlaxoSmithKline	Intervention: Drug 1: SM Drug 2: FP Drug 3: FP + SM Total daily dose: Drug 1: 100 µg Drug 2: 200 µg Drug 3: 200 +100 Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: low Drug 3: low Delivery device: Drug 1: Diskus Drug 2: Diskus Drug 3: Diskus Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 90 Drug 2: 89 Drug 3: 88 Mean age (years): Drug 1: 34 Drug 2: 32 Drug 3: 36 Sex (% female): Drug 1: 60 Drug 2: 49 Drug 3: 53 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 16 (18) Drug 2: 11 (12) Drug 3: 12 (14) Adverse events caused withdrawal (%): Drug 1: 2 Drug 2: 1 Drug 3: 0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Murray et al.{Murray, 2004 #273} 2004 USA Multicenter (33 sites) GlaxoSmithKline	Intervention: Drug 1 Baseline: SM Drug 1 Endpoint: SM Drug 2 Baseline: FP Drug 2 Endpint: FP Drug 3 Baseline: FP+SM Drug 3 Endpoint: FP+SM Number in group (n): Drug 1- baseline: 90 Drug 1- endpoint: 90 Drug 2- baseline: 89 Drug 2- endpoint: 89 Drug 3- baseline: 88 Drug 3- endpoint: 88	Rescue med use during 24 hour period: Drug 1- baseline: puffs per day: 4.9 Drug 1-endpoint: reduction from baseline, puffs per day/% reduction: -2.6/54% Drug 2-baseline: 4.1 Drug 2-endpoint: -1.8 (0.23) / 46% Drug 3 - baseline: 4.1 Drug 3- endpoint: -2.8 (0.31)/61% P values: FP and Sal vs FP P <=0.01; FP and SM vs SM P <= 0.04 Nocturnal awakenings: D1 base: mean % nights w/ no awakenings: 65.1 D1 end: mean change from baseline: 26.4% D2 base: 71.5 D2 end: 21.1 (3.2) D3 base: 65.1 D3 end: 29.8 (3.7) Asthma Control Score: D1 base: Asthma symptom score (0-5): 2.3 D1 end: mean change: -0.9; % improvement from baseline: 41% D2 base: 2.4 D2 end: -0.9 (0.1); 39% D3 base: 2.3 D3 end: -1.3 (0.1); 57% P: FP and SM vs FP P <=0.01; FP and SM vs SM P <= 0.04 Other: D1 base: Days with no asthma symptoms, %: 1.9 D1 end : 25.6 D2 base: 4.0 D2 end: 24.6 (4.1) D3 base: 1.8 D3 end: 40.6 (4.7) P: FP and SM vs FP P <=0.01; FP and SM vs SM P <= 0.04

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Murray et al.{Murray, 2004 #273} 2004 USA Multicenter (33 sites) GlaxoSmithKline	Overall adverse events reported (%): Drug 1: drug related 12 Drug 2: 13 Drug 3: 17 Oral candidiasis- thrush (%): Drug 1: 0? Drug 2: 3 Drug 3: 5 Sore throat (%): Drug 1: 2 Drug 2: 4 Drug 3: 1 Headache (%): Drug 1: 4 Drug 2: 2 Drug 3: 3 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: NR	Compliance Mean trmt compliance 94 to 95% 15 patients (3-7% in groups) had compliance less than 80%	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
907	Nathan et al.{Nathan, 1999 #907} 1999 United States Multicenter - 25 Glaxo Wellcome	Study design: RCT Double-blind Duration: 26 weeks N=386 Enrolled: NR, NR, 386 ITT Analysis: Yes	: Non-smoking males or females at least 12 years of age whoe had been diagnosed with asthma for at least 3 months and who demonstrated a FEV1 of 65 o 90%, an increase in FEV1 of >/= 12% with albuterol, and who preformed reproducible FEV1 maneuvers at screening. Only treated with daily or as needed short acting beta agonists who had not used inhaled or oral CS regulary within 6 months of the screening visit. Female patients were non-lactating, had negative pregnancy test, or were surgically sterile, postmenopausal for at least 1 year, or using birth control for at least 1 month prior to study. Asthma Severity: Mild Moderate Severe Other: unclear from description, only told that they must have persistent

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Nathan et al.{Nathan, 1999 #907} 1999 United States Multicenter - 25 Glaxo Wellcome	Intranasal corticosteroids or intranasal cromolyn sodium were allowed only if the dose remained unchanged throughout the study. As needed albuterol was allowed.	Prior treatment with: ICS last 6 months Other: Decline in FEV1 of >/= 15% after saline inhalation, astham instability as indicated by an asthma-related hospital admission in the 30 days before the screenign visit or by requring > 12 puffs of albuterol on 3 of the last 7 days of the screening period; hypersensitivity to sympathomimetic drugs, BDP, or any component of an aerosol of MDI, use of any other prescription or OTC medication which might affect the course of asthma or interaqct with sympathomimetic amines; clinically signficant abnormal 12-lead ECG, or evidence of significant concurrent disease like glaucoma, diabetes, or HTN.	Yes: 2 week screening where patients continued on albuterol

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Nathan et al.{Nathan, 1999 #907} 1999 United States Multicenter - 25 Glaxo Wellcome	Intervention: Drug 1: SM Drug 2: BDP Drug 3: Placebo Total daily dose: Drug 1: 84mcg Drug 2: 336mcg Drug 3: 0 Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: medium Drug 3: NA Delivery device: Drug 1: MDI Drug 2: MDI Drug 3: MDI Is dosing comparable between treatment groups? NA: LABA versus ICS versus placebo	# in group (n): Drug 1: 128 Drug 2: 129 Drug 3: 129 Mean age (years): Drug 1: 30.7 Drug 2: 29.9 Drug 3: 29.1 Sex (% female): Drug 1: 54 Drug 2: 57 Drug 3: 50 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 30 (23%) Drug 2: 23 (18%) Drug 3: 28 (22%) Overall: 81 (20.98%) Adverse events caused withdrawal (%): Drug 1: NR Drug 2: NR Drug 3: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Nathan et al.{Nathan, 1999 #907} 1999 United States Multicenter - 25 Glaxo Wellcome	Intervention: Drug 1 Baseline: SM Drug 1 Endpoint: SM Drug 2 Baseline: BDP Drug 2 Endpoint: BDP Drug 3 Baseline: Placebo Drug 3 Endpoint: Placebo Number in group (n): Drug 1- baseline: 128 Drug 1- endpoint: 128 Drug 2- baseline: 129 Drug 2- endpoint: 129 Drug 3- baseline: 129 Drug 3- endpoint: 129	Rescue med use day: Drug 1 -endpoint: mean change in % of rescue free days = 36% Drug 2 - endpoint: 28% Drug 3 - endpoint: 16% P value: 0.016 for Sal versus BDP; <0.001 for SM and BDP compared to placebo Rescue med use at night: Drug 1 - endpoint: mean increase in % of rescue free nights = 23% Drug 2 - endpoint: 23% Drug 3 - endpoint: 9% P value: </= 0.014 for SM and BDP versus placebo Asthma exacerbations: D1 end: number of patients experiencing at least one exacerbation = 16-17% D2 end: 16-17% D3 end: 16-17% P: NS - NR Day time symptom control: D1 - end: change in % of symptom free days = NR (figure) D2 - end: NR D3 - end: NR P: NS between SAL and BDP at baseline; BUD group better than SAL and placebo for change in % of symptom free days through the 2week post treatment period, p<0.032 Night time symptom control: D1 - end: % of symptom free nights = 41% D2 - end: 34% D3 - end: 41% P: NS between SAL and BDP, NR Nocturnal awakenings: D1 end: mean increase in % of nights without awakenings = 18% D2 end: 17% D3 end: 7% P: 0.005 for Sal versus placebo; NS for Sal versus BDP - NR Other:

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Nathan et al.{Nathan, 1999 #907} 1999 United States Multicenter - 25 Glaxo Wellcome	Overall adverse events reported (%): Drug 1: at least one potentially drug related event = 14 (11%) Drug 2: 17 (13%) Drug 3: 7 (5%) Drug 5: NR Serious adverse events (%): Drug 1: 1 Drug 2: 1 Drug 3: 1 Cough (%): Drug 1: 4 Drug 2: 1 Drug 3: NR Other (%): Drug 1: chest tightness after inhaler use = 1 Drug 2: 2 Drug 3: 2 Additional adverse events and comments: No clinically significant changes in physical exam or vital signs.	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
713	Nathan et al.{Nathan, 2001 #713} 2001 United States Multicenter (15) Schering-Plough Research Institute	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=227 Enrolled: NR/NR/227 randomized ITT Analysis: No another type of analysis was used (define): patients who received at least one dose of study medication and hwo had postbaseline data	Age: >/= 12 FEV1 expressed as a percent of the predicted value: between 60 - 90% Reversability of FEV1: >/= 12% Days with asthma symptoms: asthma for > 6 months using ICS for at least 30 days Previous use of corticosteroids: maintained on prescribed inhaled steroids at least 30 days before entering the study Duration of condition: at least 6 months Asthma Severity: Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Nathan et al.{Nathan, 2001 #713} 2001 United States Multicenter (15) Schering-Plough Research Institute	Rescue med	Pregnant or lactating Concommitant diseases: clinically significant oral candidiasis, respiratory disease, or disease other than asthma Current treatment with: required daily nebulized beta2 agonist Smoking - current or former: within the previous 6 months : emergency hospital treatment twice in the previous 6 months; hospitalized for an asthma exacerbation within the previous 3 months; required intubation for asthma within the previous 5 years.	Yes: 1-2 week run-in; continued treatment with their previously prescribed inhaled corticosteroid.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Nathan et al.{Nathan, 2001 #713} 2001 United States Multicenter (15) Schering-Plough Research Institute	Intervention: Drug 1: placebo Drug 2: MOM Drug 3: MOM Drug 4: BDP Total daily dose: Drug 1: 0 Drug 2: 200mcg Drug 3: 400mcg Drug 4: 336mcg Steroid dosing range (Low, medium or high): Drug 2: low Drug 3: medium Drug 4: low Delivery device: Drug 1: MDI, DPI Drug 2: DPI Drug 3: DPI Drug 4: MDI Is dosing comparable between treatment groups? NA: purposefully comparing a low to moderate of same corticosteroid	# in group (n): Drug 1: 57 Drug 2: 57 Drug 3: 56 Drug 4: 57 Mean age (years): Drug 1: 42 Drug 2: 40 Drug 3: 40 Drug 4: 40 Sex (% female): Drug 1: 39 Drug 2: 33 Drug 3: 37 Drug 4: 40 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Drug 4: NR Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Drug 4: 100 Optional - Current methylxanthine (i.e. theophylline) use (%): Drug 1: 1.75 Drug 2: 8.77 Drug 3: 1.79 Drug 4: 10.5	Number (%) withdrawn: Drug 1: NR Drug 2: NR Drug 3: NR Drug 4: NR Optional - Withdrew due to lack of efficacy (%): Drug 1: 44 Drug 2: 9 Drug 3: 4 Drug 4: 11 Adverse events caused withdrawal (%): Drug 1: 8.8 Drug 2: 1.8 Drug 3: 3.6 Drug 4: 1.8

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Nathan et al.{Nathan, 2001 #713} 2001 United States Multicenter (15) Schering-Plough Research Institute	Intervention: Drug 1: placebo Drug 2: MOM Drug 3: MOM Drug 4: BDP Number in group (n): Drug 1: 57 Drug 2: 57 Drug 3: 56 Drug 4: 57	Rescue med use day: Drug 1: mean at baseline: 3.70; change from baseline to endpoint: 1.31 (0.38) Drug 2: 3.21/-1.18 (0.39) Drug 3: 2.86/-0.94 (0.39) Drug 4 3.85/-1.05 (0.39) P < 0.01 for all active versus placebo Day time symptom control: D1: change from baseline AM wheezing score 0.32 (0.07), AM difficulty breathing score 0.20 (0.09), AM cough score 0.22 (0.07) D2: AM wheezing score -0.14 (0.7), AM difficulty breathing score -0.22 (0.09), AM cough score -0.11 (0.07) D3: AM wheezing score -0.29 (0.8), AM difficulty breathing score -0.25 (0.09), AM cough score -0.05 (0.08) D4: AM wheezing score -0.11 (0.7), AM difficulty breathing score -0.10 (0.09), AM cough score 0.02 (0.07) P <0.01 for all active versus placebo except BDP MDI was P <0.02 for am difficulty breathing score versus placebo and BDP MDI was NS for AM cough score versus placebo Nocturnal awakenings: D1: mean at baseline: 0.41; change from baseline 0.09 (0.13) D2: 0.14/-0.09 (0.13) D3: 0.28/-0.18 (0.13) D4: 0.25/0.06 (0.13) P = NS Other: D1: Asthma worsening 56.1% D2 : 13.8% D3: 10.9% D4: 22.8% P < 0.01 for placebo versus active treatment Other Relevant Health Outcome Results: No statistically significant differences between BDP and MF in asthma symptom sc

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Nathan et al.{Nathan, 2001 #713} 2001 United States Multicenter (15) Schering-Plough Research Institute	Oral candidiasis- thrush (%): Drug 1: 0 Drug 2: 4 Drug 3: 11 Drug 4: 5 Dysphonia (%): Drug 1: 0 Drug 2: 4 Drug 3: 4 Drug 4: 2 Headache (%): Drug 1: 2 Drug 2: 5 Drug 3: 2 Drug 4: 4 Hoarseness (%): Drug 1: 2 Drug 2: 7 Drug 3: 2 Drug 4: 0 Other (%): Drug 1: flatulence: 0 Drug 2: 4 Drug 3: 0 Drug 4: 0	Compliance 220/227 were compliant with study medication dosing and took >75% of the specified doses.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
121	Nathan et al.{Nathan, 2006 #121} 2006 US Multicenter (45 sites) GlaxoSmithKline	Study design: RCT Double-blind Duration: 12 weeks N=365 Enrolled: 755 screened, NR, 365 ITT Analysis: Yes	Age: >=12yr FEV1 expressed as a percent of the predicted value: 40-85 Reversability of FEV1: >=15% 30min s/p albuterol 180mcg INH Previous use of corticosteroids: >=3mo prior to screening, no change in regimen >=1 month prior to screening at the following total daily doses: BDP, 378 to 840 mcg; TAA, 900 to 1600 mcg; FLUN, 1250 to 2000 mcg; FP 440to 660 mcg of MDI aerosol or 400 to 600 mcg of inhalation powder; or BUD 800 to 1200 mcg Duration of condition: required pharmacotherapy for at least 6mo prior to the start of the study Other: for women: negative pregnancy test at screening, acceptable method of birth control >=1mo prior to participation, surgically sterile or post menopausal; FEV1 within 15% of the value obtained at the beginning of the run-in period. Asthma Severity: Mild Moderate Not or poorly controlled Other: severity based on baseline characteristics and withdrawal criteria

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Nathan et al.{Nathan, 2006 #121} 2006 US Multicenter (45 sites) GlaxoSmithKline	albuterol PRN	Pregnant or lactating: pregnant Concommitant diseases: Hx life-threatening asthma; abnormal findings on chest radiography; a clinically significant abnormality on a 12-lead electrocardiogram(ECG) or a laboratory abnormality at screening;and significant concurrent disease (eg, glaucoma, hypertension). Current treatment: medications that could affect the courseof asthma or interact with sympathomatic amines; use of oral or injectablecorticosteroids within the previous month; Smoking - current or former: within the previous year or >=10PY Hx Other: hypersensitivity reaction to sympathomatic drugs orcorticosteroids; Patients were not eligible for double-blindtreatment if they had >3 nights with awakenings dueto asthma that required treatment with albuterol orhad 3 days when they required ---12 puffs/d of albuterol during the 7 days before the randomization visit (i.e. during the second week of the run-in)	Yes: 2-week, single-blind,PLA (HFA MDI) run-in period during which patients continued to use their usual ICS and were provided with an albuterol CFC MDI* to use asneeded for relief of symptoms during the run-in anddouble-blind treatment periods. Patients were alsoprovided with a MiniWright peak flowmeter (ClementClark, Inc., London, United Kingdom) and instructedin its use.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Nathan et al.{Nathan, 2006 #121} 2006 US Multicenter (45 sites) GlaxoSmithKline	Intervention: Drug 1: FP/SM Drug 2: FP Drug 3: SM Drug 4: placebo Total daily dose: Drug 1: 440/84mcg Drug 2: 440mcg Drug 3: 84mcg Drug 4: NA Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Drug 3: NA Drug 4: NA Delivery device: Drug 1: HFA MDI Drug 2: CFC MDI Drug 3: CFC MDI Drug 4: HFA MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 94 Drug 2: 91 Drug 3: 91 Drug 4: 89 Mean age (years): Drug 1: 38.8 Drug 2: 39.1 Drug 3: 37.5 Drug 4: 41.1 Sex (% female): Drug 1: 61 Drug 2: 63 Drug 3: 62 Drug 4: 56 Optional - Race (% white): Drug 1: 78 Drug 2: 82 Drug 3: 88 Drug 4: 87 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Drug 4: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Drug 4: 100 Other: Drug 1: baseline FEV1, % predicted 68.3	Number (%) withdrawn: Drug 1: 13.8 Drug 2: 22.2 Drug 3: 37.4 Drug 4: 61.8 Optional - Withdrew due to asthma exacerbations (%): Drug 1: 7.4 Drug 2: 12.1 Drug 3: 25.3 Drug 4: 53.4 Adverse events caused withdrawal (%): Drug 1: 1.1 Drug 2: 2.2 Drug 3: 4.4 Drug 4: 2.2 Optional - Protocol violation (%): Drug 1: 3.2 Drug 2: 2.2 Drug 3: 2.2 Drug 4: 3.4 Optional - Other reasons for withdrawal (%): Drug 1: 2.1 Drug 2: 5.5 Drug 3: 5.5 Drug 4: 2.2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Nathan et al.{Nathan, 2006 #121}	Intervention:	Rescue med use during 24 hour period:
2006	Drug 1 Baseline: FP/SM	Drug 1- baseline: 3.1
	Drug 1 Endpoint: FP/SM	Drug 1-endpoint: 1.5
US	Drug 2 Baseline: FP	Drug 2-baseline: 3.2
Multicenter (45 sites)	Drug 2 Endpoint: FP	Drug 2-endpoint: 2.7
	Drug 3 Baseline: SM, placebo	Drug 3 - baseline: 3.3, 2.7
GlaxoSmithKline	Drug 3 Endpoint: SM, placebo	Drug 3- endpoint: 2.4, 4.3
		P values: FP/SM vs FP or SM or placebo, p<0.001
	Number in group (n):	
	Drug 1- baseline: 94	Asthma exacerbations:
	Drug 1- endpoint: 94	Causing withdrawal, %
	Drug 2- baseline: 91	D1 end: 7
	Drug 2- endpoint: 91	D2 end: 11
	Drug 3- baseline: 91, 89	D3 end: 24, 54
	Drug 3- endpoint: 91. 89	P: FP/SM vs SM or placebo, p<0.001; FP/SM vs FP NS
		Symptom control during 24 hour period:
		D1 base: Sx-free days, % 21.6
		D1 end: 40.1
		D2 base: 14.8
		D2 end: 29.8
		D3 base: 16.5, 23.3
		D3 end: 30.5, 14.2
		P: FP/SM vs SM or placebo, p<0.001
		Nocturnal awakenings:
		D1 base: Nights without awakenings, % 92.6
		D1 end: 96.7
		D2 base: 92.5
		D2 end: 91.9
		D3 base: 87.8, 91.7
		D3 end: 87.3, 76.9
		P: FP/SM vs SM or placebo, p<0.001
		Other:
		D1 base: asthma Sx score 1.6
		D1 end : 1.1
		D2 base: 1.6
		D2 end: 1.4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Nathan et al.{Nathan, 2006 #121} 2006 US Multicenter (45 sites) GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 69 Drug 2: 69 Drug 3: 66 Drug 4: 60 Serious adverse events (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Drug 4: 1.1 Dysphonia (%): Drug 1: palpitations 0-2 Cough (%): Drug 1: unspecified oro-pharyngeal plaques 0-2 Sore throat (%): Drug 1: 7 Drug 2: 13 Drug 3: 7 Drug 4: 6 Headache (%): Drug 1: 15 Drug 2: 16 Drug 3: 21 Drug 4: 12 Upper respiratory tract infection (%): Drug 1: 24 Drug 2: 15 Drug 3: 19 Drug 4: 12 Respiratory infection (%): Drug 1: viral 5 Drug 2: 5 Drug 3: 5 Drug 4: 4 Other (%): Drug 1: MSK pain 7 Drug 2: 2 Drug 3: 8 Drug 4: 3	Compliance Compliance with the study medication was assessed based on the data recorded on a patient diary card. Every morning an devening, patients were to record yes or no on the card to indicate whether or not the dose had been taken. 95-98% across treatment groups	Fair: while randomization and masking at multiple levels, and ITT analysis appear adequate, there is a large withdrawal rate (and large differential withdrawal between groups) Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
736	Nelson et al.{Nelson, 2000 #763} 2000 United States Multicenter Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N = 447 Number screened: NR/NR/447 enrolled ITT Analysis: Yes	Male and female patients aged 15 years and older were eligibleif they had had asthma for at least 6 months and if they had beentaking low-to-moderate doses of an ICS for at least 30 days before screening (included BDP 252 to 420 µg/d, BUD 400µg/d, FLUN 1000 µg/d, FP 176 to 220 µg/d, or TAA 600 to 800 µg/d). At the screening visit, all patients wererequired to have a FEV1 between 50% and 80% of the predicted normal and an increase in FEV1 of at least 12% within 30 minutes of the inhalation of 2 puffs (180 µg) of albuterol aerosol. Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Nelson et al.{Nelson, 2000 #763} 2000 United States Multicenter Glaxo Wellcome	Albuterol	Other: Pregnant or lactating female patients were excluded, as were patients with life-threatening asthma, patients who had been hospitalizedfor asthma within the previous 3 months, or those with significantconcurrent diseases including a recent upper or lower respiratorytract infection. Medications that could confound the evaluation of study treatments were prohibited, including oral orparenteral corticosteroid therapy within 30 days of screening, theophylline or other bronchodilators, other LM, or cromolyn or nedocromil therapy. 3-week run-in period, during which their prior ICS was switched to FP 100 ìg twice daily delivered through the Diskusinhaler. Baseline information related to asthma control (FEV1, peak expiratory flow [PEF], symptoms, and albuterol rescue use) wasobtained during the last week of the run-in period. Only those patients who remained symptomatic (and thereby demonstrated the need for an additional controller medication) were eligible to continue. Patients who were not symptomatic during the run-in periodwere withdrawn.	Yes: 3-week run-in period, during which their prior ICS was switched to FP 100 ìg twice daily delivered through the Diskusinhaler. Baseline information related to asthma control (FEV1, peak expiratory flow [PEF], symptoms, and albuterol rescue use) was obtained during the last week of the run-in period. Only those patients who remained symptomatic (and thereby demonstrated theneed for an additional controller medication) were eligible to continue.Patients who were not symptomatic during the run-in period were withdrawn.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Nelson et al.{Nelson, 2000 #763} 2000 United States Multicenter Glaxo Wellcome	Intervention: Drug 1: FP/SM Drug 2: FP/ML Total daily dose: Drug 1: 200mcg/100 Drug 2: 200mcg/10 Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Delivery device: Drug 1: Diskus Drug 2: Diskus Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 222 Drug 2: 225 Mean age (years): Drug 1: 40.2 (14.4) Drug 2: 43 (13.7) Sex (% female): Drug 1: 61% Drug 2: 60% Current smokers (%): Drug 1: NR Drug 2: NR Optional - Disease duration (years): Overall: 92% had for > 5 years Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: NR (11) Drug 2: NR (13) Adverse events caused withdrawal (%): Drug 1: 2.7 Drug 2: 1.8

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Nelson et al.{Nelson, 2000 #763} 2000 United States Multicenter Glaxo Wellcome	Intervention: Drug 1: FP/SM Drug 2: FP/ML Number in group (n): Drug 1: 222 Drug 2: 225	Rescue med use during 24 hour period: Drug 1- baseline: mean baseline puffs/day: 3.77 Drug 1-endpoint: mean change from baseline: -1.55 (0.14) Drug 2-baseline: 3.73 Drug 2-endpoint: -1.14 (0.12) P = 0.014 Asthma exacerbations: D1 end: 2 D2 end: 6 P = 0.031 Day time symptom control: D1 - base: mean overall daytime symptom score (0-5), baseline: 1.36 D1 - end: mean change from baseline: -0.49 (0.04) D2 - base: 1.33 D2 - end: -0.41 (0.03) P = 0.199 Emergency room visits: D1: 0 D2: 0.4% (#1) Hospitalizations: D1 0 D2: 0 Other: D1 base: mean % Days with no albuterol use baseline: 14.0 D1 end : mean change from baseline: + 26.3 (2.3) D2 base: 15.8 D2 end: 19.1 (2.1) P = 0.032 Other: D1 end : mean change from baseline of Shortness of Breath Score -0.56 (0.05), Chest tightness score -0.49 (0.05) , Wheeze score -0.41 (0.05) D2 end: Shortness of Breath Score -0.40 (0.04), Chest tightness score -0.43 (0.04) , Wheeze score -0.38 (0.05) P = 0.017, 0.521, 0.279

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Nelson et al.{Nelson, 2000 #763} 2000 United States Multicenter Glaxo Wellcome	Serious adverse events (%): Drug 1: 0.5 Drug 2: 0.4 Oral candidiasis- thrush (%): Drug 1: 1 Drug 2: 2 Sore throat (%): Drug 1: 1 Drug 2: 3 Headache (%): Drug 1: 2 Drug 2: 1 Hoarseness (%): Drug 1: 2 Drug 2: <1	Compliance Compliance with study medication was assessed by pill count for the oral medication and by dose counter on the Diskus inhaler for inhaled medication. Compliance rates with study medication were high (96%-97%).	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
401	Nelson et al.{Nelson, 2003 #401} 2003 United States (33 sites) Clinical research centers GlaxoSmithKline	Study design: RCT Double-blind Duration: 12 weeks N=283 Enrolled: 525 screened; 283 randomized. ITT Analysis: Yes	: Male and females >/= 12 years of age with a medical history of asthma requiring asthma therapy for a least 6 months preceding the study. FEV1 between 40 and 85% of predicted for ages 18 and older or Polgar standards for ages 12 to 17. 15% or greater increase in FEV1 within 30 minutes after 2 inhalations of albuterol and must have been treated during the previous month with an as needed short acting beta agoinst alone. During the screening period, must demonstrate a total 24 hour asthma symptom score of 7 or higher during the 7 days before randomization. Asthma symptom score was a 6 point scal ranging from 0 (no symptoms) to 5 (symptoms so severe that the patient could not go to work or perform normal daily activities); FEV1 between 40-85% and be within 15% of the FEV1 obtained at the beginning of the screening period. Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Nelson et al.{Nelson, 2003 #401} 2003 United States (33 sites) Clinical research centers GlaxoSmithKline	Albuterol as needed during run-in and randomization.	Other: NR	Yes: 2 week single-blind placebo screening period to evaluate eligibility, compliance, obtain baseline data, and confirm asthma stability.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Nelson et al.{Nelson, 2003 #401} 2003 United States (33 sites) Clinical research centers GlaxoSmithKline	Intervention: Drug 1: FP plus SM Drug 2: FP Drug 3: SM Total daily dose: Drug 1: 88mcg Drug 2: 88mcg Drug 3: 42mcg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Drug 3: NA Delivery device: Drug 1: HFA MDI Drug 2: CFC MDI Drug 3: CFC MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 95 Drug 2: 97 Drug 3: 91 Mean age (years): Drug 1: 29 Drug 2: 34 Drug 3: 34 Sex (% female): Drug 1: 48 Drug 2: 47 Drug 3: 47 Current smokers (%): Drug 1: NR Optional - Previous ICS use (%): Drug 1: NR Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 9 (9%) Drug 2: 8 (8%) Drug 3: 9 (10%) Optional - Withdrew due to asthma exacerbations (%): Drug 1: 1 Drug 2: 3 Drug 3: 8 Overall: p = 0.024 (FP plus SM vs SM) Adverse events caused withdrawal (%): Drug 1: 3 Drug 2: 5 Drug 3: 2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Nelson et al.{Nelson, 2003 #401} 2003 United States (33 sites) Clinical research centers GlaxoSmithKline	Intervention: Drug 1: FP plus SM Drug 2: FP Drug 3: SM Number in group (n): Drug 1- endpoint: 95 Drug 2- endpoint: 97 Drug 3- endpoint: 91	Rescue med use during 24 hour period: Mean change in puffs per day Drug 1-endpoint: -2.4 (0.31) Drug 2-endpoint: -1.8 (0.21) Drug 3- endpoint: -1.6 P values: NS Symptom control during 24 hour period: Mean change in symptom score D1 end: -1.0 (0.11) D2 end: -0.8 (0.09) D3 end: -0.8 P: NS Day time symptom control: Mean change of % days with no asthma symptoms = 30 D1 - end: 30.3 (4.27) D2 - end: 24.9 (3.71) D3 - end: 29.6 P: NS [% nights with no awakenings, mean change (SE): D1 end: 19.6 (3.15) D2 end: 20.5 (3.26), P=NS Days able to participate in sports and/or physical activity: Mean change of % of Rescue free days D1 end: 40.0 D2 end: 26.5 D3 end: 34.3 P: p = 0.028 FP plus SM versus FP

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Nelson et al.{Nelson, 2003 #401} 2003 United States (33 sites) Clinical research centers GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 17% Drug 2: 16% Drug 3: 15%	Compliance Compliance with study medication was evaluated according to the data recorded on the diary cards by the subject. Each subject recorded on his/her diary card every AM and PM "yes" or "no" as the whether or not the dose of study medicaiton was taken. Mean compliance rates ranged from 96% to 97% across treatment groups.	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1998	Nelson et al.{Nelson, 2006 #1998} 2006 SMART UDA, Multiceneter GlaxoSmithKline	Study design: DB Randomized Observational study N=26355	Male and female subjects aged 12 years; a diagnosis of asthma (per investigator clinical judgement) and were currently receiving a prescription asthma medication. However, subjects could not have previously used inhaled longacting β2-agonists.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Nelson et al.{Nelson, 2006 #1998} 2006 SMART UDA, Multiceneter GlaxoSmithKline	Concurrent use of other prescription asthma medication(s) was permitted	Pregnancy and/or lactation, or any significant systemic disease that in the opinion of the investigator may place a subject at risk; history of any adverse reaction (including immediate or delayed hypersensitivity reaction) to any sympathomimetic amine drug; or current use of B-blockers.	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Nelson et al.{Nelson, 2006 #1998} 2006 SMART UDA, Multiceneter GlaxoSmithKline	SM (84 mcg/d) vs. placebo	# in group (n): Drug 1: 13176 Drug 2: 13179 Mean age (years): Drug 1: 39.2 Drug 2: 39.1 Sex (% female): Drug 1: 64 Drug 2: 64 Caucasian/African-American/Hispanic/Asian/Other Drug 1: 71/18/8/12 Drug 2: 72/18/8/1/2	NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Nelson et al.{Nelson, 2006 #1998} 2006 SMART UDA, Multiceneter GlaxoSmithKline	Intervention: Drug 1: SM Drug 2: Placebo Number in group (n): Drug 1: 13176 Drug 2: 13179	See adverse events

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Nelson et al.{Nelson, 2006 #1998} 2006 SMART UDA, Multiceneter GlaxoSmithKline	Respiratory-related deaths or life threatening experiences: no significant difference between SM and placebo (50 vs. 36; RR=1.4; 95% CI: 1.25, 15.34) Respiratory-related deaths: significant increase with SM compared to placebo (24 vs. 11; RR=2.16; 95% CI: 1.06, 4.41) Asthma-related deaths: significant increase with SM vs. placebo (13 vs. 3; RR 4.37; 95% CI: 1.25 , 15.34) Combined asthma-related deaths or life-threatening experiences: significant increase with SM vs. placebo (37 vs. 22; RR, 1.71; 95% CI, 1.01, 2.89) Subgroup analysis, African American participants: Respiratory-related deaths or life threatening experiences: significant increase in SM vs. placebo (20 vs. 5; RR=4.10; 95% CI, 1.54 to 10.90) Combined asthma-related deaths or life-threatening experiences: significant increase in SM vs. placebo (19 vs. 4; RR=4.92; 95% CI, 1.68, 14.45)	No	NA Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
730	Newhouse et al, Newhouse 2000 #730} 2000 Canada Multicenter (17) Forest Laboratories	Study design: RCT : blinding/masking NR (perhaps not done) Duration: 6 weeks N=Abstract reports 179 randomized, but results show 154 analyzed Enrolled: NR ITT Analysis: No another type of analysis was used (define): Very close to ITT: authors report using ITT analysis, but they excluded 1 individual from the BUD group in the analysis and do not explain why.	Age: 18-75 FEV1 expressed as a percent of the predicted value: FEV1 40-85% predicted Reversability of FEV1: increase of FEV1 of at least 12% after two puffs of salbutamol via MDI Previous use of corticosteroids: use of ICS for at least 30 days; requiring at least 800mcg/d and up to 2000mcg/d of BDP, FP, or BUD : documented history of moderate asthma. Had to meet the following criteria over the 2-week run-in: 1) best prebronchodilator FEV1 was at least 90% of their best prebronchodilator FEV1 obtained at their first visit; 2) mean asthma symptom score was no greater than 8 per day, with the patient taking no more than a mean of 8 puffs (800mcg) of salbutamol per day during the second week of the run-in. Asthma Severity: Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Newhouse et al, Newhouse 2000 #730} 2000 Canada Multicenter (17) Forest Laboratories	Drugs prohibited during the study: other orally inhaled steroids, antileukotrienes, oral steroids, cromolyn/nedocromil, nasal steroids, oral B-adrenergic agonists, SM, ipratropium, theophylline, and FM.	Prior treatment with: oral or parenteral corticosteroids on 2 or more occasions in the preceeding 3 months, LABAs in the prio 2 weeks. Concommitant diseases: significant pulmonary disease other than asthma, significant illness that could interfere with the assessment of effiacy and safety in the study, unstable reversible airway obstruction. Current treatment with....: see Q16 Other: significant pulmonary disease other than asthma, significant illness that could interfere with the assessment of effiacy and safety in the study, a hx of hospitalization for exacerbation of asthma in the 6 wks before their first visit, immunotherapy other than an established maintenance program, URI w/in 30 days of first visit	Yes: 2 weeks, had to meet criteria listed above. Number entering run-in was NR, unclear # not meeting criteria in run-in for each group.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Newhouse et al, Newhouse 2000 #730} 2000 Canada Multicenter (17) Forest Laboratories	Intervention: Drug 1: FP Drug 2: BUD Total daily dose: Drug 1: 1500 mcg Drug 2: 1200 mcg Steroid dosing range (Low, medium or high): Drug 1: Medium Drug 2: Medium Delivery device: Drug 1: Aerochamber Drug 2: Turbuhaler (DPI)	# in group (n): Drug 1: 75 Drug 2: 79 Mean age (years): Drug 1: 44.0 Drug 2: 42.8 Sex (% female): Drug 1: 60 Drug 2: 57 Optional - Race (% white): Drug 1: 90.7 Drug 2: 92.4 Current smokers (%): Drug 1: 5.3 Drug 2: 5.1 Optional - Rescue medication use (puffs per day): Drug 1: mean 2.5 Drug 2: 2.7 Other: Drug 1: FEV1 (mean % predicted): 83.0 Drug 2: 78.5 Other: Drug 1: mean nocturnal awakenings: 0.1/night Drug 2: 0.1/night Other: Drug 1: mean daily asthma symptom score: 4.1 Drug 2: 3.8	Number (%) withdrawn: Drug 1: 11 (14.7) Drug 2: 3 (3.8) Optional - Other reasons for withdrawal (%): Drug 1: no reasons reported Drug 2: no reasons reported

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Newhouse et al, Newhouse 2000 #730} 2000 Canada Multicenter (17) Forest Laboratories	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint Drug 2 Baseline: BUD Number in group (n): Drug 1- baseline: 75 Drug 2- baseline: 78	Rescue med use during 24 hour period: Drug 1- baseline: change in mean salbutamol usage from baseline: 0.4 puffs/day Drug 2-baseline: 0.1 puffs/d P values: 0.333 (Flun vs BUD) Symptom control during 24 hour period: D1 base: change from baseline in mean daily symptom score: 0.1 P: 0.92 Night time symptom control: D1 - base: change from baseline in mean nocturnal awakenings: 0.1 awakening/night P: 0.849 Other Relevant Health Outcome Results: no statistically significant differences in mean change from baseline in salbutamol usage for either group. [For efficacy, there were no statistically significant differences between the two groups

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Newhouse et al, Newhouse 2000	Overall adverse events reported (%): Drug 1: 48 Drug 2: 54.4 Headache (%): Drug 1: 6.7 Drug 2: 3.8 Suppression of HPA axis (%): Drug 1: NR Drug 2: NR Other (%): Drug 1: flu syndrome: 4.0 Drug 2: 6.3 Other (%): Drug 1: flu syndrome: 4.0 Drug 2: 6.3 Other (%): Drug 1: Paresthesia: 2.7 Drug 2: 0.0 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: Pre-Cortrosyn plasma cortisol levels at baseline (13.4 vs 14.7; p 0.558) and after 6 weeks (14.9 vs 14.7; p 0.697) of treatment were comparable in the FLUN and BUD groups. The response at 30 minutes (mean) was greater in the FLU group, both at baseline (increases of 9.4 vs 7.3; p 0.026) and after 6 weeks of treatment (9.2 vs 6.9; p 0.017). The response at 60 minutes was comparable (increases of 12.6 vs 10.4; p 0.077 AND 12.5 vs 10.5; p 0.053). NOTE: this doesn't give any clinical information about how many were adrenally insufficient, if any. It just gives average lab values. Additional adverse events and comments: monilia, nonooral 2.7 vs 2.5; migraine 2.7 vs 0.0; emesis 2.7 vs 0.0; insomnia 1.3 vs 2.5; back pain 1.3 vs 2.5; monilia, oral 0.0 vs 5.1.	NR	Fair Fair No
#730} 2000 Canada Multicenter (17) Forest Laboratories			

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
38	Noonan et al.{Noonan, 2006 #38} 2006 USA Multicenter AstraZeneca	Study design: RCT Double-blind Duration: 12 weeks N=596 Enrolled: 1373/701/596 ITT Analysis: No another type of analysis was used (define): yes, for primary outcome, but not for the secondary outcomes	Age: 12 years or more FEV1 expressed as a percent of the predicted value: 45-85% Reversability of FEV1: 12% or more Previous use of corticosteroids Duration of condition: >=6 months Other: mod or severe asthma Asthma Severity: Moderate Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Noonan et al.{Noonan, 2006 #38} 2006 USA Multicenter AstraZeneca	Salbutamol	Prior treatment: systemic corticosteroids within 4 weeks Smoking - current or former: more than 10 pack years- current status not collected Other: hospitalization or emergency treatment within 6 months	Yes: 2-week run-in period, patients discontinued use of current asthma therapy and receivedsingle-blind BUD pMDI 80ìg/inhalation, administered as two inhalations (160ìg) twice daily,

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Noonan et al.{Noonan, 2006 #38} 2006 USA Multicenter AstraZeneca	Intervention: Drug 1: BUD/FM Drug 2: BUD Drug 3: FM Drug 4: BUD + FM Drug 5: Placebo Total daily dose: Drug 1: 320/9 Drug 2: 320 Drug 3: 9 Drug 4: 320/9 Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Delivery device: Drug 1: pMDI Drug 2: pMDI Drug 3: DPI Drug 4: pMDI and DPI Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 124 Drug 2: 109 Drug 3: 123 Drug 4: 115 Drug 5: 125 Mean age (years): Drug 1: 41.8 Drug 2: 40.7 Drug 3: 40.0 Drug 4: 40.3 Drug 5: 41.9 Sex (% female): Drug 1: 64.5 Drug 2: 65.1 Drug 3: 65.0 Drug 4: 56.5 Drug 5: 57.6 Optional - Race (% white): Drug 1: 79 Drug 2: 77.1 Drug 3: 74 Drug 4: 77.4 Drug 5: 80.8 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Drug 4: NR Drug 5: NR Optional - Disease duration (years): Drug 1: 23.1 Drug 2: 23.2	Number (%) withdrawn: Drug 1: 27 (22%) Drug 2: 31 (28%) Drug 3: 63 (51%) Drug 4: 29 (25%) Drug 5: 75 (60%) Overall: 225 (38%) Optional - Withdrew due to lack of efficacy (%): Drug 1: 10.5 worsening asthma Drug 2: 20.2 Drug 3: 35.8 Drug 4: 11.3 Drug 5: 50 Adverse events caused withdrawal (%): Drug 1: 6.5 Drug 2: 3.7 Drug 3: 4.1 Drug 4: 7.8 Drug 5: 3.2 Optional - Lost to follow-up (%): Drug 1: 0.8 Drug 2: 0.8 Drug 3: 0.9 Drug 4: 1.7 Drug 5: 0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Noonan et al.{Noonan, 2006 #38} 2006 USA Multicenter AstraZeneca	Intervention: Drug 1 Baseline: BUD/FM and BUD Drug 1 Endpoint: BUD/FM and BUD Drug 2 Baseline: FM and BUD+FM Drug 2 Endpint: FM and BUD+FM Drug 3 Baseline: Placebo Drug 3 Endpoint: Placebo Between group comparisons: BUD/FM minus BUD, BUD/FM minus FM, BUD/FM minus BUD + FM, BUD/FM minus PBO Number in group (n): Drug 1- endpoint: 121 and 109 Drug 2-endpoint: 119 and 113 Drug 3- endpoint:124	Rescue med use during 24 hour period: inhalations/day D1- baseline:: 2.1 and 2.74 D1-endpoint: mean change: -1.00 and -0.78 D2-baseline: 2.5 and 2.25 D2-endpoint: -0.26 and -1.50 D3 - baseline: 2.44 D3- endpoint: 0.83 Between group comparisons: -0.51 (-1.05, 0.03), -1.01 (-1.54, -0.49), 0.42 (-0.11, 0.95), -2.05 (-2.57, -1.54) P >= 0.001 Asthma exacerbations: D: 7 (5.6%) and 5 (4.6) D2 17 (13.8) and 6 (5.2) D3 end: 16 (12.8) Between group comparisons: (95% CI): 1.25 (0.38, 4.04), 0.38 (0.15, 0.95) P ≤ 0.05, 1.11 (0.36, 3.43), 0.42 (0.17, 1.06) % of symptom free days: D1 base: 10.7 and 10.26 D1 end: mean change: 23.14 and 9.50 D2 base: 10.78 and 7.89 D2 end: 2.85 and 21.80 D3 base: 6.80 D3 end: 2.37 Between group comparisons:15.47(7.19, 23.74), 22.51 (14.43, 30.59), 2.36 (-5.85, 10.58), 23.41 (15.44, 31.38) P < 0.001 for all comparisons except combo vs. combo Nocturnal awakenings: % awakening free nites D1 base: 74.88 and 74.46 D1 end: 12.67 and 15.1 D2 base: 76.71 and 76.64 D2 end: 9.36 and 13.44 D3 base: 71.72 D3 end: 8.57 Between group comparisons:-2.16 (-7.38, 3.06), 2.4 Daytime symptom score D1 base: 1.04 and 1.13 D1 end : -0.32 and-0.19 D2 base: 1.10 and 1.11 D2 end: -0.05 and -0.35 D3 base: 1.14 D3 end: 0.06 Betv Night symptom score D1 base: 0.92 and 0.95 D1 end : -0.22 and -0.10 D2 base: 0.96 and 0.93 D2 end: -0.04 and -0.27 D3 base: 1.03 D3 end: 0.11 Between group comparisons:: -0.15 (-0.28, -0.03), -0 Withdrawal due to predefined event: n (%) D1 end : 13 (10.5) and 22 (20.2) D2 en Other Relevant Health Outcome Results: survival analysis demonstrated significantly longer time to w/drawal d/t worsening a

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Noonan et al.{Noonan, 2006 #38} 2006 USA Multicenter AstraZeneca	Oral candidiasis- thrush (%): Drug 1: 3.2 Drug 2: 0 Drug 3: 0 Drug 4: 0.9 Drug 5: 0 Cough (%): Drug 1: 0 Drug 2: 0 Drug 3: 0.8 Drug 4: 0.9 Drug 5: 1.6 Sore throat (%): Drug 1: 1.6 Drug 2: 0 Drug 3: 0 Drug 4: 0.9 Drug 5: 0.8 Headache (%): Drug 1: 0 Drug 2: 0 Drug 3: 1.6 Drug 4: 1.7 Drug 5: 0.8 Other (%): Drug 1: tremor: 0 Drug 2: 0.9 Drug 3: 1.6 Drug 4: 0.9 Drug 5: 0	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4741	Norjavaara et al.{Norjavaara, 2003 #4741} 2003 Sweden Population -based AstraZeneca	Study design: Observational Database analysis : retrospective cohort Duration: 1995-98 N=293948	: Data were derived from the Swedish Medical Birth Register, which includes 99% of births in Sweden. During 1995 -1998, 293, 948 newborn infants were identified; compared mothers who used BUD vs those that did not Asthma Severity: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Norjavaara et al.{Norjavaara, 2003 #4741} 2003 Sweden Population -based AstraZeneca	NA	multiple births and stillbirths	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Norjavaara et al.{Norjavaara, 2003 #4741} 2003 Sweden Population -based AstraZeneca	Intervention: Drug 1: BUD Drug 2: Controls Total daily dose: Drug 1: NR Drug 2: NR Steroid dosing range (Low, medium or high): Drug 1: NR Drug 2: NR Delivery device: Drug 1: NR Drug 2: NR Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 2968 Drug 2: 290980 Mean age (years): Drug 1: NR Drug 2: NR Sex (% female): Drug 1: 100 Drug 2: 100 Current smokers (%): Drug 1: NR Drug 2: NR Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 0	NA

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Norjavaara et al.{Norjavaara, 2003 #4741} 2003 Sweden Population -based AstraZeneca	Intervention: Drug 1: BUD Drug 2: Controls Number in group (n): Drug 1: 2968 Drug 2: 290980	Other Relevant Health Outcome Results: (note: significance tests are compared to 'all' births in the population) --The 2968 mothers who reported use of BUD during early pregnancy had infants with normal gestational age, birth wt, and length, with no increased rate of stillbirths or multiple births. --Gestational age was normal but statistically significantly lower (not clinically significant) in boys whose mothers reported BUD use in early pregnancy (mean 39.4 weeks vs 39.5; P < 0.001) • Birth weight was normal but statistically significantly lower in girls and boys whose mothers reported BUD use in early pregnancy (mean 3460 vs 3500 for girls and 3600 vs 3630 grams; P < 0.01 and P < 0.001, respectively) • No difference in birth length was observed after adjustments for mother's height and gestational age were made • Rate of stillbirths and multiple births did not differ among groups. • Rate of caesarean birth was higher in women taking BUD early in pregnancy (P < 0.05)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Norjavaara et al.{Norjavaara, 2003 #4741} 2003 Sweden Population -based AstraZeneca	NA	NR	

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
633	O'Byrne et al.{O'Byrne, 2001 #633} 2001 Multinational - eastern europe, canada, spain Multicenter - 198 centers Astra Zeneca listed in affiliations Not reported: Astra Zeneca	Study design: RCT Double-blind Duration: 1 year N=1970 Enrolled: NR, 2525 enrolled, 1970 randomized ITT Analysis: Yes	: Patients were >/=12 yr of age with mild asthma. Group A patients corticosteroid-free) had used no inhaled corticosteroid for >/=3 mo, had a FEV 1 >/=80% predicted normal after inhaling 1 mg terbutaline. Group B patients were taking</=400 mcg/d of inhaled BUD or its equivalent for >/=3 mo, with a FEV1 >/= 70% predicted normal after terbutaline. Randomized patients demonstrated a need for two or more inhalations per week of rescue medication during the last 2 wk of run-in, a >/= 15% variability in peak expiratory flows (PEF), or a>/= 12% increase in FEV1 after terbutaline. Asthma Severity: Mild Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
O'Byrne et al.{O'Byrne, 2001 #633} 2001 Multinational - eastern europe, canada, spain Multicenter - 198 centers Astra Zeneca listed in affiliations Not reported: Astra Zeneca	No additional treatments were allowed unless the patient had a severe exacerbation, after which medications could be added at the physician's discretion. Short acting beta agonist could be used for rescue.	Other: NR	Yes: The study had a 4-wk run-in, when Group A patients took placebo and Group B patients took BUD 100 mcg twice daily. Patients completed a daily diarycard during the run-in.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
O'Byrne et al.{O'Byrne, 2001 #633} 2001 Multinational - eastern europe, canada, spain Multicenter - 198 centers Astra Zeneca listed in affiliations Not reported: Astra Zeneca	Intervention: Drug 1: Group A: Placebo Drug 2: Group A: BUD 200 / BUD 200 /FM Drug 3: Group B: BUD 200 / BUD 200 / FM Drug 4: Group B: BUD 400 / BUD 400 / FM Total daily dose: Drug 1: 0 Drug 2: 200mcg / 200mcg/ 9mcg Drug 3: 200mcg / 200mcg/ 9mcg Steroid dosing range (Low, medium or high): Drug 1: NA Drug 2: low / low Drug 3: low / low Drug 4: low / low Delivery device: Drug 1: NA Drug 2: DPI Drug 3: DPI Drug 4: DPI Is dosing comparable between treatment groups? NA: ICS vs ICS/LABA - ICS dosing is comparable across groups except placebo	# in group (n): Drug 1: 239 Drug 2: 228 / 231 Drug 3: 322 / 323 Drug 4: 312 / 315 Mean age (years): Drug 1: 30.6 Drug 2: 30.6 / 31.2 Drug 3: 38.1 / 36.5 Drug 4: 37.5 / 36.8 Sex (% female): Drug 1: 57.7 Drug 2: 59.2 / 63.2 Drug 3: 56.2 / 55.4 Drug 4: 57.4 / 59.1 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Drug 4: NR Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Drug 3: 100 Drug 4: 100 Other: Drug 1: days with symptoms (%) = 2.4 Drug 2: 2.3 / 2.3 Drug 3: 2.1 / 2.0 Drug 4: 2.0 / 2.1 Other: Drug 1: Nights with awakenings (%)	Number (%) withdrawn: Drug 1: Total for group A = 144 (19%) Drug 2: Total for group A = 144 (19%) Drug 3: Total for group B = 180 (13%) Drug 4: Total for group B = 180 (13%) Overall: 324 (16%) Adverse events caused withdrawal (%): Drug 1: NR Drug 2: NR Drug 3: NR Drug 4: NR Overall: 3 Optional - Other reasons for withdrawal (%): Drug 1: NR Drug 2: NR Drug 3: NR Drug 4: NR Overall: 13

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
O'Byrne et al.{O'Byrne, 2001 #633} 2001 Multinational - eastern europe, canada, spain Multicenter - 198 centers Astra Zeneca listed in affiliations Not reported: Astra Zeneca	Intervention: Drug 1: Group A: Placebo Drug 2: Group A: BUD 200 / BUD 200 /FM Drug 3: Group B: BUD 200 / BUD 200 / FM Drug 4: Group B: BUD 400 / BUD 400 / FM Number in group (n): Drug 1: 239 Drug 2: 228 / 231 Drug 3: 322 / 323 Drug 4: 312 / 315	Rescue med use during 24 hour period: **Need different group outcomes** Drug 1: adjusted mean number per day during treatment = 0.75 Drug 2: 2. 0.51 3. 0.51 Drug 3: 4. 0.89 5. 0.66 Drug 4: 6. 0.75 7. 0.63 P values: Group A: BUD 200 vs placebo = p = 0.0008; Bud 200/FM vs BUd 200 = p = 0.97; BUD 200/FM vs placebo = p = 0.0008 ; Group B: BUD 400 vs BUD 200 = p = 0.052; BUD 200/FM or BUD 400/FM vs placebo = p = 0.0001; BUD 200 / FM vs BUD 400 = p = 0.17 Asthma exacerbations: D1 : adjusted mean at end - rate per year of severe exacerbations = 0.77 D2: 2. 0.29 3. 0.34 D3: 4. 0.92 5. 0.56 D4: 6. 0.96 7. 0.36 P: Group A: BUD 200 vs placebo = p = 0.0001; BUD 200/FM vs BUD 200 = p = 0.50; BUD 200/FM vs placebo = p = 0.0001; Group B: BUD 400 vs BUD 200 = p = 0.069; BUD 200/FM or BUD 400/FM vs placebo = p = 0.0001; BUD 200 / FM vs BUd 400 = p = 0.0001 Day time symptom control: D1 : adjusted mean at end of days with symptoms (%) = 29.4 D2: 2. 23.1 3. 21.5 D3: 4. 32.8 5. 27.4 D4: 6. 29.7 7. 25.1 P: Group A: BUD 200 vs placebo = p = 0.0074; Bud 200/FM vs BUd 200 = p = 0.4 Nocturnal awakenings: D1: adjusted mean at end nights with awakenings (%) = 7.0 D2: 2. 2.5 3. 3.1 D3: 4. 6.0 5. 5.4 D4: 6. 6.0 7. 4.5 P: Group A: BUD 200 vs placebo = p = 0.0001; Bud 200/FM vs BUD 200 = p = 0.5 Other Relevant Health Outcome Results: Group A: In the placebo group, asthma was poorly controlled in 14.4% of days. Pati = 0.38, 95% CI = 0.25 to 0.57), asthma symptoms, nocturnal awakening, and numb Group B: In the BUD 100mcg group, asthma was poorly controlled on 13% of days

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
O'Byrne et al.{O'Byrne, 2001 #633} 2001 Multinational - eastern europe, canada, spain Multicenter - 198 centers Astra Zeneca listed in affiliations Not reported: Astra Zeneca	NR	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
275 Combo	O'Byrne et al.{O'Byrne, 2005 #275} 2005 Multinational (22 countries) Multicenter (246 centers) AstraZeneca, Lund, Sweden	Study design: Head to head - straight forward comparison RCT Double-blind Duration: 1 year N=2760 Enrolled: NR/NR/3251 enrolled / 2760 randomized after run-in ITT Analysis: Yes	Outpatients aged 4 to 80 years with asthma treated with 400 to 1,000 mcg/day of ICS for adults and 200 to 500 mcg/day for children (4–11 years) with a history of one or more asthma exacerbation in the last year were enrolled. All patients had been using a constant dose of ICS for 3 or more months. Patients had an FEV1 60–100% of predicted with 12% or more reversibility. To be eligible for randomization, patients had to have used 12 or more inhalations (or eight or more in children) of as-needed medication during the last 10 days of run-in. Asthma severity: Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
O'Byrne et al.{O'Byrne, 2005 #275} 2005 Multinational (22 countries) Multicenter (246 centers) AstraZeneca, Lund, Sweden	Terbutaline as needed	Patients using 10 or more inhalations of reliever on any 1 day (or seven or more for children) or with an asthma exacerbation during run-in	Yes- elucidate....: duration=NR; randomization occurred after run-in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
O'Byrne et al.{O'Byrne, 2005 #275} 2005 Multinational (22 countries) Multicenter (246 centers) AstraZeneca, Lund, Sweden	Intervention: Drug 1: BUD/FM + SABA Drug 2: BUD/FM maintainence & relief Drug 3: BUD + SABA Total daily dose: Drug 1: 160/9 mcg Drug 2: 160/9 mcg Drug 3: 320 Is dosing comparable between treatment groups? NA: Even for the ICS, 12% were age 4-11 which have different dose levels from adults	# in group (n): Drug 1: 909 Drug 2: 925 Drug 3: 926 Mean age (years): Drug 1: 36 Drug 2: 35 Drug 3: 36 Sex (% female): Drug 1: 57 Drug 2: 54 Drug 3: 55 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Optional - Current use of LABA (%): Drug 1: 29 Drug 2: 27 Drug 3: 28 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 148 (16.3) Drug 2: 122 (13.2) Drug 3: 142 (15.3)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
O'Byrne et al.{O'Byrne, 2005 #275} 2005 Multinational (22 countries) Multicenter (246 centers) AstraZeneca, Lund, Sweden	Drug 1 Baseline: Bud/FM + SABA Drug 1 Endpoint: Bud/FM + SABA Drug 2 Baseline: BUD/FM as maintainence & reliever Drug 2 Endpint: BUD/FM as maintainence & reliever Drug 3 Baseline: Bud+ SABA Drug 3 Endpoint: Bud+ SABA	Rescue med use during 24 hour period: Drug 1- baseline: Reliever free days 8.3 Drug 1-endpoint: 54 Drug 2-baseline: 8.2 Drug 2-endpoint: 55 Drug 3 - baseline: 8.8 Drug 3- endpoint: 45 P values: Both combos vs. Bud P < 0.001 Rescue med use day: Drug 1- baseline: 1.69 Drug 1 -endpoint: 0.84 Drug 2 - baseline: 1.74 Drug 2 - endpoint: 0.73 Drug 3 - baseline: 1.69 Drug 3 - endpoint: 1.03 P value: All comparisons P < 0.001 Rescue med use at night: Drug 1- baseline: 0.73 Drug 1 - endpoint: 0.37 Drug 2 - baseline: 0.72 Drug 2 - endpoint: 0.28 Drug 3- baseline: 0.72 Drug 3 - endpoint: 0.43 P value: BUD/FM +SABA vs. BUD + SABA: P=0.003; BUD/FM maint + relief vs. BUD+SABA: P<0.001 Asthma exacerbations: Patients with severe exacerbations, %: D1 end: 21 D2 end: 11 D3 end: 19 Symptom control during 24 hour period: D1 base: Asthma symptom score (0-6) 1.4 D1 end: 0.50 D2 base: 1.5

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
O'Byrne et al.{O'Byrne, 2005 #275} 2005 Multinational (22 countries) Multicenter (246 centers) AstraZeneca, Lund, Sweden	Overall adverse events reported (%): Drug 1: 52 Drug 2: 54 Drug 3: 57 Oral candidiasis- thrush (%): Drug 1: 1 Drug 2: 1 Drug 3: 1 Dysphonia (%): Drug 1: 1 Drug 2: 1 Drug 3: 1 Sore throat (%): Drug 1: Pharyngitis 10 Drug 2: 10 Drug 3: 9 Headache (%): Drug 1: 4 Drug 2: 3 Drug 3: 5 Respiratory infection (%): Drug 1: 16 Drug 2: 17 Drug 3: 20 Rhinitis (%): Drug 1: 7 Drug 2: 6 Drug 3: 8	Adherence Self-reported compliance with maintenance therapy was similar in all groups, with incomplete records on 12 to 13% of days/year, self-reported compliance on 84 to 85% of days/year, and noncompliance reported on 3% of days.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
698	O'Connor et al.{O'Connor, 2001 #698} 2001 Multinational, Multicenter - Eastern Europe, South America (6 study centers, 20 countries) University hospital Schering-Plough Research Institute	Study design: RCT Double-blind : with respect to the MF dosage and evaluator-blind with respect to the FP group Duration: 12 weeks N=733 Enrolled: NR,NR, 733 randomised ITT Analysis: Yes	: 12 years and older of either sex who had a history of asthma for at least 6 months and using an ICS daily for at least 30 days. Had to be on a stable daily regimen of ICS within predefined dosage limits. Baseline FEV1 between 60 to 90% of predicted and >/=12% reversibility. Non-smokers or had to have stopped smoking >6 months before screening and had to be free of clinically significant diseases other than asthma. All clinical lab values had to be normal. Asthma Severity: Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
O'Connor et al.{O'Connor, 2001 #698} 2001 Multinational, Multicenter - Eastern Europe, South America (6 study centers, 20 countries) University hospital Schering-Plough Research Institute	Albuterol for rescue, Maintenance of theophylline if a stable dose had been established as part of the patient's regimen before screening visit.	Smoking - current or former : Treated within the past 3 months with methotrexate, cyclosporine, or gold, required oral glucocorticoids for > 14 days during the 6 months before screening, or systemic steroids or an investigational drug in the previous month. Daily use of > 1.0mg of nebulized B2 agonists or use of any long acting inhaled B2 agoinst, immunotherapy, unless on a stable maintenance, inpatient hospitalization for asthma control within the last 3 months, ventilator support during the past 5 years, and hospitalization for management of airway obstruction or ER treatmetn for asthma twice during the previous 6 months. Increase in FEV1 of >/=20% between screening and baseline, use of >12 inhalations per day of albuterol on any 2 consecutive days between screening and baseline, a respiratory tract infection during the 2 weeks before screening or sclinically significant oropharyngeal candidiasis. Women who were premenarcheal, pregnant, or breastfeeding. Additional medications prohibited after screening included those linked to significant hepatotoxicity (ex: MT	Yes: 1 to 2 weeks, patients continued treatment with their usual prescribed ICS.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
O'Connor et al.{O'Connor, 2001 #698} 2001 Multinational, Multicenter - Eastern Europe, South America (6 study centers, 20 countries) University hospital Schering-Plough Research Institute	Intervention: Drug 1: MF - 100 Drug 2: MF - 200 Drug 3: MF - 400 Drug 4: FP Total daily dose: Drug 1: 200mcg Drug 2: 400mcg Drug 3: 800mcg Drug 4: 500mcg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: medium Drug 3: high Drug 4: medium Delivery device: Drug 1: DPI Drug 2: DPI Drug 3: DPI Drug 4: DPI Is dosing comparable between treatment groups? NA: Dose range for Mometasone; only equivalent for medium doses of each	# in group (n): Drug 1: 182 Drug 2: 182 Drug 3: 184 Drug 4: 184 Mean age (years): Drug 1: 42 Drug 2: 42 Drug 3: 42 Drug 4: 40 Sex (% female): Drug 1: 55 Drug 2: 60 Drug 3: 62 Drug 4: 61 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Drug 4: 0 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Drug 4: 100	Number (%) withdrawn: Drug 1: 35 (19%) Drug 2: 22 (12%) Drug 3: 22 (12%) Drug 4: 22 (12%) Adverse events caused withdrawal (%): Drug 1: 5 Drug 2: 3 Drug 3: 5 Drug 4: 4 Overall: 32

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
O'Connor et al.{O'Connor, 2001 #698} 2001 Multinational, Multicenter - Eastern Europe, South America (6 study centers, 20 countries) University hospital Schering-Plough Research Institute	Intervention: Drug 1: MF - 100 Drug 2: MF - 200 Drug 3: MF - 400 Drug 4: FP Number in group (n): Drug 1: 182 Drug 2: 182 Drug 3: 184 Drug 4: 184	Rescue med use during 24 hour period: Drug 1: change in mcg per day from baseline = -13.23 Drug 2: -94.84 Drug 3: -38.1 Drug 4: -52.06 P values: NS except P </=0.05 for MF 200 versus MF - 100 Day time symptom control: D1 : change from baseline in wheeze, difficulty breathing, cough = -0.01; -0.02; -0.07 D2: -0.04; -0.05; -0.07 D3: -0.11; -0.11; -0.11 D4: -0.13; -0.20; -0.12 P: all NS except P </= 0.05 for FP 250 versus both MF 100 and MF 200 Nocturnal awakenings: D1 : change from baseline = 0.07 D2: 0.01 D3: -0.06 D4: 0.14 P = NS except P </= 0.05 for FP 250 versus MF 100

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
O'Connor et al.{O'Connor, 2001 #698} 2001 Multinational, Multicenter - Eastern Europe, South America (6 study centers, 20 countries) University hospital Schering-Plough Research Institute	Overall adverse events reported (%): Drug 1: 20 Drug 2: 26 Drug 3: 30 Drug 4: 29 Drug 5: NR Oral candidiasis- thrush (%): Drug 1: 1 Drug 2: 7 Drug 3: 10 Drug 4: 10 Drug 5: NR	Compliance Treatment compliance and compliance int he use of rescue medication at each visit by examining the devices and by counting the doses used.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
186	Ostrom et al.{Ostrom, 2005 #186} 2005 USA Multicenter (46 outpatient clinics) GSK	Study design: RCT Double-blindDouble-dummy Duration: 12 weeks N = 342 Number screened: NR/NR/342 ITT Analysis: Yes	Age: 6-12 FEV1 expressed as a percent of the predicted value: 60-85%, with an adjustment for African-Americans Duration of condition: at least 6 month history of chronic asthma Other: required use of B2-agonist bronchodilators over 3 months before study; had to demonstrate >/= 12% increase in FEV1 within 20 minutes after 2 puffs of albuterol or one albuterol nebule at screening, or have a documented >/= 12% reversibility in FEV1 within 12 months before study Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Ostrom et al.{Ostrom, 2005 #186} 2005 USA Multicenter (46 outpatient clinics) GSK	Patients on theophylline, cromolyn, or nedocromil could continue use during run-in, but these drugs were discontinued before randomization. Albuterol allowed as needed during study.	Other: life-threatening asthma; hospitalization for asthma within previous 3 months; acute viral respiratory infections within 2 weeks of study; use of inhaled or systemic corticosteroids, inhaled long-acting B2-agonists, anticholinergics, or anti-leukotriene agents within pre-defined intervals before study	Yes: 8-14 day run-in, patients discontinued previous bronchodilator therapy and instead received inhaled albuterol as needed

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Ostrom et al.{Ostrom, 2005 #186} 2005 USA Multicenter (46 outpatient clinics) GSK	Intervention: Drug 1: FP Drug 2: ML Total daily dose: Drug 1: 50 mcg 2X/day Drug 2: 5 mg/day Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Delivery device: Drug 1: powder inhaler Drug 2: chewable tablet Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 172 Drug 2: 170 Mean age (years): Drug 1: 9.1 Drug 2: 9.6 Sex (% female): Drug 1: 37% Drug 2: 32% Optional - Race (% white): Drug 1: NR Drug 2: NR Optional - Rescue medication use (puffs per day): Drug 1: 2.26 (0.12) Drug 2: 2.42 (0.12) Optional - % of rescue free days: Drug 1: 27.5 (2.2) Drug 2: 23.3 (2.1) Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 22 (13%) Drug 2: 36 (21%) Optional - Withdrew due to lack of efficacy (%): Drug 1: 0 Drug 2: 1% Optional - Withdrew due to asthma exacerbations (%): Drug 1: 5% Drug 2: 8% Adverse events caused withdrawal (%): Drug 1: 2% Drug 2: 2% Optional - Consent withdrawn (%): Drug 1: 2% Drug 2: 5% Optional - Other reasons for withdrawal (%): Drug 1: 3% Drug 2: 5%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Ostrom et al.{Ostrom, 2005 #186} 2005 USA Multicenter (46 outpatient clinics) GSK	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: ML Drug 2 Endpint: ML Number in group (n): Drug 1- baseline: 172 Drug 1- endpoint: 168 Drug 2- baseline: 170 Drug 2- endpoint: 167	Rescue med use during 24 hour period: Drug 1- baseline: 2.26 (0.12) Drug 1-endpoint: -1.43 (0.14) Drug 2-baseline: 2.42 (0.12) Drug 2-endpoint: -1.23 (0.12) P = 0.18 Rescue med use day: Drug 1- baseline: 1.67 (0.10) Drug 1 -endpoint: -1.01 (0.12) Drug 2 - baseline: 1.79 (0.10) Drug 2 - endpoint: -0.92 (0.10) P = 0.100 Rescue med use at night: Drug 1- baseline: 0.63 (0.06) Drug 1 - endpoint: -0.39 (0.07) Drug 2 - baseline: 0.68 (0.06) Drug 2 - endpoint: -0.21 (0.06) P < 0.001 Day time symptom control: D1 - base: Daytime asthma symptom score: 1.55 (0.06) D1 - end: -0.81 (0.08) D2 - base: 1.63 (0.06) D2 - end: -0.75 (0.07) P = 0.202 Night time symptom control: D1 - base: Nighttime asthma symptom score: 0.69 (0.05) D1 - end: -0.40 (0.05) D2 - base: 0.68 (0.05) D2 - end: -0.19 (0.05) P < 0.001 Other: D1 base: % symptom-free days: 20.4 (2.1) D1 end : 37.7 (3.4) D2 base: 17.2 (1.9)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Ostrom et al.{Ostrom, 2005 #186} 2005 USA Multicenter (46 outpatient clinics) GSK	Overall adverse events reported (%): Drug 1: 69 Drug 2: 71 Serious adverse events (%): Drug 1: 0 Drug 2: 0.6% Cough (%): Drug 1: 10 Drug 2: 6 Sore throat (%): Drug 1: 10 Drug 2: 12 Headache (%): Drug 1: 13 Drug 2: 12 Upper respiratory tract infection (%): Drug 1: 12 Drug 2: 11 Hoarseness (%): Drug 1: </=1 Drug 2: </=1 Other (%): Drug 1: fever: 10 Drug 2: 7	Compliance	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
40	Papi et al.{Papi, 2007 #40} Multinational, 13 centers in Europe Chiesi Farmaceutici	Study design: RCT Double-blindDouble-dummy Duration: 12 weeks N=219 Enrolled: 240 screened, 219 randomized ITT Analysis: No another type of analysis was used (define): excluded from analysis patients without post-baseline data, but well done and their ITT population includes all those receiving a dose (all but 3 patients)	Age: 18-65 yrs. FEV1 expressed as a percent of the predicted value: 50-80 Previous use of corticosteroids: daily dose less than 1000mcg BDP equivalent unable to control symptoms defined as: presence of daily asthma symptomsmore than once a week, night-time asthma symptoms morethan twice a month and daily use of short-acting b2-agonists, i.e. moderate to high doses of ICS in moderate persistent asthmatics Other: or daily use of beta agonists; not adequately controlled during run-in Asthma Severity: Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Papi et al.{Papi, 2007 #40} Multinational, 13 centers in Europe Chiesi Farmaceutici	Oral corticosteroids were permitted only in the case of asthma exacerbations. Inhaled or oral sodium cromoglycate or nedocromil sodium and theophyllines taken at study entry were permitted at a constant dose throughout the study period. ICS were continued at an unchanged dose during the run-in period, while all the other anti-asthma medications were not permitted at any time.	Prior treatment: see below Concommitant diseases: COPD Current treatment: long-acting beta-agonists, anticholinergics or antihistamines in the previous2 weeks; and/or with topical or intra-nasal corticosteroids andleukotriene antagonists in the previous 4 weeks; and change ofICS dose in the previous 4 weeks Smoking - current or former: current or >= 10 PY Other: severe asthma exacerbation or symptomatic infection of the airways in the previous 8 weeks; three or more courses of oral corticosteroids or hospitalisationdue to asthma in the previous 6 months; increase in PEF >=15% during run-in Rx with <= 1000mcg/d BPD equivalent	Yes: 2wks, Inhaled rescue salbutamol was permitted at any timebut >=6 hr before pulmonary function tests (PFT). Oralcorticosteroids were permitted only in the case of asthma exacerbations. Inhaled or oral sodium cromoglycate ornedocromil sodium and theophyllines taken at study entrywere permitted at a constant dose throughout the studyperiod. ICS were continued at an unchanged dose during therun-in period, while all the other anti-asthma medicationswere not permitted at any time. Patients whose asthma was not adequately controlled at end of runin were randomized.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Papi et al.{Papi, 2007 #40} Multinational, 13 centers in Europe Chiesi Farmaceutici	Intervention: Drug 1: BDP/F = BDP/FM (brand name Foster) 100/6mcg pMDI two puffs twice daily Drug 2: BUD/FM = BUD/FM 200/6mcg DPI two puffs twice daily (Symbicort Turbuhaler) Total daily dose: Drug 1: 400/24mcg Drug 2: 800/24mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Delivery device: Drug 1: pMDI (extra-fine formulation with hydrofluoroalkane(HFA) propellant in pMDI) Drug 2: DPI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 109 Drug 2: 110 Mean age (years): Drug 1: 43.4 Drug 2: 46.0 Sex (% female): Drug 1: 57.9 Drug 2: 57.8 Optional - Disease duration (years): Drug 1: 11.8 Drug 2: 12.4 Other: Drug 1: ICS dose mcg beclamethasone dopropionate equivalent 787.9 Drug 2: 808.0 Other: Drug 1: FEV1%predicted 70.5 Drug 2: 69.3 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 6/109 (5.5) Drug 2: 13/110 (11.8) Adverse events caused withdrawal (%): Drug 2: 1/110 (0.9) Optional - Protocol violation (%): Drug 1: 3/109 (2.8) includes poor compliance Drug 2: 9/110 (8.2) Optional - Consent withdrawn (%): Drug 2: 2/110 (1.8) Optional - Other reasons for withdrawal (%): Drug 1: 3/109 (2.8) Drug 2: 1/110 (0.9)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Papi et al.{Papi, 2007 #40} Multinational, 13 centers in Europe Chiesi Farmaceutici	Intervention: Drug 1 Baseline: BDP/F Drug 1 Endpoint: BDP/F Drug 2 Baseline: BUD/F Drug 2 Endpoint: BUD/F Number in group (n): Drug 1- baseline: 109 Drug 1- endpoint: 107 Drug 2- baseline: 110 Drug 2- endpoint: 109	Rescue med use during 24 hour period: Drug 1- baseline: 2.16 (+/_1.15) puffs/day Drug 1-endpoint: 0.76 (0.92) Drug 2-baseline: 2.28 (1.5) Drug 2-endpoint: 0.87 (1.04) P values: NS between groups Asthma exacerbations: D1 end: 17/107 (15.9%) D2 end: 12/109 (11.0%) P: NR Day time symptom control: D1 - base: daytime symptom scores: reported as difference from baseline D1 - end: -0.93 (0.78) D2 - end: -0.86 (0.86) P < 0.001 for each vs baseline; NS between groups Night time symptom control: D1 - base: nighttime symptom scores: reported difference from baseline D1 - end: -0.73 (0.75) D2 - end: -0.66 (0.84) P < 0.001 for each vs baseline; NS between groups Other: D1 baseD1 end : days of exacerbation: days of exposure 0.013 (0.04) D2 end: 0.023 (0.11) Other Relevant Health Outcome Results: primary outcome (PEF) ... thus showing that BDP/F was noninferior to BUD/F.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Papi et al.{Papi, 2007 #40}	Overall adverse events reported (%): Drug 1: 15 (13.8) Drug 2: 18 (16.5) Serious adverse events (%): Drug 1: 0 Drug 2: 0 Sore throat (%): Drug 1: nasopharyngitis 1.8 Drug 2: 4.6 Respiratory infection (%): Drug 1: 5.5 Drug 2: 6.4 Other (%): Drug 1: worsening of asthma 14.7 Drug 2: 11.0 Other (%): Drug 1: Bronchitis 6.4 Drug 2: 4.6 Other (%): Drug 1: HSV 0.9 Drug 2: 2.8 Additional adverse events and comments: only reported if greater than 2%, although one patient receiving BUD/FM withdrew due to throat pain, paplitations, and hand tremors. do not know where lines are drawn between URI, respiratory infection, and bronchitis	NR	Fair Fair No
Multinational, 13 centers in Europe			
Chiesi Farmaceutici			

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1072	Pauwels et al.{Pauwels, 1997 #1072} Juniper et al.{Juniper, 1999 #853} Multinational Multicenter Astra Draco	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=852 Enrolled: 1114/852/852	Other: 18 to 70 years old, who had had asthma for at least six months and had been treated with an inhaled glucocorticoid for at least three months were enrolled. The FEV 1 at base line had to be at least 50 percent of the predicted value, 21 with an increase of at least 15 percent in FEV1 from the base-line value after the inhalation of 1 mg of terbutaline. Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Pauwels et al.{Pauwels, 1997 #1072} Juniper et al.{Juniper, 1999 #853} Multinational Multicenter Astra Draco	terbutaline	Other: Patients taking more than 2000 mg of beclomethasone or 1600 mg of BUD daily by pressurized metereddose inhaler, 800 mg of BUD daily by Turbuhaler dry-powder inhaler or 800 mg of FP daily were excluded. They were also excluded if they had had three or more courses of oral glucocorticoids or had been hospitalized for asthma during the previous six months.	Yes: 4 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Pauwels et al.{Pauwels, 1997 #1072} Juniper et al.{Juniper, 1999 #853} Multinational Multicenter Astra Draco	Intervention: Drug 1: Low BUD Drug 2: Low BUD + FM Drug 3: High BUD Drug 4: High BUD + FM Total daily dose: Drug 1: 200 Drug 2: 200+24 Drug 3: 800 Drug 4: 800+24 Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Drug 3: medium Drug 4: medium Delivery device: Drug 1: Turbuhaler Drug 2: Turbuhaler Drug 3: Turbuhaler Drug 4: Turbuhaler Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 213 Drug 2: 210 Drug 3: 214 Drug 4: 215 Mean age (years): Drug 1: 42 Drug 2: 41 Drug 3: 44 Drug 4: 42 Sex (% female): Drug 1: 49.3 Drug 2: 50.5 Drug 3: 52.3 Drug 4: 52.6 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Drug 4: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Drug 4: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: Overall- 158 (19%) Overall: 158 (19%) Adverse events caused withdrawal (%): Drug 1: n=6 Drug 2: 6 Drug 3: 8 Drug 4: 9 Overall: 3.4%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Pauwels et al.{Pauwels, 1997 #1072} Juniper et al.{Juniper, 1999 #853} Multinational Multicenter Astra Draco	Intervention: Drug 1 Baseline: low BUD / Low BUD+FM Drug 1 Endpoint: low BUD / Low BUD+FM Drug 2 Baseline: High BUD Drug 2 Endpoint: High BUD Drug 3 Baseline: High BUD+ FM Drug 3 Endpoint: High BUD + FM P-values (Define comparison): both Form groups vs placebo groups; and both low BUD vs both high Number in group (n): Drug 1- baseline: 213/210 Drug 1- endpoint: 213/210 Drug 2- baseline: 214 Drug 2- endpoint: 214 Drug 3- baseline: 215 Drug 3- endpoint: 215	Rescue med use day: Drug 1 -endpoint: 0.91/0.57 Drug 2 - endpoint: 0.82 Drug 3 - endpoint: 0.44 P < 0.001 and 0.08 Rescue med use at night: Drug 1 -endpoint: 0.29/0.18 Drug 2 - endpoint: 0.2 Drug 3 - endpoint: 0.11 P <0.001 and 0.003 Asthma exacerbations: Severe/mild (no/pt/yr) Drug 2 - endpoint: 0.91/35.4 and 0.67/21.3 Drug 2 - endpoint: 0.46/22.3 Drug 3 - endpoint: 0.34/13.4 P = 0.01/<0.001 and <0.001/<0.001 Symptom control during 24 hour period: Episode free days (mean % yr) Drug 1 -endpoint:: 41.7/51.1 Drug 2 - endpoint: 45.7 Drug 3 - endpoint: 54.8 P = 0.001 and 0.16 Day time symptom control: Mean symtom score day 0.5/0.52 Drug 1 -endpoint: 0.57/0.46 Drug 2 baseline: 0.49 Drug 2 - endpoint: 0.53 Drug 3 baseline: 0.52 Drug 3 - endpoint: 0.33 P: <0.001 and 0.01 Night time symptom control: Mean symtom score night 0.3/0.27 Drug 1 -endpoint: 0.37/0.31 Drug 2 baseline: 0.26

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Pauwels et al.{Pauwels, 1997 #1072}	Additional adverse events and comments: see withdrawals due to AEs above	Compliance	Fair Fair
Juniper et al.{Juniper, 1999 #853} Multinational Multicenter Astra Draco		13 patients withdrew because of non-compliance	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4785 Combo	Pavord et al.{Pavord, 2007 #4785} 2007 SOLTA study group UK multicenter GlaxoSmithKline	Study design: RCT Double-blind single dummy Duration: 12 weeks N=66 Enrolled: NR ITT Analysis: Yes	Asthma patients aged 18-50 years, non-smokers and receiving a stable dose of up to 400 mcg of BDP a day or equivalent ICS, but requiring further therapy; likelihood of compliance with the protocol requirements and ability, following instruction, to use an Accuhaler and mini-Wright peak flow meter. For randomisation: a baseline FEV1 of 61-85% of the predicted normal value; and a PC20 < 8 mg/ml with methacholine challenge. At least one of the following: diary card recording of symptoms (score of one or more for day and night combined)on >= 4 of the last seven days of the run-in period; recorded use of relief medication (inhaled Ventolin) on >= 2 different days during the last seven days of the run-in period; and a period variation in PEF of >= 10% over the last seven days of the run in period. Patients who did not meet the latter three criteria were able to repeat the run-in period once more. Asthma severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Pavord et al.{Pavord, 2007 #4785} 2007 SOLTA study group UK multicenter GlaxoSmithKline	Rescue med but not specified	Pregnant or lactating; Smoking - current or former; Were taking or had previously taken additional asthma medication, other than an ICS or short acting B2-agonist or oral corticosteroids in the last three months; acute respiratory infection or exacerbation of asthma within four weeks of screening, any additional underlying lung disease, or any significant disease warranting exclusion; hospitalisation or emergency treatment (for > 24 hours) for acute asthma in the last 12 months; were a smoker, had smoked in the last six months, or had a smoking history of 10 pack years or more; pregnant or lactating women, or women of child-bearing potential not using adequate contraception; evidence of alcohol, drug, or solvent abuse; hypersensitivity to any component of the study formulations, or taking medication contraindicated in combination with the study formulations; and previous entry to the study or receipt of any investigational drugs within four weeks of screening.	Yes- elucidate....: 2 week run in to determine eligibility for randomization

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Pavord et al.{Pavord, 2007 #4785} 2007 SOLTA study group UK multicenter GlaxoSmithKline	Intervention: Drug 1: SM/FP Drug 2: FP/ML Total daily dose: Drug 1: 100/200 Drug 2: 200/10 Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Delivery device: Drug 1: MDI Drug 2: MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 33 Drug 2: 33 Mean age (years): Drug 1: 36.3 Drug 2: 34.4 Sex (% female): Drug 1: 55 Drug 2: 42 Current smokers (%): Drug 1: 0 Drug 2: 0 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 9 (27.3%) Drug 2: 4 (12.1%) Overall: 19.6% Adverse events caused withdrawal (%): Drug 1: 6 Drug 2: 12

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Pavord et al.{Pavord, 2007 #4785}	Intervention:	Rescue med use day:
2007	Drug 1 Baseline: SFC	Drug 1- baseline: median rescue free days 14%
SOLTA study group	Drug 1 Endpoint: SFC	Drug 1 -endpoint: 73%
	Drug 2 Baseline: FP/M	Drug 2 - baseline: 29%
UK	Drug 2 Endpoint: FP/M	Drug 2 - endpoint: 70%
multicenter		P = NS
	Number in group (n):	
GlaxoSmithKline	Drug 1- baseline: 33	Rescue med use at night:
	Drug 1- endpoint: 33	Drug 1- baseline: median rescue free nights 50%
	Drug 2- baseline: 33	Drug 1 - endpoint: 93%
	Drug 2- endpoint: 33	Drug 2 - baseline: 71%
		Drug 2 - endpoint: 82%
		Treatment difference 16.5%; 95% CI 1.4%, 36.1%; P = 0.01
		Day time symptom control:
		D1 - base: Symptom free day 14%
		D1 - end: 71%
		D2 - base: 29%
		D2 - end: 67%
		Mean difference in change 13.2%, 95% CI - 1.9%, 32.9%, P = 0.064
		Night time symptom control:
		D1 - base: Symptom free night 52%
		D1 - end: 89%
		D2 - base: 57%
		D2 - end: 82%
		Mean difference in change 13.3%; 95% CI -1.5%, 34.5%; P = 0.055

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Pavord et al.{Pavord, 2007 #4785} 2007 SOLTA study group UK multicenter GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 31 AEs in 19 subjects Drug 2: 31 AEs in 21 subjects Serious adverse events (%): Drug 1: 2 Drug 2: 0	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
596	Pearlman et al.{Pearlman, 2002 #596} 2002 United States Multicenter - 51 sites Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N = 432 Number screened: 1151 screened, NR, 432 randomized ITT Analysis: Yes	: Male and female, aged 15 and older, whith asthma for at least 6 months and treated with oral or inhaled short-acting beta agoinsts on a scheduled or as needed basis for at least 6 weeks before screening. FEV1 between 50 and 80% of predicted and an increase in FEV1 of at least 12% within 30 minutes of albuterol. Patients had not used inhaled, oral, or parenteral steroids for at least 6 weeks before screening. Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Pearlman et al.{Pearlman, 2002 #596} 2002 United States Multicenter - 51 sites Glaxo Wellcome	beta agoinst for rescue	Prior treatment with: no corticosteroids (all types) for at least 6 weeks prior Other: Pregnancy and or lactation, life-threatening asthma, hospitalizaiton attributable to asthma within 3 months of screening, significant concurrent diseases including a recent upper or lower RTI. Medications prohibited througout the study included inhaled, oral, or IV steroids, theophylline or other bronchodilators, anticholingergics, LTRA, cromoly, and nedocromil.	Yes: 8 to 14 day run-in. All oral and inhaled short acting beta agoinsts were replaced with inhaled albuterol. Only those patients who remained symptomatic and thereby demonstrated the need for a controlled medication were eligile to continue. Patients were considered symptomatic if they required rescue albuterol on 5 ormore day s during the 7 days preceeding reandomization OR they had a diary card symptom score of >/= 2 on 3 or more days during this 7 day time period for chest tightness, wheezing, or shortness of breath.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Pearlman et al.{Pearlman, 2002 #596} 2002 United States Multicenter - 51 sites Glaxo Wellcome	Intervention: Drug 1: FP/SM Drug 2: ML Total daily dose: Drug 1: 200mcg/ 100mcg Drug 2: 10mg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: NA Delivery device: Drug 1: DPI - Diskus Drug 2: capsule enclosed tablet Is dosing comparable between treatment groups? Not applicable- why not?: ICS/LABA vs LTRA	# in group (n): Drug 1: 216 Drug 2: 216 Mean age (years): Drug 1: 35 Drug 2: 36 Sex (% female): Drug 1: 54 Drug 2: 55 Current smokers (%): Drug 1: NR Drug 2: NR Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 45 (21%) Drug 2: 33 (15%) Overall: 78 (18%) Adverse events caused withdrawal (%): Drug 1: 2 Drug 2: 3

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Pearlman et al.{Pearlman, 2002 #596} 2002 United States Multicenter - 51 sites Glaxo Wellcome	Intervention: Drug 1 Baseline: FP/SM Drug 1 Endpoint: FP/SM Drug 2 Baseline: ML Drug 2 Endpoint: ML Number in group (n): Drug 1- baseline: 216 Drug 1- endpoint: 216 Drug 2- baseline: 216 Drug 2- endpoint: 216	Rescue med use during 24 hour period: Drug 1- baseline: use per 24 hours = 5.1 Drug 1-endpoint: change at endpoint = -3.6 Drug 2-baseline: 4.9 Drug 2-endpoint: change at endpoint = -2.2 P </= 0.001 for FP/SM vs ML at endpoint Symptom control during 24 hour period: D1 base: combined symptoms score = 1.6 D1 end: change at endpoint = -1.0; % reduction 60% D2 base: 1.5 D2 end: change at endpoint = -0.7; 41% reduction P </= 0.001 for FP/SM vs ML at endpoint Day time symptom control: D1 - base: % symptom free days = 7.9 D1 - end: mean change at endpoint = 40.3 D2 - base: 5.8 D2 - end: change at endpoint = 27 P </= 0.001 for FP/SM vs ML at endpoint Night time symptom control: D1 - base: % nights with no awakenings = 59.9 D1 - end: change at endpoint = 29.8 D2 - base: 60.2 D2 - end: change at endpoint = 19.6 P = 0.011 for FP/SM vs ML at endpoint Nocturnal awakenings: D1 base: nights/week with awakenings = 2.8 D1 end: change at endpoint = -2.2 D2 base: 2.7 D2 end: change at endpoint = -1.6 P </= 0.001 for FP/SM vs ML at endpoint AQLQ - overall: [illegible]

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Pearlman et al.{Pearlman, 2002 #596} 2002 United States Multicenter - 51 sites Glaxo Wellcome	Overall adverse events reported (%): Drug 1: 62 Drug 2: 62 Serious adverse events (%): Drug 1: 0 Drug 2: 0 Headache (%): Drug 1: 2 Drug 2: 1 Hoarseness (%): Drug 1: 3 Drug 2: 1 Other (%): Drug 1: experienced at least one aE during the study that was considered to be potentially related to treatment = 8 Drug 2: 11 Other (%): Drug 1: dry mouth = <1 Drug 2: 1 Other (%): Drug 1: nausea = 0 Drug 2: <	Compliance Calculated using diary counts of number of pills and inhalations taken on a daily basis. Compliance with the Diskus device and with the oral capsules was similar between treatment groups and was approximately 99% with both.	Good Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4633	Peters et al.{Peters, 2007 #4633} 2007 American Lung Association Asthma Clinical Research Centers USA Multicenter GSK	Study design: RCT Double-blind Duration: 16 weeks N = 500 Number screened: 1309/787/500 ITT Analysis: Yes	: physician-diagnosed asthma; an age of 6 years or older and a FEV1 of 60% or more of the predicted value before administration of a bronchodilator; and a reversibility of airway obstruction by 12% or more with the use of a beta-agonist or a provocative concentration of methacholine producing a 20% decrease in FEV1 of 8 mg per milliliter or less within the previous 2 years. Inclusion criteria after the run-in period: adequate adherence (i.e., completion of at least 10 of the previous 14 days of daily diary cards and fluticasone treatment for at least 21 of the previous 28 days); a prebronchodilator FEV1 of at least 80% of the predicted value; a score on the Asthma Control Questionnaire 17 of less than 1.5 (range, 0 to 6, with lower values indicating less-severe asthma and 0.5 unit as the minimal clinically important difference18); fewer than 16 puffs of a rescue betaagonist used per week during the final 2 weeks of the run-in period (except as medication before exercise); no hospitalization, urgent medical care (for asthma), oral corticosteroid use, or use of additional asthma Asthma Severity: Controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Peters et al.{Peters, 2007 #4633} 2007 American Lung Association Asthma Clinical Research Centers USA Multicenter GSK	NR	NR	Yes: 4-6 weeks stable on 200 ug FP

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Peters et al.{Peters, 2007 #4633} 2007 American Lung Association Asthma Clinical Research Centers USA Multicenter GSK	Intervention: Drug 1: FP Drug 2: FP + SM Drug 3: ML Total daily dose: Drug 1: 200 µg Drug 2: 100 + 50 Drug 3: 5-10 mg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Drug 3: N/A Delivery device: Drug 1: Diskus Drug 2: Diskus	# in group (n): Drug 1: 169 Drug 2: 165 Drug 3: 166 Mean age (years): Drug 1: 29.3 Drug 2: 30.8 Drug 3: 32.4 Sex (% female): Drug 1: 60.9 Drug 2: 62.4 Drug 3: 57.2 Current smokers (%): Drug 1: former 10.1 Drug 2: 18.2 Drug 3: 17.5 Optional - Previous ICS use (%): Drug 1: 39.6 Drug 2: 43.0 Drug 3: 53.0 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 13 (7.7%) Drug 2: 16 (9.7%) Drug 3: 20 (12.0%) Adverse events caused withdrawal (%): Drug 1: 0.5 Drug 2: 0 Drug 3: 0.6

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Peters et al.{Peters, 2007 #4633} 2007 American Lung Association Asthma Clinical Research Centers USA Multicenter GSK	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: FP + SM Drug 2 Endpoint: FP + SM Drug 3 Baseline: ML Drug 3 Endpoint: ML P-values (Define comparison): P for FP+SM vs FP, M vs FP, ML vs FP+SM Number in group (n): Drug 1- baseline: 169 Drug 1- endpoint: 168 Drug 2- baseline: 165 Drug 2- endpoint: 161 Drug 3- baseline: 166 Drug 3- endpoint: 165	Rescue med use during 24 hour period: % OF DAYS WITH USE Drug 1-endpoint: 18.2 (14.1-22.3) Drug 2-endpoint: 17.1 (12.8-21.3) Drug 3- endpoint: 22.9 (18.8-27.0) P values: 0.69, 0.09, 0.06 Symptom control during 24 hour period: Mean (95% CI): % DAYS SYMPTOM FREE D1 end: 85.8 (82.8-89.6) D2 end: 82.7 (78.9-86.6) D3 end: 78.7 (74.9-82.4) P: ns FOR ANY (0.48, 0.10, 0.35) Nocturnal awakenings:: % of patients D1 end: 16.7% D2 end: 17.3% D3 end: 25.4% P: 0.92, 0.04, 0.06 AQLQ - overall: mean Mini-AQLQ: 15 yrs or more/ 6-14 yrs: D1 base: 5.74 (0.89)/6.48 (0.57) D1 end: 5.8 (5.7-5.9)/ 6.6 (6.4-6.8) D2 base: 5.902 (0.79)/ 6.14 (0.73) D2 end: 5.8 (5.7-6.0)/6.6 (6.4-6.8) D3 base: 5.76 (0.84)/6.09 (0.69) D3 end: 5.8 (5.7-5.9)/ 6.4 (6.2-6.5) P: NS for any (0.66, 0.82, 0.8)/(0.82, 0.19, 0.14) Other Asthma QOL instrument: Mean ASUI (Asthma Symptom Utility Index): D1 end: 0.89 (0.88-0.90) D2 end: 0.89 (0.88-0.90) D3 end: 0.89 (0.88-0.90) P: 0.85, 0.44, 0.53 Asthma Control Score: ACQ mean: enrollment/baseline D1 base: 1.63 (0.74)/0.67 (0.38) D1 end: 0.73 (0.67-0.78) D2 base: 1.79 (0.83)/0.72 (0.38) D2 end: 0.71 (0.65-0.76) D3 base: 1.64 (0.86)/0.70 (0.40) D3 end: 0.82 (0.76-0.89) P: 0.58, 0.02, 0.004

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Peters et al.{Peters, 2007 #4633} 2007 American Lung Association Asthma Clinical Research Centers USA Multicenter GSK	Severe adverse events (%): Drug 1: 3.6 Drug 2: 2.5 Drug 3: 2.4 Headache (%): Drug 1: 71.4 Drug 2: 68.3 Drug 3: 70.9 P = NS Upper respiratory tract infection (%): Drug 1: 37.5 Drug 2: 38.5 Drug 3: 26.7 P = 0.85, 0.03, 0.02 Rhinitis (%): Drug 1: 71.4 Drug 2: 79.9 Drug 3: 67.3 P = NS Hoarseness (%): Drug 1: 54.8 Drug 2: 53.4 Drug 3: 47.3 P = NS Other (%): Drug 1: Fever 26.9 Drug 2: 22.4 Drug 3: 15.2 P = 0.33, < 0.01, 0.09 Other (%): Drug 1: Viral res infection 15.5 Drug 2: 13.7 Drug 3: 7.3 P = 0.77, 0.04, 0.08 Other (%): Drug 1: Nausea and vomitting 33.0 Drug 2: 23.0 Drug 3: 21.2 P = 0.03, 0.01, 0.79	Adherence Adherence according to drug dispensing records during follow-up - median FP 93.2 FP+sal 93.3% ML 90.5%	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
66	Pohunek et al.{Pohunek, 2006 #66} Multiplnational (European), multicenter (80), outpatient children AstraZeneca	Study design: RCT Double-blind Double-dummy Other: 7 days of the run-in, Duration: 12 wks N=630 Enrolled: 809 enrolled/630 randomized after run in ITT Analysis: Yes	Age: 4-11 Days with asthma symptoms: >= 1 clinically important exercise induced bronchoconstriction per week during; To be randomized, patients had to have a total asthma-symptom score [sum of night-time and daytime symptom scores, both ranging from 0 to 3, where 0 ¼ no symptoms and 3 ¼ unable to perform normal activities (or to sleep) because of symptoms] of at least one on a minimum of four of the last 7 days of the run-in period. Previous use of corticosteroids: ICS use for > 3 months prior to study Other? (List all others): diagnosis of asthma for a minimum of 6 months.; PEF >= 50% of predicted normal; All subjects needed to demonstrate the ability to use aTurbuhaler device and peak flow meter correctly.; during the last 7 days of the run-in, patients had to have a mean morning PEF of 50–85% of the postbronchodilatory PEF obtained 15 min after inhalation of terbutaline at enrolment. Asthma Severity: Mild ModerateSevereNot or poorly controlledOther? Please explain: Symptomatic

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Pohunek et al.{Pohunek, 2006 #66} MultiplNational (European), multicenter (80), outpatient children AstraZeneca	terbutaline as needed for relief; use of inhaled anticholinergics, B-blockers, xanthines, and other anti-asthma products were not permitted during the study.	Prior treatment with: systemic steroids within 30 days Concommitant diseases: "any significant disease or concommittant disorder; any respiratory infection affecting asthma control within the 30 days before enrolment Current treatment: Beta blockers (excluding eye drops) , xanthines, and "other anti-ashtma prodcuts" Other: unable to use Turbuhaler device; known or suspected hypersensitivity to the study medication or inhaled lactose	Yes: 10-14 day; patients continued their prestudy ICS dose

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Pohunek et al.{Pohunek, 2006 #66} MultiplNational (European), multicenter (80), outpatient children AstraZeneca	Intervention: Drug 1: BUD (Pulmicort) 100 µg two inhalations twice daily Drug 2: BUD 100ug (Pulmicort) + FM 4.5ug (Oxis) (as a separate inhaler) two inhalations twice daily Drug 3: BUD 80 µg/ FM 4.5ug (Symbicort, combined in one inhaler); two inhalations twice daily Total daily dose: Drug 1: 400 mcg Drug 2: 400 mcg + 18 mcg Drug 3: 320 / 18 Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Drug 3: low Delivery device: Drug 1: Turbuhaler Drug 2: Turbuhaler Drug 3: Turbuhaler Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 213 Drug 2: 201 Drug 3: 216 Mean age (years): Drug 1: 8.2 Drug 2: 8.1 Drug 3: 8.1 Sex (% female): Drug 1: 66/213 Drug 2: 64/201 Drug 3: 76/216 Optional - Disease duration (years): Drug 1: 2 Drug 2: 3 Drug 3: 3 Optional - Rescue medication use (puffs per day): Drug 1: 0.82 Drug 2: 0.89 Drug 3: 0.96 Optional - Previous ICS use (%): Drug 1: 100 (inclusion criteria) Drug 2: 100 Drug 3: 100 Optional - Current use of LABA (%): Drug 1: 41 Drug 2: 41 Drug 3: 40 Current use of ICS at baseline (%): Drug 1: 100 (inclusion criteria) Drug 2: 100	Number (%) withdrawn: Drug 1: 13/213 (6.1) Drug 2: 11/201 (5.5) Drug 3: 14/216 (6.5) Adverse events caused withdrawal (%): Drug 1: <1% Drug 2: 1% Drug 3: 0 Optional - Other reasons for withdrawal (%): Drug 1: A total of 38 patients (BUD/FM,n 14; BUD, n 13; BUD + FM in separate inhalers, n 11) discontinuedthe study: 27 as a result of the eligibilitycriteria not being fulfilled; three as a result ofadverse events; and eight for other reasons. A total of 592 patients completed the study.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Pohunek et al.{Pohunek, 2006 #66}	Intervention:	Rescue med use during 24 hour period:
	Drug 1 Baseline: BUD	Drug 1- baseline: 0.82 inhalations/24 h
MultiplNational (European), multicenter	Drug 1 Endpoint: BUD	Drug 1-endpoint: mean for 12-week treatment period: 0.36 inhalations/24 h
(80), outpatient children	Drug 2 Baseline: BUD + FM	Drug 2-baseline: 0.88
	Drug 2 Endpoint: BUD + FM	Drug 2-endpoint: 0.41
AstraZeneca	Drug 3 Baseline: BUD/FM	Drug 3 - baseline: 0.96
	Drug 3 Endpoint: BUD/FM	Drug 3- endpoint: 0.37
		P values: NS
	Number in group (n):	
	Drug 1- baseline: 213	Day time symptom control:
	Drug 1- endpoint: 213	D1 - base: Symptom-free days; mean (%) 20.8
	Drug 2- baseline: 201	D1 - end: mean for 12-week treatment period: 52.8
	Drug 2-endpoint: 201	D2 - base: 17.7
	Drug 3- baseline: 216	D2 - end: 50.6
	Drug 3- endpoint: 216	D3 - base: 19.5
		D3 - end: 52.5
		P: NS
		Night time symptom control:
		D1 - base: mean Night-time awakenings (%) 16.9
		D1 - end: mean (%) over 12-week treatment: 6.6
		D2 - base: 17.0
		D2 - end: 7.1
		D3 - base: 18.4
		D3 - end: 6.8
		P: NS
		AQLQ - overall:
		D1 base: see below: PAQLQ
		Other Asthma QOL instrument:
		D1 base: PAQLQ(S) score (range 1–7) mean: 5.8
		D1 end: mean at 12 week visit: 6.2
		D2 base: 5.8
		D2 end: 6.2
		D3 base: 5.7
		D3 end: 6.2
		P: NS

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Pohunek et al.{Pohunek, 2006 #66}	Overall adverse events reported (%): Drug 1: 40 Drug 2: 37 Drug 3: 39 Serious adverse events (%): Drug 1: 1.4 Drug 2: 2.5 Drug 3: 1.4 Oral candidiasis- thrush (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Dysphonia (%): Drug 1: 1 Drug 2: <0.5 Drug 3: 1 Hoarseness (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Other (%): Drug 1: Tremor 0 Drug 2: 1 Drug 3: 0 Other (%): Drug 1: Tachycardia <0.5 Drug 2: 0 Drug 3: 0 Other (%): Drug 1: palpitations 0 Drug 2: 0 Drug 3: 0	NR	Fair Fair No
MultiplNational (European), multicenter (80), outpatient children AstraZeneca			

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
521	Price et al.{Price, 2002 #521} 2002 UK and Ireland Multicenter AstraZeneca UK Ltd.	Study design: RCT double-blind parallel-group study Duration: 28 weeks N=505 ITT Analysis: ?	> 12 years with a diagnosis of asthma confirmed in the clinical record for > 3 months; randomized after 4 weeks trmt were stable, rerandomized

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Price et al.{Price, 2002 #521} 2002 UK and Ireland Multicenter AstraZeneca UK Ltd.		severe or recently unstable asthma; nebulised therapy, oral corticosteroids, leukotriene antagonist, or long acting b2 agonist; a clinically relevant upper respiratory tract infection in the 4 weeks leading up to. and irreversible chronic airways disease	

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Price et al.{Price, 2002 #521} 2002 UK and Ireland Multicenter AstraZeneca UK Ltd.	Intervention: Drug 1: Eformoterol Drug 2: Placebo Total daily dose: Drug 1: 18 µg Drug 2: NA Steroid dosing range: NA Delivery device: Drug 1: Turbohaler Drug 2: Turbohaler Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 250 Drug 2: 255 Mean age (years): Drug 1: 37.2 Drug 2: 38.3 Sex (% female): Drug 1: 61.2 Drug 2: 57.6	Number (%) withdrawn: Drug 1: 19.6 Drug 2: 22.0 Adverse events caused withdrawal (%): Drug 1: 1 Drug 2: 2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Price et al.{Price, 2002 #521} 2002 UK and Ireland Multicenter AstraZeneca UK Ltd.	Intervention: Drug 1: BUD +Eformoterol Drug 2: BUD +Placebo # in group (n): Drug 1: 250 Drug 2: 255	Symptoms: BUD + eFM > BUD [frequency of poorly controlled days, days/patient/6months: 10.0 vs 14.2, frequency ratio 0.70 (95% CI: 0.52 to 0.95; P=0.02); # of symptom-free days: 89.0 vs 71.6, difference 17.4 (95% CI: 6.4, 28.7; P=0.002) Exacerbations: BUD + eFM > BUD [Frequency of mild exacerbations per patient: 7.2 vs 10.5 per 6 months, frequency ratio 0.69 (95% CI: 0.49, 0.96; P=0.03) Rescue med use: BUD + eFM > BUD [Day and nighttime use: lower in BUD + eFM group (data NR, p<0.001); # of rescue-free days: 77.4 vs 57.1, difference 20.3 (95% CI: 9.4, 31.4; P<0.001) Quality of life: No difference [improvement in overall QoL score: 0.23 vs 0.03, difference between treatments = 0.20, P=0.1] Missed work or school: No difference [% of days taken off work or school because of asthma (P=NS, data NR)]

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Price et al.{Price, 2002 #521} 2002 UK and Ireland Multicenter AstraZeneca UK Ltd.	NR	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
472	Price et al.{Price, 2003 #472} 2003 COMPACT Study Group Multinational Multicenter (but neither is clear!) Merck	Study design: RCT Single-blind Duration: 16 weeks N = 889 Number screened: 1192/NR/889 ITT Analysis: Yes	: non-smokers or ex-smokers (stopped for at least 6 months and <12 pack yearhistory) diagnosed with asthma for >1 year, aged 15–75 years, who were not optimally controlled in spite of a regular ICS prescription at doses of 600–1200 mg/day for BUD, BDP, TAA, FLUN, and 300–800 mg/day for FP; FEV 1 values >50% predicted at visits 1 and 3, together with >12% improvement in FEV1 after b agonist administration, and symptoms requiring β-agonist treatment of at least 1 puff/day during the last 2 weeks of the run in period. Asthma Severity: Mild Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Price et al.{Price, 2003 #472} 2003 COMPACT Study Group Multinational Multicenter (but neither is clear!) Merck	rescue beta agonist	Other: other active pulmonary disorders, respiratory infection within 3 weeks of visit 1 or during the run in period, treatment in an emergency setting within 2 months of visit 1, systemic corticosteroid treatment within 1 month, cromones or LTRAs within 2 weeks, long acting antihistamine within 1 week (astemizole 3 months), or long acting b agonists or anticholinergic agents within 24 hours.	Yes: 4 week run in period during which patients were switched to BUD Turbohaler (800 mg/day (200 mg, two puffs twice daily). After 1 week single blind ML placebo was added

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Price et al.{Price, 2003 #472} 2003 COMPACT Study Group Multinational Multicenter (but neither is clear!) Merck	Intervention: Drug 1: BUD+ML Drug 2: BUD Total daily dose: Drug 1: 800/10 Drug 2: 1600 Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: high Delivery device: Drug 1: Turbohaler/tablet Drug 2: Turbohaler Is dosing comparable between treatment groups? NA: ICS plus LTRA vs ICS	# in group (n): Drug 1: 448 Drug 2: 441 Mean age (years): Drug 1: 43 Drug 2: 43 Sex (% female): Drug 1: 59 Drug 2: 61 Optional - Race (% white): Drug 1: 77.2 Drug 2: 76.6 Current smokers (%): Drug 1: 0 Drug 2: 0 Optional - Disease duration (years): Drug 1: 18 Drug 2: 17 Current use of ICS at baseline (%): Drug 1: 100 (730) Drug 2: 100 (746) Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 20 (5) Drug 2: 26 (6) Overall: 46 (5)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Price et al.{Price, 2003 #472} 2003 COMPACT Study Group Multinational Multicenter (but neither is clear!) Merck	Intervention: Drug 1 Baseline: BUD+ML Drug 1 Endpoint: BUD+ML Drug 2 Baseline: BUD Drug 2 Endpoint: BUD Number in group (n): Drug 1: 448 Drug 2: 441	Rescue med use during 24 hour period: change from baseline beta-agonist used per day Drug 1-endpoint: -0.78 Drug 2-endpoint: -0.75 P = 0.510 Asthma exacerbations: Median days w/exacerbations D1 end: 6.7% D2 end: 6.3% P= 0.781 Symptom control during 24 hour period: Median asthma free days D1 end: 86.7% D2 end: 82.2 P = 0.371 Day time symptom control: Daytime symptom score change from baseline D1 - end: -0.34 D2 - end: -0.35 P = 0.908 Courses of steroids: % patients requring oral steroids or admission to hospital = D1 end: 1.6 D2 end: 2.3 P = 0.472 Nocturnal awakenings: D1 base: 12.3% of nights D1 end: 2.3% D2 base: 13.8% D2 end: 3.9% NS between bud/mont and bud P = 0.353 AQLQ - overall: D1 base: change from baseline= 4.7

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Price et al.{Price, 2003 #472} 2003 COMPACT Study Group Multinational Multicenter (but neither is clear!) Merck	Overall adverse events reported (%): Drug 1: 37.1 Drug 2: 41.3 Respiratory infection (%): Drug 1: 11.6 Drug 2: 16.6 P < 0.05	Adherence Self-reported treatment adherence was high in both groups for both tablets and inhalers with >95% of days reported as fully compliant with treatment.	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
105	Price et al.{Price, 2006 #105} 2006 COMPACT unclear other than Multicenter; methods reported more in-depth elsewhere. NR	Study design: Observational Database analysisOther -please explain!: post hoc analysis of subgroup of patients from a large RCT Duration: 12 weeks N = 410 for this analysis Number screened: NA, post hoc analysis of a larger RCT (n=889 in the larger RCT) ITT Analysis: Unable to determine	Age: Adult FEV 1 expressed as a percent of the predicted value: >=50% during last 2wks of run-in peroid Reversability of FEV1: >=12% s/p SABA Other: asthma patients with allergic rhinitis; >=1 puff/day SABA during last 2 weeks of run-in; allergic rhinitis by self-report and later confirmed by a physician; prior treatment with ICS (600–1200 lg/day of BUD, beclomethasone, TAA,or FLUN or 300–800 lg/day of fluticasone) Asthma Severity: Moderate Severe Not or poorly controlled Other: severity based on previous ICS dose and NIH asthma treatment guidelines, 2003

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Price et al.{Price, 2006 #105} 2006 COMPACT unclear other than Multicenter; methods reported more in-depth elsewhere. NR	medications for allergy control, including but not limited to intrnasal steroids and antihistamines	Other: see larger study	Yes: 1-month run-in period, adult patients whose asthma was not optimally controlled with ICS were switched from their current medication to 800 mcg/day of inhaled BUD (TurbohalerTM 200 mcg, two puffs daily; AstraZeneca UK Ltd, Luton, UK). Inadequate control of asthma was determined by investigators for their patients who were taking regular prescriptionsfor 600–1200 mcg/day of BUD, BDP, TAA,or FLUN or 300–800 mcg/day of FP.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Price et al.{Price, 2006 #105} 2006 COMPACT unclear other than Multicenter; methods reported more in-depth elsewhere. NR	Intervention: Drug 1: ML+BUD Drug 2: dBUD Total daily dose: Drug 1: 10mg/800mcg Drug 2: 1600mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: high Delivery device: Drug 1: MDI Drug 2: MDI Is dosing comparable between treatment groups? NA: objective to compare medium dose BUD + ML with high dose BUD	# in group (n): Drug 1: 221 Drug 2: 189 Mean age (years): Drug 1: 42.3 Drug 2: 41.4 Sex (% female): Drug 1: 59.3 Drug 2: 57.1 Optional - Race (% white): Drug 1: 77.4 Drug 2: 78.3 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Disease duration (years): Drug 1: 17.9 Drug 2: 18.5 Optional - Rescue medication use (puffs per day): Drug 1: 2.1 Drug 2: 2.1 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Other: Drug 1: nocturnal awakenings (nights/wk) 2.8 Drug 2: 2.7 Other:	

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Price et al.{Price, 2006 #105} 2006 COMPACT unclear other than Multicenter; methods reported more in-depth elsewhere. NR	Intervention: Drug 1 Baseline: ML+BUD (with AR) Drug 1 Endpoint: ML+BUD (with AR) Drug 2 Baseline: dBUD (with AR) Drug 2 Endpoint: dBUD (with AR) Number in group (n): Drug 1- baseline: 216 Drug 1- endpoint: 216 Drug 2- baseline: 184 Drug 2- endpoint: 184	Nocturnal awakenings: Mean nights/week, % D1 end: with AR/without AR: 2.3/2.3 D2 end: 5.5/2.5 P = 0.171 (for ML +BUD with AR vs BUD with AR); P = 0.778 for without AR comparison Other: Median number asthma-free days (any day free of oralcorticosteroid use, emergency care, nocturnal awakenings, with useof >= puffs b-agonist), % D1 end : with AR/without AR: 87.3/ 85.2 D2 end: 79.8/83.7 P = 0.14 (for ML +BUD with AR vs BUD with AR); P = 0.63 for without AR comparison Other: Beta-agonist use, %decrease: patient with AR (and without AR) D1 end : 27.8 (and 26.3) D2 baseD2 end: 21.0 (30.4) For those with AR, least squares mean diff -5.87 (95% CI -6.59, 19.33) p=0.279; for those w/o AR, least squares mean diff -4.08 (95% CI -16.27, 8.10) p=0.510 Other: Achieved control of asthma at 12 wks as defined by reaching an AM PEF >= 80%, daily asthma symptoms score >1 on no more than 2 days, and no more than2 days of b-agonist use per week, % D1 end : with/without AR: 11.1/11.5 D2 end: 5.3/8.9 P = 0.04 for with AR comparison; 0.37 without AR comparison

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Price et al.{Price, 2006 #105} 2006 COMPACT unclear other than Multicenter; methods reported more in-depth elsewhere. NR	NA	NR	Fair

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
928	Raphael et al.{Raphael, 1999 #928} 1999 USA Specialty asthma and primary care centers. (23) GlaxoSmithKline	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=399 Enrolled: NR ITT Analysis: Yes	: nonsmoking; males and females; 12 years or older with an established diagnosis of chronic asthma requiring daily inhaled corticosteroid therapy for at least 6 months; Only subjects using 8 to 12 puffs/day of either BDP or TAA acetonide for at least 1 month before the study were eligible; subjects were required to have an FEV1 between 45% and 80% of predicted normal value at the screening visit and at baseline; reversable lung function (12% or greater increase in FEV1 after 2 puffs of albuterol Asthma Severity: Mild Moderate Severe Not or poorly controlled : most were moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Raphael et al.{Raphael, 1999 #928} 1999 USA Specialty asthma and primary care centers. (23) GlaxoSmithKline	Stable theophylline and/or SM	Smoking - current or former : oral or intravenous corticosteroids, leukotriene modifiers, sodium cromoglycate, or nedocromil sodium for 1 month before the study.	Yes

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Raphael et al.{Raphael, 1999 #928} 1999 USA Specialty asthma and primary care centers. (23) GlaxoSmithKline	Intervention: Drug 1: FP Drug 2: BDP Total daily dose: Drug 1: 164/440 Drug 2: 336/672 Steroid dosing range (Low, medium or high): Drug 1: low/medium Drug 2: low/medium Delivery device: Drug 1: MDI Drug 2: MDI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 99/104 Drug 2: 101/95 Mean age (years): Drug 1: 38.4/37.8 Drug 2: 41.5/39.8 Sex (% female): Drug 1: 54/52 Drug 2: 68/59 Optional - Race (% white): Drug 1: 92/95 Drug 2: 90/96 Current smokers (%): Drug 1: 0/0 Drug 2: 0/0 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100	Number (%) withdrawn: Drug 1: 27(27)/22(21) Drug 2: 40(40)/22(23) Optional - Withdrew due to lack of efficacy (%): Drug 1: 17/15 Drug 2: 26/17 Adverse events caused withdrawal (%): Drug 1: 3/3 Drug 2: 4/2 Optional - Other reasons for withdrawal (%): Drug 1: 7/3 Drug 2: 10/4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Raphael et al.{Raphael, 1999 #928} 1999 USA Specialty asthma and primary care centers. (23) GlaxoSmithKline	Intervention: Drug 1 Baseline: FP88/FP220 Drug 1 Endpoint: FP88/FP220 Drug 2 Baseline: BDP168/336 Drug 2 Endpoint: BDP168/336 P-values (Define comparison): FP vs BDP Number in group (n): Drug 1- endpoint: 99/101 Drug 2- endpoint: 104/95	Rescue med use during 24 hour period: Drug 1- baseline: mean puffs/day: 3.4(0.3)/3.2(0.3) Drug 1-endpoint: change from baseline in puffs per day -0.9(0.2)/-0.5(0.2) Drug 2-baseline: 3.4/3.2 Drug 2-endpoint: 0.0/-0.3 P = 0.004 Rescue med use day: Drug 1- baseline: % days with no albuterol use (% rescue free days): 26.4(3.7)/28.9(3.6) Drug 1 -endpoint: change in % days no use15.8/11.0 Drug 2 - baseline: 22.7/27.1 Drug 2 - endpoint: 5.0/7.7 P = 0.10 Symptom control during 24 hour period: D1 base: % days with no symptoms: 15.6/16.9 D1 end: change % days no symptoms: 14.0/8.7 D2 base: 17.3/19.6 D2 end: 4.9/4.4 P = 0.027 Day time symptom control: D1 - base: symptom score (0-3): 1.21(0.06)/1.27(0.06) D1 - end: Change from baseline: -0.24/-0.26 D2 - base: 1.14/1.20 D2 - end: -0.05/-0.15 P = 0.024 Nocturnal awakenings: D1 base: 0.19/0.27 D1 end: change in night awakenings -0.03/-0.12 D2 base: 0.20/0.22 D2 end: -0.03/-0.07 P = 0.458

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Raphael et al.{Raphael, 1999 #928} 1999 USA Specialty asthma and primary care centers. (23) GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 9 Drug 2: 15 P = 0.664 Oral candidiasis- thrush (%): Drug 1: 1 Drug 2: 4 P: <=0.472 Dysphonia (%): Drug 1: 3 Drug 2: 7 P = 0.577 Sore throat (%): Drug 1: 1 Drug 2: 3 P = 0.797 Headache (%): Drug 1: 1 Drug 2: 3 P = 0.721	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
2548	Riccioni et al.{Riccioni, 2004 #2548} 2004 Italy Respiratory Pathophysiology Center, Department of Internal Medicine and Aging NR	Study design: RCT Other: NR Duration: 12 weeks N = 40 Number screened: NR ITT Analysis: Unable to determine	PEF increased at least 15% after a 15- to 20-minute inhalation of short-acting β2-agonist Asthma Severity: Mild

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Riccioni et al.{Riccioni, 2004 #2548} 2004 Italy Respiratory Pathophysiology Center, Department of Internal Medicine and Aging NR	NR	Other: emergency treatment for an asthma exacerbation within the last month; respiratory tract infections in the last 4 weeks; hospitalization for asthma during the 3 months preceding the enrollment; presence of autoimmune, hepatic, or renal disorders, malabsorption, drug or alcohol addiction; pregnancy or lactation; chronic bronchitis; emphysema; cystic fibrosis; bronchiectasis; gastroesophageal reflux; and poor knowledge of Italian language.	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Riccioni et al.{Riccioni, 2004 #2548} 2004 Italy Respiratory Pathophysiology Center, Department of Internal Medicine and Aging NR	Intervention: Drug 1: montelukast Drug 2: zafirlukast Total daily dose: Drug 1: 10 mg Drug 2: 40 mg Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 20 Drug 2: 20 Mean age (years): Drug 1: 27.4 Drug 2: 26.1 Sex (% female): Drug 1: 45 Drug 2: 50 Current smokers (%): Drug 1: NR Drug 2: NR Current use of ICS at baseline (%): Drug 1: NR Drug 2: NR Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: NR Drug 2: NR Adverse events caused withdrawal (%): Drug 1: NR Drug 2: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Riccioni et al.{Riccioni, 2004 #2548} 2004 Italy Respiratory Pathophysiology Center, Department of Internal Medicine and Aging NR	Intervention: Drug 1: montelukastL Drug 2: zafirlukast Number in group (n): Drug 1: 20 Drug 2: 20	Rescue med use during 24 hour period: Total # of SABA uses during trial Drug 1-endpoint: 25 Drug 2-endpoint: 27 P = NS AQLQ - overall: D1 base: 4.7 D1 end: 5.5 D2 base: 4.8 D2 end: 5.7 P = NS AQLQ - symptoms: D1 base: 5.0 D1 end: 5.7 D2 base: 4.9 D2 end: 5.6 P = NS AQLQ - environment: D1 base: 4.6 D1 end: 5.3 D2 base: 4.7 D2 end: 5.6 P = NS AQLQ - emotions: D1 base: 4.7 D1 end: 5.3 D2 base: 4.8 D2 end: 5.8 P = NS AQLQ - activities: D1 base: 5.1 D1 end: 5.9 D2 base: 5.0 D2 end: 5.7 P = NS .

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Riccioni et al.{Riccioni, 2004 #2548} 2004 Italy Respiratory Pathophysiology Center, Department of Internal Medicine and Aging NR	NR	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4743	Ringdal et al.{Ringdal, 1996 #4743} 1996 Multinational Multicenter NR: 2 authors affiliated with GlaxoSmithKline	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=518 Enrolled: NR/NR/518 ITT Analysis: Yes	Age: 18-75 FEV1 expressed as a percent of the predicted value: between 45% and 90% Other: clear response to bronchodilator therapy, defined as a mean morning PEF over the last 7 days of run-in period of </= 90% of response obtained following administration of salbutamol 400 mcg or 800 mcg at start of treatment period; required two or more doses of a bronchodilator, or to have had asthma symptoms (total score >/= 2) on at least 4 of last 7 dyas of run-in period Asthma Severity: Moderate Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Ringdal et al.{Ringdal, 1996 #4743} 1996 Multinational Multicenter NR: 2 authors affiliated with GlaxoSmithKline	Salbutamol as rescue medication; all concomitant asthma medicatin (except B2-agonists other than salbutamol) permitted provided they had been taken at a constant dosage for 4 wks prior to visit 1 and during run-in.	Pregnant or lactating Prior treatment: oral corticosteroids Concommitant diseases: which might have interfered with assessment of study medication : reversible airways obstruction was unstable; if they had received oral corticosteroids; had a RTI or been admitted to hospital for respiratory disease during 4 weeks prior to study entry; or if they had required 16 or more doses of rescue salbutamol during last 6 days of run-in period; hypersensitivity to ICS, evidence of alcohol or drug abuse	Yes: 2 week run-in where patients received their usual inhaled steroid and switched to study drug at start of treatment period

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Ringdal et al.{Ringdal, 1996 #4743} 1996 Multinational Multicenter NR: 2 authors affiliated with GlaxoSmithKline	Intervention: Drug 1: FP Drug 2: BUD Total daily dose: Drug 1: 800 mcg Drug 2: 1600 mcg Steroid dosing range (Low, medium or high): Drug 1: high Drug 2: high Delivery device: Drug 1: DPI Drug 2: DPI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 256 Drug 2: 262 Mean age (years): Drug 1: 47.6 Drug 2: 48.3 Sex (% female): Drug 1: 42.6% Drug 2: 49.6% Optional - Race (% white): Drug 1: 88.7% Drug 2: 90.8% Current smokers (%): Drug 1: 16.8% Drug 2: 20.6% Optional - Disease duration (years): Drug 1: 17.4 (14.6) Drug 2: 17.7 (12.8) Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Other: Drug 1: No. exacerbations requiring change of meds in last 12 months: 1.1 (1.5) Drug 2: 1.1 (2.3) Other: Drug 1: patients hospitalized at least once n last 12 months due to exacerbation n (%): 27 (10.5%) Drug 2: 29 (11.1%)	Number (%) withdrawn: Drug 1: 25 (9.8%) Drug 2: 24 (9.2%) Optional - Withdrew due to lack of efficacy (%): Drug 1: 0.78% Drug 2: 0.38% Adverse events caused withdrawal (%): Drug 1: 3.9% Drug 2: 5.0% Optional - Lost to follow-up (%): Drug 1: 1.6% Drug 2: 1.1% Optional - Protocol violation (%): Drug 1: 1.2% Drug 2: 0.8% Optional - Other reasons for withdrawal (%): Drug 1: 2.3% Drug 2: 1.9%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Ringdal et al.{Ringdal, 1996 #4743} 1996 Multinational Multicenter NR: 2 authors affiliated with GlaxoSmithKline	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: BUD Drug 2 Endpoint: BUD Number in group (n): Drug 1- baseline: 256 Drug 2- baseline: 262	Asthma exacerbations: D1 end: 16% of patients D2 end: 19.5% P = NS Day time symptom control: D1 - base: median percentage of days with symptom score < 2 : 33.3% D1 - end: weeks 1-12: 85.7% D2 - base: 33.3 D2 - end: 88.3 P = 0.42 for comparison of 85.7 vs 88.3 (week 1-12 comparison, not change from baseline) Night time symptom control: D1 - base: % of symptom free nights (median): 28.6% D1 - end: week 1-12: 73.2% D2 - base: 33.3 D2 - end: 77.5 P = 0.43 for 73.2 vs 77.5 Other: D1 base: % days with no additional bronchodilator use: 0.0 D1 end : week 1-12: 27.8 D2 base: 0.0 D2 end: 16.2 P = 0.12 for weeks 1-12 comparison Other: D1 base: % nights with no additional bronchodilator use: 26.7 D1 end : week 1-12: 75.9 D2 base: 28.6 D2 end: 74.8 P =: 0.32 for week 1-12 comparison Other Relevant Health Outcome Results: Explanation of data reported above: "Day time symptom control" refers to % of days with symptom score <2 median) baseline & Week 1-12; "Night-time symptom control" refers to % of symptom-free nights (median) baseline & Week 1-12 There was no significant difference in total number of patients reporting exacerbatic

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Ringdal et al.{Ringdal, 1996 #4743} 1996 Multinational Multicenter NR: 2 authors affiliated with GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 61.7 Drug 2: 61.5 Serious adverse events (%): Drug 1: 2.7 Drug 2: 3.4 Sore throat (%): Drug 1: 5.9 Drug 2: 4.2 Upper respiratory tract infection (%): Drug 1: 21.5 Drug 2: 24.9 Rhinitis (%): Drug 1: 11.3 Drug 2: 8.0 Other (%): Drug 1: exacerbation & related events: 14.5 Drug 2: 17.6 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: Suppression of the HPA axis of clinical concern was seen in six (2.3%) FPpatients compared with eleven (4.2%) BUD patients. However, this difference did not attain statistical significance. Additional adverse events and comments: Data reported most common defined as experienced by >/= 4% of patients in each treatment group	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
503	Ringdal et al.{Ringdal, 2002 #503} 2002 EDICT Multinational (11 European countries) Primary care and hospital respiratory clinics Glaxo Wellcome Research	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=428 Enrolled: 520/NR/428 ITT Analysis: Yes	: Male and female patients aged 16-75 yrs. with a clinical history of reversible airways obstruction and who were symptomatic on ICS. Reversibility was defined as an increase in FEV1 of>/=15% from baseline,15min after inhaling 400 mg of salbutamol. At Visit 2, patients also had to have a predicted FEV1 of 50-85%, and either a symptom score (day and night combined) of at least 2 or use of salbutamol for symptomatic relief (not prophylaxis) on 2 or more occasions, on at least 4 of the last 7 evaluable days of the run-in period. Asthma Severity: Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Ringdal et al.{Ringdal, 2002 #503} 2002 EDICT Multinational (11 European countries) Primary care and hospital respiratory clinics Glaxo Wellcome Research	Salbutamol	Other: changed their ICS dose or received oral corticosteroids, LM or nasal corticosteroids (other than FP), in the 4 weeks before Visit 1, or any LABAs in the 2 weeks before Visit 1; had a recent history of upper or lower respiratory tract infection; were smokers with a history of 10 pack years or more; or had an acute asthma exacerbation within 1 month.	Yes: 2 week run in on prestudy meds

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Ringdal et al.{Ringdal, 2002 #503} 2002 EDICT Multinational (11 European countries) Primary care and hospital respiratory clinics Glaxo Wellcome Research	Intervention: Drug 1: SM/FP Drug 2: FM+BUD Total daily dose: Drug 1: 100mcg/500mcg Drug 2: 24mcg/1600mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Delivery device: Drug 1: Diskus Drug 2: Turbuhalers Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 212 Drug 2: 216 Mean age (years): Drug 1: 46.5 Drug 2: 48.1 Sex (% female): Drug 1: 60 Drug 2: 51 Current smokers (%): Drug 1: 0 Drug 2: 0 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 23 (10.8) Drug 2: 26 (12) Adverse events caused withdrawal (%): Drug 1: 4.2 Drug 2: 4.2

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Ringdal et al.{Ringdal, 2002 #503} 2002 EDICT Multinational (11 European countries) Primary care and hospital respiratory clinics Glaxo Wellcome Research	Intervention: Drug 1 Baseline Drug 1 Endpoint: SM/FP Drug 2 Endpoint: FM+BUD Number in group (n): Drug 1- endpoint: 211 Drug 2- endpoint: 215	Asthma exacerbations: The mean rate of exacerbation (mild,moderate or severe) per patient per 84 ays of treatment, according to the Poisson model D1 end: 0.472 (36% reduction compared to FM + BUD D2 end: 0.735 Ratio=0.64; 95% CI=0.51, 0.80; P < 0.001 Hospitalizations: Days on general ward D1 end: 7 D2 end: 18 Urgent care use: Unscheduled outpatients D1 end: 6 D2 end: 17 Other Relevant Health Outcome Results: SM/FP group experienced a signicantly higher percentage of nights without awakenings (difference= 4.9; 95%CI=0.0, 12.0; P =0.02), without symptoms (difference= 2.7; 95% CI= 0.0, 8.4; P =0.04), and with a symptom score <2 (difference=0.0; 95%CI=0.0,1.2; P = 0.03) than patients in the FM+BUD group

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Ringdal et al.{Ringdal, 2002 #503} 2002 EDICT Multinational (11 European countries) Primary care and hospital respiratory clinics Glaxo Wellcome Research	Overall adverse events reported (%): Drug 1: 91 AEs reported Drug 2: 78 AEs reported Serious adverse events (%): Drug 1: 0.9 Drug 2: 1.4 Oral candidiasis- thrush (%): Drug 1: 0.5 Drug 2: 4.2 Dysphonia (%): Drug 1: 2.8 Drug 2: 1.0 Sore throat (%): Drug 1: 1.9 Drug 2: 0.5 Upper respiratory tract infection (%): Drug 1: 12.3 Drug 2: 8.3 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: NR	NR	Good Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
470	Ringdal et al.{Ringdal, 2003 #470} 2003 Multinational (19 countries) Multicenter (114 centers) GlaxoSmithKline	RCT Double-blind Double-dummy 12 weeks 805 NR/NR/1168 ITT? Yes	Asthmatic patients 15 years or older required to have received ICSs for at least 4 weeks; History of reversible airways obstruction and a =>15% increase from baseline FEV1, following inhalation of up to 800 mg of salbutamol. At end of run-in during last 7 days- A mean morning PEF recorded of >50% and <85% of the value measured in the clinic following the administration of salbutamol 400 mg; A cumulative symptom score (day and night) of >=8 , and symptoms on at least 4 days Asthma Severity: Mild Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Ringdal et al.{Ringdal, 2003 #470} 2003 Multinational (19 countries) Multicenter (114 centers) GlaxoSmithKline	salbutamol for rescue relief	Other: changed their regular asthma medication, had a respiratory tract infection or required hospitalisation for an acute exacerbation of asthma in prior 4 weeks; taken oral, depot or parenteral corticosteroids in the preceding 4 weeks or on >2 occasions in the preceding 12 weeks.Patientswith a smoking history greater than 10 pack years; pregnant or lactating. FEV1 </= 50% to avoid selection of patients too severe.	Yes- 4 week run-in to prove symptomatic and uncontrolled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Ringdal et al.{Ringdal, 2003 #470} 2003 Multinational (19 countries) Multicenter (114 centers) GlaxoSmithKline	Intervention: Drug 1: FP/SM Drug 2: FP/ML Total daily dose: Drug 1: 200/100 Drug 2: 200/10 Steroid dosing range: Drug 1: low Drug 2: low Delivery device: Drug 1: Diskus Drug 2: Diskus/ tablet Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 356 Drug 2: 369 Mean age (years): Drug 1: 43 Drug 2: 43 Sex (% female): Drug 1: 54 Drug 2: 55 Current smokers (%): Drug 1: 6.2 (Ex-smokers 20.8) Drug 2: 6.2 (Ex-smokers 24.4) Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 19 (5%) Drug 2: 37(10%) Overall: p< 0.05 for FP/SAL vs FP/ML Adverse events caused withdrawal (%): Overall: 57%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Ringdal et al.{Ringdal, 2003 #470} 2003 Multinational (19 countries) Multicenter (114 centers) GlaxoSmithKline	Intervention: Drug 1 Baseline: FP/SM Drug 1 Endpoint: FP/SM Drug 2 Baseline: FP/ML Drug 2 Endpoint: FP/ML Number in group (n): Drug 1- baseline: 356 Drug 2- baseline: 369	Rescue med use day: Drug 1- baseline: Rescue free day median % = 23.5 Drug 1 -endpoint: wks 1-12 = 71.4 Drug 2 - baseline: 20.7 Drug 2 - endpoint: wks 1-12 = 66.7 P = 0.03 Odds ratio 1.29; 95% CI 1.02 to 1.63; Rescue med use at night: Drug 1- baseline: Rescue free night median % = 53.6 Drug 1 - endpoint: wks 1-12 = 92.9 Drug 2 - baseline: 56.7 Drug 2 - endpoint: wks 1-12 = 85.7 P = 0.26 odds ratio 1.15; 95% CI 0.90 to 1.47; Asthma exacerbations: D1 end: 9.6% D2 end: 14.6% P < 0.05 Day time symptom control: D1 - base: Symptom free day median % (weeks 1-12) = 7.1 D1 - end: wks 1-12 = 50 D2 - base: 7.0 D2 - end: wks 1-12 = 38.5 Odds ratio 1.32; 95% CI 1.05 to 1.65; P < 0.05 Night time symptom control: D1 - base: Symptom free night median % (weeks 1-12) = 32.1 D1 - end: wks 1-12 = 78.6 D2 - base: 30.3 D2 - end: wks 1-12 = 71.4 Odds ratio 1.28; 95% CI 1.02 to 1.61;P < 0.05

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Ringdal et al.{Ringdal, 2003 #470} 2003 Multinational (19 countries) Multicenter (114 centers) GlaxoSmithKline	Overall adverse events reported (%): Drug 1: 44 Drug 2: 42 Serious adverse events (%): Drug 1: 1 Drug 2: 1.7 Oral candidiasis- thrush (%): Drug 1: 0.7 Drug 2: 0.2 Cough (%): Drug 1: Bronchitis <1 Drug 2: 2 Sore throat (%): Drug 1: 2 Drug 2: <1 Headache (%): Drug 1: 3 Drug 2: 4 Upper respiratory tract infection (%): Drug 1: 4 Drug 2: 2 Other (%): Drug 1: Common cold 7 Drug 2: 8	Compliance The compliance with study medication was high in both groups; 96% of patients in both treatment groups returned the correct number of doses in the Diskus inhaler and 97% in both groups returned the right number of tablets according to the protocol requirements.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4806 Combo	Rojas et al.{Rojas, 2007 #4806} 2007 Multinational (9) Multicenter (52) GlaxoSmithKline	Study design: RCT Double-blind Duration: 12 weeks N=362 Enrolled: NR/NR/429 ITT Analysis: Yes	Male and female; 12 to 80 years of age; ≥6-month history of persistent asthma and a <10 pack year smoking history, who were receiving treatment with SABA only; FEV1 of ≥60 and <80% predicted normal at the randomization visit and a daytime symptom score of ≥2 on at least 4 days of the last 7 days ofthe run-in; either a reversibility of ≥15% in FEV1 or a mean morning PEF during the last 7 days of the run-in of <85% of the post-bronchodilator value at visit 2. Asthma severity: Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Rojas et al.{Rojas, 2007 #4806} 2007 Multinational (9) Multicenter (52) GlaxoSmithKline	NR	Respiratory tract infection or an asthma exacerbation duringthe run-in.	Yes- elucidate....: 2 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Rojas et al.{Rojas, 2007 #4806} 2007 Multinational (9) Multicenter (52) GlaxoSmithKline	Intervention: Drug 1: SM/FP Drug 2: FP Total daily dose: Drug 1: 100/500 Drug 2: 500 Steroid dosing range (Low, medium or high): Drug 1: Medium Drug 2: Medium Delivery device: Drug 1: Diskus/Accuhaler Drug 2: Diskus/Accuhaler Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 182 Drug 2: 180 Mean age (years): Drug 1: 40 Drug 2: 41 Sex (% female): Drug 1: 57 Drug 2: 58 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 7 (4%) Drug 2: 5 (3%) Adverse events caused withdrawal (%): Drug 1: 0 Drug 2: < 1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Rojas et al.{Rojas, 2007 #4806} 2007 Multinational (9) Multicenter (52) GlaxoSmithKline	Intervention: Drug 1 Baseline: SFC Drug 1 Endpoint: SFC Drug 2 Baseline: FP Drug 2 Endpoint: FP Number in group (n): Drug 1: 182 Drug 2: 180	Rescue med use day: Drug 1- baseline: median rescue free 0 Drug 1 -endpoint: 91% Drug 2 - baseline: 0 Drug 2 - endpoint: 73% 95%CI: 2 to 13; P < 0.001 Rescue med use at night: Drug 1- baseline: median rescue free 23% Drug 1 - endpoint: 95% Drug 2 - baseline: 14% Drug 2 - endpoint: 84% 95%CI: 1 to11; P < 0.001 Day time symptom control: D1 - base: symptom free median 0 D1 - end: 78% D2 - base: 0 D2 - end: 61% 95%CI: 1 to 16; P = 0.004 Night time symptom control: D1 - base: symptom free median 0 D1 - end: 91% D2 - base: 0 D2 - end: 75% 95%CI: 1 to 12; P =0.001

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Rojas et al.{Rojas, 2007 #4806} 2007 Multinational (9) Multicenter (52) GlaxoSmithKline	Overall adverse events reported (%): Drug 1: TAEs 19 Drug 2: 26 Oral candidiasis- thrush (%): Drug 1: 2 Drug 2: <1 Cough (%): Drug 1: 2 Drug 2: 3 Headache (%): Drug 1: 3 Drug 2: 3 Hoarseness (%): Drug 1: 1 Drug 2: <1	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
839	Shapiro et al.{Shapiro, 2000 #839} 2000 Nathan et al.{Nathan, 2003 # } 2003 United States Multicenter - (42 sites) Research Centers/ Allergy and Asthma Centers Glaxo Wellcome	RCT Double-blind 12 weeks 349 484 screened, 349 randomly assigned ITT? Yes	Previous use of corticosteroids: 12 weeks; Male and female patients at least 12 yr of age and had a medical history of asthma of at least 6 mo duration that required pharmacotherapy; FEV 1 between 40% and 85% of the predicted value. > 15% increase in FEV 1 at 30 min after two puffs (180 mcg) of inhaled albuterol, and to have received ICSs continuously for at least 12 wk; treated with BDP (462 to 672 mcg/d), TAA (1,100 to 1,600 mcg/d), FLUN (1,250 to 2,000mcg/d), or FP (440 mcg/d) for at least 4 wk prior to screening. Female patients had negative pregnancy tests and were surgically sterile, postmenopausal for at least 1 yr, or using an acceptable birth control method for at least 1 mo. Asthma Severity: seems to suggest that all except very poorly controlled were allowed

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Shapiro et al.{Shapiro, 2000 #839} 2000 Nathan et al.{Nathan, 2003 # } 2003 United States Multicenter - (42 sites) Research Centers/ Allergy and Asthma Centers Glaxo Wellcome	Albuterol as needed for relief of symptoms.	Smoking - current or former: >10 Py Other: History of life-threatening asthma; hypersensitivity reaction to sympathomimetic drugs or corticosteroids; smoking within the year previous to the study or a smoking history of 10 packyears; use of oral or injectable corticosteroid therapy within the month preceding the study; use of intranasal corticosteroid therapy (except for FP [Flonase; Glaxo Wellcome Inc.]) during the study; use of daily oral corticosteroid treatment within the 6 mo preceding the study; use of any other prescription or over-the-counter medication that could have affected the course of asthma or interacted with sympathomimetic amines; abnormal chest radiographs; clinically significant abnormal 12- lead ECGs; or a history of significant concurrent disease (e.g., glaucoma, diabetes, hypertension).	Yes- 2-wk, single-blind, placebo-controlled screening period to evaluate eligibility, assess compliance with therapy, obtain baseline data, and confirm asthma stability. During the screening period, patients continued to take their inhaled corticosteroid in addition to placebo delivered from a Diskus device.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Shapiro et al.{Shapiro, 2000 #839} 2000 Nathan et al.{Nathan, 2003 # } 2003 United States Multicenter - (42 sites) Research Centers/ Allergy and Asthma Centers Glaxo Wellcome	Intervention: Drug 1: Placebo Drug 2: SM/FP Drug 3: SM Drug 4: FP Total daily dose: Drug 1: NA Drug 2: 100mcg/500mcg Drug 3: 100mcg Drug 4: 500mcg Steroid dosing range: Drug 1: NA Drug 2: medium Drug 3: NA Drug 4: medium Delivery device: Drug 1: DPI Drug 2: DPI Drug 3: DPI Drug 4: DPI Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 93 Drug 2: 84 Drug 3: 88 Drug 4: 84 Mean age (years): Drug 1: 38 Drug 2: 38 Drug 3: 39 Drug 4: 40 Sex (% female): Drug 1: 59 Drug 2: 52 Drug 3: 51 Drug 4: 46 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Drug 4: 0 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Drug 4: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Drug 4: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 64/90 (71%) Drug 2: 13/81 (16%) Drug 3: 44/85 (52%) Drug 4: 22/81 (27%) Optional - Withdrew due to lack of efficacy (%): Drug 1: 62% Drug 2: 4% Drug 3: 38% Drug 4: 22% Adverse events caused withdrawal (%): Drug 1: 0 Drug 2: 0 Drug 3: 2 Drug 4: 0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Shapiro et al.{Shapiro, 2000 #839} 2000 Nathan et al.{Nathan, 2003 # } 2003 United States Multicenter - (42 sites) Research Centers/ Allergy and Asthma Centers Glaxo Wellcome	Intervention: Drug 1: Placebo Drug 2: SM/FP Drug 3: SM Drug 4: FP Number in group (n): Drug 1: 90 Drug 2t: 81 Drug 3: 84 Drug 4: 81	Rescue med use during 24 hour period: Drug 1: baseline: 3.8 puffs/d; change from baseline = 0.9 Drug 2t: 3.5/-2.3 (0.4) Drug 3: 3.8/0 (0.3) Drug 4: 3.2/-0.9 (0.2) P </= 0.036 SM/FP and SM and FP versus placebo; P </= 0.003 Sal/FP versus Sal; P </= 0.015 Sal/FP versus FP Asthma exacerbations: D1: 15 (17%) D2: 2 (2%) D3: 10 (12%) D4: 6 (7%) P = NR Symptom control during 24 hour period: D1 base: see below, symptom score Day time symptom control: D1: % Days with no asthma symptoms, baseline/ (change from baseline) = 24.1/-7.9 D2: 26.5/33.8 (4.6) D3: 19.2/2.1 (3.6) D4: 23.5/15.4 (4.2) P </= 0.036 Sal/FP and FP versus placebo; P </= 0.003 Sal/FP versus Sal; P </= 0.015 Sal/FP versus FP Night time symptom control: D1: % nights with no awakenings, baseline/ (change from baseline) = 89.1/-12.0 D2: 90.7/7.2 (1.9) D3: 89.7/-8.0 (3.6) D4: 90.5/2.8 (2.4) P </= 0.036 Sal/FP and FP versus placebo; P </= 0.003 Sal/FP versus Sal; P </= 0.015 Sal/FP versus FP AQLQ - activities: D1: -0.19 D2: 1 (0.13) D3: -0.003 (0.14)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Shapiro et al.{Shapiro, 2000 #839} 2000 Nathan et al.{Nathan, 2003 # } 2003 United States Multicenter - (42 sites) Research Centers/ Allergy and Asthma Centers Glaxo Wellcome	Serious adverse events (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Drug 4: 0 Oral candidiasis- thrush (%): Drug 1: 0 Drug 2: 4 Drug 3: 0 Drug 4: 2 Cough (%): Drug 1: 0 Drug 2: 2 Drug 3: 1 Other (%): Drug 1: 0 Drug 2: unspecified candidiasis = 2 Drug 4: 4 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: HPA axis assessments. No clinically significant differences among treatment groups with respect to morning plasma cortisol abnormalities or response to synthetic corticotropin stimulation. At baseline, one patient each in the placebo (3%), SM (3%), and FP (3%) treatment groups had morning plasma cortisol concentrations , 5 mg/dl. At endpoint, the number of patients with morning plasma cortisol concentrations , 5 mg/dl was similar in the placebo (two; 6%), combination-product (one; 3%), SM (none), and FP (two; 6%) treatment groups. At baseline, one patient each in the placebo (3%) and FP (3%) treatment groups had poststimulation cortisol levels , 18 mg/dl. The numbers of patients with poststimulation increases in cortisol levels of , 7 mg/dl after 12 wk of treatment were three (8%), fo Additional adverse events and comments: Holter monitor, 12-lead ECG. Continuous 24-h ambulatory electrocar	Compliance Compliance was measured with the dose counter on the Diskus device. Mean treatment compliance rates ranged from 91% to 95% across treatment groups. From 8% to 14% of patients in each group had compliance rates, 80%. No patient was withdrawn from the study because of poor compliance with study medication.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1069	Simons et al.{Simons, 1997 #1069} 1997 Canada Glaxo Wellcome	Study design: RCT Double-blind Duration: 12 weeks N=241 Enrolled: 315 "enrolled"/241 randomized ITT Analysis: Yes	: 6 to 14 years; clinically stable asthma, less than one month of treatment at any time with inhaled or oral glucocorticoids for asthma, no glucocorticoid treatment for asthma within three months, a forced expiratory volume in one second (FEV 1) of more than 70 percent after the bronchodilator had been withheld for 6 hours, a 10 percent increase in FEV 1 30 minutes after the inhalation of 400 mg of albuterol, the requirement of less than 8 mg of methacholine per milliliter to decrease the FEV 1 by 20 percent (PC 20), and the ability to refrain from using study medications for 36 hours and from using rescue albuterol for 6 hours before visits.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Simons et al.{Simons, 1997 #1069} 1997 Canada Glaxo Wellcome	Inhaled albuterol as needed, cromolyn sodium, nedocromil, or theophylline for asthma or topical glucocorticoids or histamine□ H1-receptor antagonists for allergic rhinitis or atopic dermatitis, in unchanged doses.	Other: any emergency department visits or hospitalizations for asthma within the prior three months, a history of life-threatening asthma, and a history of adverse reactions to the medications used in the study.	Yes

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Simons et al.{Simons, 1997 #1069} 1997 Canada Glaxo Wellcome	Intervention: Drug 1: beclomethasone Drug 2: SM Drug 3: Placebo Total daily dose: Drug 1: 400 Drug 2: 100 Drug 3: NA Steroid dosing range (Low, medium or high): Drug 1: medium (>=12 years age), high if <12 y/o Delivery device: Drug 1: Diskhaler Drug 2: Diskhaler Drug 3: Diskhaler Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 81 Drug 2: 80 Drug 3: 80 Mean age (years): Drug 1: 9.6 Drug 2: 8.8 Drug 3: 9.5 Sex (% female): Drug 1: 41 Drug 2: 40 Drug 3: 45 Current smokers (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Other: Drug 1: Height (cm)140.0 Drug 2: 134.6 Drug 3: 138.5 Other: Drug 1: other asthma medications: 22 % Drug 2: 26 Drug 3: 26 Overall: 25% Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: including withdrawals d/t exacerbations: 14 (17%) Drug 2: 22 (28) Drug 3: 25(31) Optional - Withdrew due to asthma exacerbations (%): Drug 1: n=5 Drug 2: 15 Drug 3: 15 Adverse events caused withdrawal (%): Drug 1: 4 Drug 2: 5 Drug 3: 4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Simons et al.{Simons, 1997 #1069} 1997 Canada Glaxo Wellcome	Intervention: Drug 1 Baseline: BDP Drug 1 Endpoint: BDP Drug 2 Baseline: SM Drug 2 Endpoint: SM Drug 3 Baseline: Placebo Drug 3 Endpoint: Placebo Number in group (n): Drug 1: 81 Drug 2: 80 Drug 3: 80	Rescue med use during 24 hour period: % of days and nights albuterol not required Drug 1-endpoint: 92 Drug 2-endpoint: 88 Drug 3- endpoint: 83 Placebo vs BDP P< 0.001 Missed days of school: No school missed due to asthma (% of children) D1 end: 81 D2 end: 88 D3 end: 66 P = NR Nocturnal awakenings: % of night D1 end: 1 D2 end: 1 D3 end: 1 P = NR Other: % of children , albuterol not required D1 end : 95 D2 end: 91 D3 end: 84 Placebo vs BDP P = 0.03

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Simons et al.{Simons, 1997 #1069} 1997 Canada Glaxo Wellcome	Growth: Drug 1: height increase 3.96 cm Drug 2: 5.4 cm Drug 3: 5.04 cm Drug 5: BDP vs - placebo P = 0.018 and vs SM P = 0.004	Compliance Compliance > 75% (% children) BDP 100 SM 99 Placebo 99	Fair: attrition high, but that includes withdrawals due to exacerbations Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
665 541 500 5106	Soler et al. Buhl et al. 2001, 2002 + unpublished data (FDA) Multinational Multicenter Novartis Pharma AG and Genetech Inc	Study design: RCT Duration: 28 wks (16 wk stable ICS phase followed by 8 wk reduction phase and 4 wk stable phase); 24 wk DB extension N=546	Age 12-75; diagnosis of asthma of at least 1 yr duration; who met standard ATS criteria; and the following additional criteria: a positive skin-prick test to at least one allergen, serum tottal IgE level ≥30 and ≤700 IUmL-1 and body weight ≤150 kg to allow optimal OM dosing; baseline FEV1 off bronchodilators ≥40% and ≤80% of predicted increasing by ≥12% within 30 min of taking inhaled salbutamol; a mean total daily symptom score of ≥3.0 (maximum 9) during the 14 days prior to randomization; treatment with ICSs in doses equivalent to 500–1,200 mcg of BDP per day for ≥3 months prior to randomization and use of B2-adrenoceptor agonists on an as-needed or regular basis. Asthma had to be stable, with no significant change in regular medication and no acute exacerbation requiring additional corticosteroid treatment for ≥1 month prior to the screening visit. Moderate-severe allergic asthma

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Soler et al. Buhl et al. 2001, 2002 + unpublished data (FDA) Multinational Multicenter Novartis Pharma AG and Genetech Inc	Rescue medication with salbutamol (100 mcg/puff)	Patients regularly taking oral corticosteroids were not included.	Yes

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Soler et al. Buhl et al. 2001, 2002 + unpublished data (FDA) Multinational Multicenter Novartis Pharma AG and Genetech Inc	Drug 1: OM 0.016 mg/kg IgE IU/mL per 4 weeks SQ n=274 Drug 2: Placebo NA n=272	Age: Drug 1: OM 40 Drug 2: Placebo 39 Sex (% female): Drug 1: OM 48.5 Drug 2: Placebo 53.3 Race (% white): Drug 1: OM 93 Drug 2: Placebo 89 Current smokers (%) 0 ICS (%): Drug 1: OM 100 Drug 2: Placebo 100	Withdrawals: Drug 1: OM 19 (6.9%) Drug 2: PL 40 (14.7%) Withdrawals due to AEs: Drug 1: OM 0 (0%) Drug 2: PL 5 (1.8%)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Soler et al. Buhl et al. 2001, 2002 + unpublished data (FDA) Multinational Multicenter Novartis Pharma AG and Genetech Inc	Intervention: Drug 1: OM Drog 2: Placebo Number in group (n): Drug 1: 274 Drug 2: 272	• Symptoms: Change in total asthma symptom scores during stable steroid phase statistically significant vs. placebo (data NR; P < 0.001). Improvement in symptom scores continued during steroid reduction phase (data NR; P< 0.01) Median proportion of low symptom days for 28 week period: OM 0.06 vs. placebo 0 (P < 0.001) • Night symptoms: Better improvements in night-time symptom scores in OM patients during both phases of study (data NR; P < 0.01 at week 16 and week 28) • Exacerbations: Asthma exacerbations per patient lower in OM patients vs. placebo patients in stable-steroid phase: 0.28 (0.15-0.41) vs. 0.66 (0.49-0.83); P<0.001 and in steroid reduction phase: 0.36 (0.24-0.48) vs. 0.75 (0.58-0.92); P < 0.001. Percentage of patients with ≥ 1 exacerbation significantly lower in OM group vs. placebo group for stable-steroid phase (12.8% vs. 30.5%; P<0.001) and in steroid reduction phase (15.7% vs. 29.8%; P < 0.001) • Rescue med use: Median number of puffs of rescue med lower in OM group than placebo group during both treatment phases (data NR; P < 0.001) • QoL: Greater percentage of OM patients achieved a clinically significant improver Overall AQLQ change (0.83 vs. 0.59) at week 16, P = NR; Overall AQLQ change (• Missed school: Mean number of school days missed [0.12 (± 0.48) vs. 1.25 (± 3.8 • Missed work: Mean number (± SD) of work days missed [0.51 (± 1.7) vs. 0.44 (±

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Soler et al. Buhl et al. 2001, 2002 + unpublished data (FDA) Multinational Multicenter Novartis Pharma AG and Genetech Inc	Overall OM NR Placebo NR P = 0.504 Injection site reaction: OM 11.8 Placebo 7.7 EXTENSION PHASE Overall OM 63.4 Placebo 65.9 Injection site reaction OM 5.3 Placebo 4.3	NR	Good

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
37	Sorkness et al.{Sorkness, 2007 #37} Pediatric Asthma Controller Trial (PACT) US, Childhood Asthma Research and Education Centers 1st author has consulting arrangements with GSK, AstraZeneca; several other authors are pharma consultants National Heart Lung and Blood Institute	Study design: RCT Double-blind Double-dummy Duration: 48 weeks N=285 Enrolled: 648 screened/enrolled, 285 randomized ITT Analysis: Yes	Age: 6- <14 FEV1 expressed as a percent of the predicted value: >=80% at screening, >=70% at randomization : able to perform reproducible spirometry, methacholine FEV1 PC20 <=12.5mg/mL, mild-moderate persistent asthma, as definedby diary-reported symptoms or b-agonist use (not including preexercise)or peak flows < 80% calculated from the mean of morning and evening peak flows obtained during the final week of the run-inperiod, on average at least 3 times per week. Asthma Severity: Mild Moderate Other: don't know whether were controlled.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Sorkness et al.{Sorkness, 2007 #37} Pediatric Asthma Controller Trial (PACT) US, Childhood Asthma Research and Education Centers 1st author has consulting arrangements with GSK, AstraZeneca; several other authors are pharma consultants National Heart Lung and Blood Institute	albuterol	Pregnant or lactating: pregnancy or lactation; failure to practice abstinence or use a medically acceptable birthcontrol method Prior treatment with: >= 4 courses of systemic corticosteroids in thepast year Concommitant diseases: other lung diseases; respiratory tract infection, asthma exacerbation,or systemic corticosteroid use within 4 weeks; 2 or moreasthma hospitalizations in the past year; history of a life-threateningasthma exacerbation Smoking - current or former: within past year Other: weeks; 2 or moreasthma hospitalizations in the past year; history of a life-threateningasthma exacerbation, history of adverse reaction to study medications, < 75% adherence during run-in	Yes: 2 to 4 weeks, during which they received a morning and evening placebo Diskus (GlaxoSmithKline, Research Triangle Park, NC), an evening placebocapsule, and open-label albuterol metered dose inhaler (MDI) as rescue.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Sorkness et al.{Sorkness, 2007 #37} Pediatric Asthma Controller Trial (PACT) US, Childhood Asthma Research and Education Centers 1st author has consulting arrangements with GSK, AstraZeneca; several other authors are pharma consultants National Heart Lung and Blood Institute	Intervention: Drug 1: FP Drug 2: PACT (FP / SM (AM FP100/SM50, PM SM50 only) Drug 3: ML Total daily dose: Drug 1: 200mcg Drug 2: 100mcg/100mcg Drug 3: 5mg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: low Drug 3: NA Delivery device: Drug 1: Diskus (DPI) Drug 2: Diskus (DPI) Drug 3: Oral Is dosing comparable between treatment groups? NA: Study comparing ICS with 0.5 dose ICS/LABA	# in group (n): Drug 1: 96 Drug 2: 94 Drug 3: 95 Mean age (years): Drug 1: 9.8 Drug 2: 10.3 Drug 3: 9.6 Sex (% female): Drug 1: 40.6 Drug 2: 35.1 Drug 3: 40 Optional - Race (% white): Drug 1: 53.1 Drug 2: 55.3 Drug 3: 56.8 Optional - Disease duration (years): Drug 1: AGE of symptom-onset 3.5 Drug 2: 3.2 Drug 3: 2.9 Optional - Previous ICS use (%): Drug 1: past year 60.4 Drug 2: 51.1 Drug 3: 57.9 Optional - Current use of LABA (%): Drug 1: past year 10.4 Drug 2: 14.9 Drug 3: 14.7 Optional - Current methylxanthine (i.e. theophylline) use (%): Drug 1: 0 Drug 2: 0	Number (%) withdrawn: Drug 1: 10 (10.4) Drug 2: 13 (13.8) Drug 3: 12 (12.6)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Sorkness et al.{Sorkness, 2007 #37} Pediatric Asthma Controller Trial (PACT) US, Childhood Asthma Research and Education Centers 1st author has consulting arrangements with GSK, AstraZeneca; several other authors are pharma consultants National Heart Lung and Blood Institute	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: PACT (FP/SM) Drug 2 Endpoint: PACT (FP/SM) Drug 3 Baseline: ML Drug 3 Endpoint: ML Number in group (n): Drug 1- baseline: 96 Drug 1- endpoint: 86 Drug 2- baseline: 94 Drug 2- endpoint: 81 Drug 3- baseline: 95 Drug 3- endpoint: 83	Symptom control during 24 hour period: % of asthma control days D1 end: 64.2 D2 end: 59.6 D3 end: 52.5 FP vs PACT P = 0.27; FP vs M p = 0.004; PACT vs M P = 0.08 Day time symptom control: Change from baseline in % asthma control days D1 - end: 32.2 D2 - end: 33.3 D3 - end: 22.3 FP vs PACT P = 0.80; FP vs M P = 0.023; PACT vs M P = 0.011 Asthma Control Score: ACQ (Asthma Control Questionnaire), change from baseline (95% CI) D1 end: -0.69 (-0.84, -0.54) D2 end: -0.55 (-0.75, -0.35) D3 end: -0.45 (-0.58, -0.33) FP vs PACT P = 0.25; FP vs M P = 0.018; PACT vs M P = 0.42 Other Relevant Health Outcome Results: During the 48 weeks, FP and PACT both superior to ML for percent of asthma control days.; The number needed to treat for both fluticasone monotherapy and PACT combination compared with montelukast was approximately 6.5, meaning that 7 children would need to be treated with fluticasone monotherapy or PACT combination instead of ML to achieve 1 additional treatment response defined as a 20% increase in asthma control days.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Sorkness et al.{Sorkness, 2007 #37} Pediatric Asthma Controller Trial (PACT) US, Childhood Asthma Research and Education Centers 1st author has consulting arrangements with GSK, AstraZeneca; several other authors are pharma consultants National Heart Lung and Blood Institute	Growth: Drug 1: growth, cm, change from baseline: 5.32 Drug 2: 5.26 Drug 3: 5.72 Drug 5: FP vs PACT 0.80; FP vs M 0.13; PACT vs M 0.08 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: The unadjusted and intent-to-treat mean increase in height from baseline over 48 weeks was 5.361.8 cm with fluticasone monotherapy, 5.3 6 1.5 cm with PACT combination, and 5.7 6 2.0 cm with ML monotherapy (Table II). Differences among the therapies in this outcome were about 0.4 to 0.46 cm less for fluticasone monotherapy and PACT combination compared with ML monotherapy, respectively, but these differences were not statistically significant, including when age-stratified (data not shown). Additional adverse events and comments: Stated were monitoring safety and efficacy in methods, but did not report adverse events	Adherence Adherence to study medications estimated from Diskus indicator was 90% (interquartile range, 86.0% to 97.7%) and from Electronic Drug Exposure Monitor records was 86% (interquartile range, 77.5% to 96.9%). Did not report between-groups.	Fair: no explanation of randomization and allocation concealment, and masking of outcome assessors. Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
212	Stelmach et al.{Stelmach, 2005 #212} 2005 Poland University clinic NR	Study design: RCT Double-blind Double-dummy Duration: 6 months N = 51 Number screened: NR/NR/51 eligibility ITT Analysis: No another type of analysis was used (define): two patients with exacerbations were excluded from analysis	: Aged 6–18 with newly diagnosed asthma and sensitive to house-dust mites (Dermatophagoides pteronyssinus or/and Dermatophagoides farinae) participated in the 7-month study. Diagnosis of asthma was established by typical symptoms and improvement in the prebronchodilator FEV1 >/=15% after salbutamol (200 mg). Subjects had not received corticosteroids and anti-leukotriene therapy prior to the study. The study took place from April to October 2003, when the exposure to dust was at a constant level and all children remained in the same environment. Asthma Severity: Not or poorly controlled Other: newly diagnosed asthma and sensitivity to house dust mites

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Stelmach et al.{Stelmach, 2005 #212} 2005 Poland University clinic NR	NR	Other: previous treatment with ICS or anti-leukotriene therapy	Yes: First visit, put on beta agoinst as needed for symptomatic relief for 4 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Stelmach et al.{Stelmach, 2005 #212} 2005 Poland University clinic NR	Intervention: Drug 1: BUD 400 Drug 2: BUD 800 Drug 3: ML Total daily dose: Drug 1: 400mcg Drug 2: 800mcg Drug 3: 5-10mg Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: medium Drug 3: NA Delivery device: Drug 1: DPI Drug 2: DPI Drug 3: tablet Is dosing comparable between treatment groups? NA: different ICS dosing and can't compare to ML	# in group (n): Drug 1: 15 Drug 2: 18 Drug 3: 16 Overall: 51 Mean age (years): Drug 1: 12 Drug 2: 12 Drug 3: 12 Sex (% female): Drug 1: 40 Drug 2: 34 Drug 3: 34 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Drug 3: 0 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 1 (6%) Drug 3: 1 (6%) Overall: 2 (4%) Optional - Withdrew due to asthma exacerbations (%): Drug 1: 6 Drug 3: 6 Overall: 4

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Stelmach et al.{Stelmach, 2005 #212} 2005 Poland University clinic NR	Intervention: Drug 1 Baseline: BUD 400 Drug 1 Endpoint: BUD 400 - 6 months Drug 2 Baseline: BUD 800 Drug 2 Endpoint: BUD 800 - 6 months Drug 3 Baseline: ML Drug 3 Endpoint: ML - 6 months Number in group (n): Drug 1- baseline: 16 Drug 1- endpoint: 15 Drug 2- baseline: 18 Drug 2- endpoint: 18 Drug 3- baseline: 17 Drug 3- endpoint: 16	Other: Clinical Score (mean) = 7 D1 end : 1.9 D2 base: 7.2 D2 end: 2.2 D3 base: 7.1 D3 end: 1.9 P = 0.12 BUD 400 vs ML; P = 0.09 BUD 400 versus BUD 800; P = 0.798 BUD 800 versus ML; no more reported; all significantly improved over baseline, P = 0.002, 0.001, 0.002 for BUD 400, BUD 800, and ML respectively

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Stelmach et al.{Stelmach, 2005 #212} 2005 Poland University clinic NR	NR	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
278	Strand et al.{Strand, 2004 #278} 2004 Denmark Multicenter (44 general practices and 1 hospital) GlaxoSmithKline NR: author 2 works for GSK	RCT Double-blind 24 weeks 150 221 screened/ 150 randomized ITT? Yes	Male and female; at least 18 years; asthma diagnosis as defined by the American Thoracic Society, and used a short-acting bronchodilator once or more per week for relief of asthma symptoms within 2 months prior to enrollment and during the baseline period; persistent asthma; The asthma diagnosis had to be confirmed in the clinical record for >3 months. The baseline diurnal PEF variation had to be >20% or one of the following determined within 3 years prior to baseline: (a) FEV1 reversibility >15% in response to bronchodilator (b) PC20 metacholine <4 mg/ml (c) diurnal PEF variation >20%. Female patients were required to have a negative pregnancy test. Asthma Severity: Mild/moderate/severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Strand et al.{Strand, 2004 #278} 2004 Denmark Multicenter (44 general practices and 1 hospital) GlaxoSmithKline NR: author 2 works for GSK	salbutamol for rescue; use of LABAs, ICS, or other long-acting asthma medication were not allowed within 2 months prior to visit 1.	Other: an asthma exacerbation during the 2-week baseline period; had an upper or lower respiratory tract or middle ear infection within 1 month prior to visit 1, serious cardiovascular disease, diabetes mellitus, untreated hypokalaemia, or thyrotoxicosis. In addition, they were excluded if they had a known or suspected hypersensitivity reaction to drug constituents, any other diseases that might interfere with the study results, or had problems operating the inhaler or peakflow meter.	Yes- 2 week baseline period

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Strand et al.{Strand, 2004 #278} 2004 Denmark Multicenter (44 general practices and 1 hospital) GlaxoSmithKline NR: author 2 works for GSK	Intervention: Drug 1: S/FP Drug 2: FP Total daily dose: Drug 1: 100/200 Drug 2: 200 Steroid dosing range: Drug 1: Low Drug 2: Low Delivery device: Drug 1: Diskus Drug 2: Diskus Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 78 Drug 2: 72 Mean age (years): Drug 1: 39 Drug 2: 38 Sex (% female): Drug 1: 51 Drug 2: 63 Current smokers (%): Drug 1: 32 Drug 2: 46 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Groups similar at baseline? No-FP group more likely to be female and more likely current smoker	Number (%) withdrawn: Drug 1: 11 (14) Drug 2: 13 (18) Adverse events caused withdrawal (%): Drug 1: 1 Drug 2: 3

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Strand et al.{Strand, 2004 #278} 2004 Denmark Multicenter (44 general practices and 1 hospital) GlaxoSmithKline NR: author 2 works for GSK	Intervention: Drug 1 Baseline: S/FP Drug 1 Endpoint: S/FP Drug 2 Baseline: FP Drug 2 Endpint: FP Number in group (n): Drug 1- endpoint: 78 Drug 2- endpoint: 72	Rescue med use during 24 hour period: Drug 1- baseline: mean days + nights without use: 22% Drug 1-endpoint: 71% Drug 2-baseline: 25% Drug 2-endpoint: 63% P values: P = 0.0497 Asthma exacerbations: # of patients having exacerbation during study D1 end: 1 D2 end: 1 P = NS Symptom control during 24 hour period: D1 base: mean Syptom free: 20% D1 end: 64% D2 base: 25% D2 end: 51% P = 0.035 Day time symptom control: D1 - base: mean symptom Score 1.4 D1 - end: 0.5 D2 - base: 1.3 D2 - end: 0.7 P = 0.0047 Night time symptom control: D1 - base: mean symptom Score 0.6 D1 - end: 0.2 D2 - base: 0.5 D2 - end: 0.2 P = 0.27 Other: D1 base: mean symptom free day 25% D1 end : 66% D2 base: 31% D2 end: 57% P = 0.022 Other: D1 base: mean symptom free nite 56% D1 end : 83% D2 base: 61% D2 end: 80% P = 0.18 Other Relevant Health Outcome Results: S/FP gave an increase from 20% to 64% and FP from 24% to 51%. The treatment difference was 13.2% in favour of S/FP (P = 0.035). When adjusted for baseline, the treatment difference in favour of S/FP was 15.3% (P = 0.008).

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Strand et al.{Strand, 2004 #278} 2004 Denmark Multicenter (44 general practices and 1 hospital) GlaxoSmithKline NR: author 2 works for GSK	Overall adverse events reported (%): Drug 1: 62 Drug 2: 58 Serious adverse events (%): Drug 1: 1 Drug 2: 3 Oral candidiasis- thrush (%): Drug 1: 1 Drug 2: 1	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
250	Szefler et al.{Szefler, 2005 #250} 2005 United States Univeristy Clinics author with numerous consulting arrangements with pharmaceutical companies NHLBI, General Clinical Research Centers at Washington University, National Jewish Medical Research Center	Study design: RCT Double-blindDouble-dummyOther, please illuminate.: cross-over Duration: 16 weeks total (two 8 week active phases) N = 144 enrolled Number screened: NR ITT Analysis: No another type of analysis was used (define)	: 6 to 17 years of age with mild-to-moderate asthma were enrolled. They had asthma symptoms or rescue bronchodilator use on average of 3 or more days per week during the previous 4 weeks and improvement in FEV1 of 12% or greaterafter maximal bronchodilation or methacholine PC20 of 12.5 mg/mL or less. They had no corticosteroid treatment within 4 weeks, no LM agents within 2 weeks. Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Szefler et al.{Szefler, 2005 #250} 2005 United States Univeristy Clinics author with numerous consulting arrangements with pharmaceutical companies NHLBI, General Clinical Research Centers at Washington University, National Jewish Medical Research Center		Other: No history of respiratory tract infection within 4 weeks of enrollment. Children were excluded for severe asthma or FEV1 of less than 70% of predicted value.	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Szefler et al.{Szefler, 2005 #250} 2005 United States Univeristy Clinics author with numerous consulting arrangements with pharmaceutical companies NHLBI, General Clinical Research Centers at Washington University, National Jewish Medical Research Center	Intervention: Drug 1: FP Drug 2: ML Total daily dose: Drug 1: 200mcg Drug 2: 5 - 10mg Steroid dosing range (Low, medium or high): Drug 1: low Delivery device: Drug 1: Diskus Drug 2: Tablet Is dosing comparable between treatment groups? NA: ICS versus LTRA	# in group (n): Drug 1: 144 Drug 2: 144 Mean age (years): Drug 1: NR Sex (% female): Drug 1: NR Current smokers (%): Drug 1: NR Optional - Previous ICS use (%): Drug 1: NR Is dosing comparable between treatment groups? NA: ICS versus LTRA Groups similar at baseline? Not reported	Number (%) withdrawn: Drug 1: 6 (4%) Drug 2: 11 (8%) Optional - Withdrew due to asthma exacerbations (%): Drug 1: 2% Drug 2: 8% Adverse events caused withdrawal (%): Drug 1: NR Drug 2: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Szefler et al.{Szefler, 2005 #250} 2005 United States Univeristy Clinics author with numerous consulting arrangements with pharmaceutical companies NHLBI, General Clinical Research Centers at Washington University, National Jewish Medical Research Center	Intervention: Drug 1: FP Drug 2: ML Number in group (n): Drug 1: 126 Drug 2: 126	Asthma exacerbations: D1: 2 (2%) D2: 10 (8%) P = 0.019

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Szefler et al.{Szefler, 2005 #250} 2005 United States Univeristy Clinics author with numerous consulting arrangements with pharmaceutical companies NHLBI, General Clinical Research Centers at Washington University, National Jewish Medical Research Center	NR	Adherence Adherence to both fluticasone and ML administration was comparable. For those who completed treatment (n = 126), mean (SD) adherence for fluticasone by Diskus counter was 94% (14) and 89% (15) for treatment periods 1 and 2, respectively. For ML, adherence was 97% (24) by tablet count and 92% (29) by eDEM for treatment period 1 and 93% (22) by tablet count and 86% (17) by eDEM for treatment period 2.	Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4770 LTRAs	Szefler et al.{Szefler, 2007 #4770} 2007 US Multicenter (55) Astra Zeneca	Enrolled: nr/nr/892 (this was already in the cell) Study design: Other open label Duration: 52 weeks N=395 Enrolled: 645/NR/395 ITT Analysis: Yes	Age: 2 to 8 : symptoms of mild persistent asthma; cumulative asthma symptom score of >=2 on >=3 of 7 consecutive days and must have required the use of B2-agonists on >=3 of 7 consecutive days during the run-in period Asthma severity: Mild Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Szefler et al.{Szefler, 2007 #4770} 2007 US Multicenter (55) Astra Zeneca	Rescue medication use was allowed in all subjects throughout the study, with 1 dose defined as either 2 puffs of a SABA from a metered-dose inhaler or 1 treatment with a nebulized SABA. Additional medications that were permitted during the study period included nasal corticosteroids, decongestants, antihistamines (other than astemizole and hydroxyzine), mucolytics, and expectorants not containing bronchodilators, antibiotics, topical hydrocortisone (<=1%), and vitamins.	Other: a history of severe or unstable asthma; had a hypersensitivity to BUD or ML sodium; had a clinically significant disease (past or present) or other medical condition that, in the opinion of the investigator, could interfere with the study or place the subject at risk because of participation in the study; had an acute exacerbation of asthma or a respiratory tract infection within 30 days before screening that, in the opinion of the investigator, could have affected the results of the study; or used ML or an inhaled corticosteroid within 1 week of screening, systemic corticosteroids within 2 weeks of screening or during the run-in period, or omalizumab within 6 months of screening	Yes: 21 day

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Szefler et al.{Szefler, 2007 #4770} 2007 US Multicenter (55) Astra Zeneca	Intervention: Drug 1: BUD Drug 2: ML Total daily dose: Drug 1: 0.5mg Drug 2: 4 or 5 mg Steroid dosing range (Low, medium or high): Drug 1: low Delivery device: Drug 1: inhalation suspension Drug 2: oral tab Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 197 Drug 2: 197 Mean age (years): Drug 1: 4.6 Drug 2: 4.7 Sex (% female): Drug 1: 38.1 Drug 2: 31.1 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 12.7 Drug 2: 12.2 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 63 (31.9) Drug 2: 52 (26.4) Adverse events caused withdrawal (%): Drug 1: 2 (1%) Drug 2: 5 (2.5%)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Szefler et al.{Szefler, 2007 #4770} 2007 US Multicenter (55) Astra Zeneca	Intervention: Drug 1 Baseline: BUD Drug 1 Endpoint: BUD Drug 2 Baseline: ML Drug 2 Endpoint: ML Number in group (n): Drug 1: 197 Drug 2: 197	Rescue med use during 24 hour period: Mean change form baseline to end of txt: Drug 1-endpoint: -1.17 Drug 2-endpoint: -1.20 P = NR Rescue med use day: Rescue med-free days, % , mean change form baseline to end of txt: Drug 1 -endpoint: 45.77 (31.38) Drug 2 - endpoint: 48.49 (27.49) P = NR Asthma exacerbations: Number/subject/year (over 52 weeks) D1 end: 1.23 D2 end: 1.63 P = 0.034 Symptom control during 24 hour period: Symptom-free days ("asthma-free days"), %, mean change from baseline to end of txt: D1 end: 27.14 D2 end: 25.64 P = NR Day time symptom control: Daytime symptom score, mean change form baseline to end of txt: D1 - end: -0.67 D2 - end: -0.64 P = NR Night time symptom control: Nighttime symptom score, mean change form baseline to end of txt: D1 - end: -0.65 D2 - end: -0.56 P = NR Courses of steroids: % of subjects receiving course of oral CS over 52 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Szefler et al.{Szefler, 2007 #4770} 2007 US Multicenter (55) Astra Zeneca	Overall adverse events reported (%): Drug 1: NR Drug 2: NR Serious adverse events (%): Drug 1: 5 events (in 4 subjects) Drug 2: 10 events (in 8 subjects) Growth: Drug 1: increases in height from baseline to 52 weeks: 110.1 cm to 116.6cm Drug 2: 110.3 to 117.1cm Sore throat (%): Drug 1: Pharyngitis: 6.1 Drug 2: 10.2 Headache (%): Drug 1: 9.6 Drug 2: 11.2 Upper respiratory tract infection (%): Drug 1: 26.9 Drug 2: 28.9 Death (%): Drug 1: 0 Drug 2: 0 Other (%): Drug 1: Pyrexia: 17.8 Drug 2: 23.4 Other (%): Drug 1: Otitis media: 11.2 Drug 2: 17.3 Other (%): Drug 1: Sinusitis: 12.7 Drug 2: 13.7	Compliance subject reported from diaries was 82.9% for BIS and 82.8% for ML	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
516	Tal et a.{Tal, 2002 #516} 2002 Multinational (48 centers in Belgium, the Czech Republic, Hungary, Israel, South Africa, Spain, and the UK. University Hospitals AstraZeneca	RCT Double-blind Double-dummy 12 weeks 286 NR/NR/NR ITT? Yes	Children of either sex between 4–17 years of age, with a diagnosis of asthma (minimum duration, 6 months), FEV1 40–90% of the predicted value at visit 1, and >/=15% reversibility of FEV1 within 15 min of inhalation of a short-actingb2-agonist, were eligible for inclusion. In addition, patients were to have received treatment with an ICS at a constant dose for at least 6 weeks prior to the study (>/=400 mg BUD Turbuhaler1; >/=600 mg BUD via pressurised metered-dose inhaler; >/=375mg FP propionate; or >/=00 mg CFC-BDP dipropionate via any inhalation device). Patients with a very low or zero asthma symptom score were eligible. Patients meeting the study randomization criteria at visit 2 of FEV1 </= 100% of predicted and a reversibility of >/= 12% (irrespective of their level of asthma symptoms) were randomized. Asthma Severity: Mild Moderate Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Tal et a.{Tal, 2002 #516} 2002 Multinational (48 centers in Belgium, the Czech Republic, Hungary, Israel, South Africa, Spain, and the UK. University Hospitals AstraZeneca	Nasal corticosteroids were allowed during the study. Inhaled terbutaline or salbutamol were used as rescue medication.	unstable asthma (defined as the use of oral, parenteral, or rectal corticosteroids within 30 days of study commencement), any respiratory infection affecting disease control within the previous 4 weeks, and known hypersensitivity to study medication or inhaled lactose. Use of inhaled corticosteroids other than study medication was not allowedthroughout the study.	Yes- 2-4 week run-in to collect data. Patients received BUD 400mcg daily.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Tal et a.{Tal, 2002 #516} 2002 Multinational (48 centers in Belgium, the Czech Republic, Hungary, Israel, South Africa, Spain, and the UK. University Hospitals AstraZeneca	Intervention: Drug 1: BUD / FM Drug 2: BUD Total daily dose: Drug 1: 320 mcg Drug 2: 400 mcg Steroid dosing range: Drug 1: low Drug 2: low Delivery device: Drug 1: Turbuhaler DPI Drug 2: Turbuhaler DPI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 148 Drug 2: 138 Overall: 286 Mean age (years): Drug 1: 11 Drug 2: 11 Sex (% female): Drug 1: 39 Drug 2: 37 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 9 (6) Drug 2: 9 (7) Adverse events caused withdrawal (%): Drug 1: 1 Drug 2: 0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Tal et a.{Tal, 2002 #516} 2002 Multinational (48 centers in Belgium, the Czech Republic, Hungary, Israel, South Africa, Spain, and the UK. University Hospitals AstraZeneca	Intervention: Drug 1 Baseline: BUD/FM Drug 2 Endpoint: BUD Number in group (n): Drug 1- endpoint: 148 Drug 2- endpoint: 138	Rescue med use during 24 hour period: Drug 1- baseline: 0.71 Drug 1-endpoint: change = -0.11 Drug 2-baseline: 0.5 Drug 2-endpoint: -0.09 -0.03 (CI = -0.19 to 0.14) = NS Asthma exacerbations: D1 end: 8 (5.4%) D2 end: 4 (2.9%) P = NR Symptom control during 24 hour period: D1 end: symptom free days % = 77.5 D2 end: 75.1 2.3 (-2.4 to 7) = NS Day time symptom control: D1 - base: Symptom free days D1 - end: 77.5% D2 - end: 75.1% Night time symptom control: D1 - end: night time awakenings % = 5.5 D2 - end: 6.6 -1.1 (-3.6 to 1.3) = NS Nocturnal awakenings: D1 base: 7.2% D1 end: 5.5% D2 base: 8.5% D2 end: 6.6% Asthma Control Score: D1 end: mean total asthma symptom score (0-6) = 0.45 D2 end: 0.48 -0.04 (-0.16 to 0.08) = NS

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Tal et a.{Tal, 2002 #516} 2002 Multinational (48 centers in Belgium, the Czech Republic, Hungary, Israel, South Africa, Spain, and the UK. University Hospitals AstraZeneca	Overall adverse events reported (%): Drug 1: NR Drug 2: NR Serious adverse events (%): Drug 1: 4.7 Drug 2: 0? Cough (%): Drug 1: 5 Drug 2: 5 Headache (%): Drug 1: 6 Drug 2: 4 Respiratory infection (%): Drug 1: 8 Drug 2: 6 Rhinitis (%): Drug 1: 7 Drug 2: 4 Other (%): Drug 1: pharyngitis = 8 Drug 2: 12 Other (%): Drug 1: viral infection = 7 Drug 2: 3 Other (%): Drug 1: aggravated asthma = 5 Drug 2: 3	Adherence Adherence to therapy was assessed by reviewing patient diary cards. Adherence to treatment, as recorded in daily diary cards, was excellent, with a median use of 100% in both groups, and at least 90% of patients taking over 95% of doses.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4771 ICS	Tantisira et al.{Tantisira, 2007 #4771} 2007 CAMP genetics ancillary study not reported in this article "multicenter study-- CAMP" Various NHLBI grants	Study design: Observational Cohort- subgroup analysis of subset of patients within an RCT Duration: 4 years N=311 Enrolled: NR ITT Analysis: NA	: Trial design and methodology have been published elsewhere. Entry criteria included asthma symptoms and/or medication use for ≥6 months in the previous year and airway responsiveness with PC20 ≤12.5 mg/mL. Exclusion criteriaincluded FEV1 <65% of predicted when off b-agonists for >4 hours,other active pulmonary disease, and the inability to perform acceptable spirometry or to complete the study protocol requirements. Asthma severity: not reported in this article

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Tantisira et al.{Tantisira, 2007 #4771} 2007 CAMP genetics ancillary study not reported in this article "multicenter study-- CAMP" Various NHLBI grants	NA	Exclusion criteria included FEV1 <65% of predicted when off b-agonists for >4 hours, other active pulmonary disease, and the inability to perform acceptable spirometry or to complete the study protocol requirements.	Yes: see CAMP; NA for this cohort study

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Tantisira et al.{Tantisira, 2007 #4771} 2007 CAMP genetics ancillary study not reported in this article "multicenter study-- CAMP" Various NHLBI grants	Intervention: Drug 1: ICS no exacerbation Drug 2: ICS yes exacerbation Drug 3: no ICS, no exacerbation Drug 4: no ICS, yes exacerbation Is dosing comparable between treatment groups? NA	Mean age (years): Drug 1: 9.1 Drug 2: 8.8 Drug 3: 9.1 Drug 4: 8.5 Sex (% female): Drug 1: 38.4 Drug 2: 50 Drug 3: 30 Drug 4: 38.7 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Drug 4: NR Groups similar at baseline? Yes	NA

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Tantisira et al.{Tantisira, 2007 #4771} 2007 CAMP genetics ancillary study not reported in this article "multicenter study-- CAMP" Various NHLBI grants	Intervention: Drug 1: ICS no exacerbation Drug 2: ICS yes exacerbation Drug 3: no ICS, no exacerbation Drug 4: no ICS, yes exacerbation # in group (n): Drug 1: 219 Drug 2: 92 Drug 3: 461 Drug 4: 269	90 Relative risk of severe exacerbations while on ICSs: White univariate: 3.88 (1.64-9.21), multivariate: 3.95 (1.64-9.51); African American univariate: 3.20 (1.23-8.31), Multivariate: 3.08 (1.00-9.47); Overall univariate 3.62 (2.02-6.49) Multivariate 3.70 (1.99-6.91)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Tantisira et al.{Tantisira, 2007 #4771} 2007 CAMP genetics ancillary study not reported in this article "multicenter study-- CAMP" Various NHLBI grants	NA	NR	Fair Fair

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
714	Tattersfield et al.{Tattersfield, 2001 #714} 2001 Multinational (France, New Zealand, Spain, UK) multicenter (19) AstraZeneca	Study design: RCT : open label, minimum effective dose Duration: 24 months N=377 (239 analyzed) Enrolled: 511 enrolled; 377 randomised; 374 started treatment; 239 completed the 2 year study	Age: 20-60 FEV1 expressed as a percent of the predicted value: >/= 65% Previous use of corticosteroids: no corticosteroid treatment by any route during the previous 3 months (apart from 1% hydrocortisone cream) and no more than 1 month of treatment with oral corticosteroids in the previous year or inhaled or nasal corticosteroids in the previous 6 months Other: at least four puffs of a short acting β2-agonist and show less than 25% variability in morning peak expiratory flow (PEF, expressed as a percentage of the highest value) during the last 7 days of the run in period with complete data. Asthma Severity: Mild

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Tattersfield et al.{Tattersfield, 2001 #714} 2001 Multinational (France, New Zealand, Spain, UK) multicenter (19) AstraZeneca	For subjects in the reference group the study doctors were asked to prescribe any asthma treatment they considered appropriate other than an inhaled corticosteroid—for example, a long acting B2 agonist, sodium cromoglycate, nedocromil sodium, ipratropium bromide or theophylline.	Pregnant or lactating Prior treatment: drugs known to affect bone mineral density Concommitant diseases: any other medical conditions : had required more than 2 weeks of bed rest in the previous 6 months	Yes: After a 2–4 week run in period in which subjects took their usual treatment, those fulfilling the entry criteria were randomised (entry criteria was showless than 25% variability in morning peak expiratory flow (PEF, expressed as a percentage of the highest value) during the last 7 days of the run in period.)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Tattersfield et al.{Tattersfield, 2001 #714} 2001 Multinational (France, New Zealand, Spain, UK) multicenter (19) AstraZeneca	Intervention: Drug 1: BUD Drug 2: BDP Drug 3: non-steriod treatment "placebo" Total daily dose: Drug 1: adjustable dosing; median for completers: 389 mcg; range 133-1729 Drug 2: 499 mcg; 176-1906 Drug 3: 0 mcg Steroid dosing range (Low, medium or high): Drug 1: range low-high Drug 2: range low-high Delivery device: Drug 1: dpi - turbohaler Drug 2: MDI with spacer Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 87 Drug 2: 74 Drug 3: 78 Mean age (years): Drug 1: 37 Drug 2: 36 Drug 3: 36 Sex (% female): Drug 1: 56 Drug 2: 56 Drug 3: 49 Current smokers (%): Drug 1: 19 Drug 2: 17 Drug 3: 22 Optional - Disease duration (years): Drug 1: 13 Drug 2: 13 Drug 3: 13 Optional - Rescue medication use (puffs per day): Drug 1: 3.2 Drug 2: 2.9 Drug 3: 2.7 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Other: Drug 1: Mean BMD: Lumbar Spine 1.15; Hip 0.96; Total body 1.17 Drug 2: Mean BMD: Lumbar Spine	Number (%) withdrawn: Drug 1: 38 (30.4%) Drug 2: 46 (38.3) Drug 3: 51 (39.5) Overall: 36% Optional - Withdrew due to lack of efficacy (%): Drug 1: 0 Drug 2: 1.4 Drug 3: 10.3 Adverse events caused withdrawal (%): Drug 1: 4.6 Drug 2: 2.7 Drug 3: 6.4 Optional - Protocol violation (%): Drug 1: 39.1 Drug 2: 58.1 Drug 3: 48.7

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Tattersfield et al.{Tattersfield, 2001 #714} 2001 Multinational (France, New Zealand, Spain, UK) multicenter (19) AstraZeneca	Intervention: Drug 1: BUD Drug 2: BDP Drug 3: non-steriod treatment "placebo" Number in group (n): Drug 1: 87 Drug 2: 74 Drug 3: 78	Other Relevant Health Outcome Results: No significant differences between BUD and BDP for day or nighttime symptom scores; data NR, shown in figure

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Tattersfield et al.{Tattersfield, 2001 #714} 2001 Multinational (France, New Zealand, Spain, UK) multicenter (19) AstraZeneca	Oral candidiasis- thrush (%): Drug 1: 3 Drug 2: 2 Drug 3: 0 Dysphonia (%): Drug 1: 2 Drug 2: 1 Drug 3: 1 Upper respiratory tract infection (%): Drug 1: 20 Drug 2: 23 Drug 3: 12 Reduction in bone mineral density (%): Drug 1: Mean (SD)Lumbar spine n=77 Month 6 –0.1 (2.7),Month 12 0.4 (3.2),Month 24 0.1 (3.3); Neck of femur n=79 Month 6 –0.2 (3.1), Month 12 –0.7 (3.3), Month 24 –0.9 (3.7); Total body n=70 Month 6 –0.1 (2.1),Month 12 0.3 (1.9), Month 24 0.6 (2.2) Drug 2: BDP n Mean (SD)Lumbar spine 68Month 6 -0.1 (2.8) Month 12 –0.1 (2.8)Month 24 –0.4 (3.7) Neck of femur 70 Month 6 –0.3 (3.6)Month 12 –0.8 (4.3)Month 24 –0.9 (4.5)Total body 60Month 6 –0.1 (1.6)Month 12 0.2 (1.8)Month 24 0.4 (2.3) Drug 3: Reference n Mean (SD)Lumbar spine 75Month 6 0.5 (2.4)Month 12 –0.0 (2.6)Month 24 0.4 (3.5)Neck of femur 75Month 6 –0.7 (3.2)Month 12 –0.3 (3.6)Month 24 –0.4 (4.1)Total body 70 60 64Month 6 0.4 (2.2)Month 12 0.5 (2.3)Month 24 0.9 (2.3) Drug 4Drug 5: NS Fractures (%): Drug 1: 1.1 Drug 2: 0 Drug 3: 0 Other (%): Drug 1: back pain 7 Drug 2: 8 Drug 3: 2	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4844 ICS	van Aalderen et al.{van Aalderen, 2007 #4844} 2007 Multinational (Belgium, Netherlands, UK) Multicenter (46 sites) writing support from Prime Medica...; Ivax pharmaceuticals	Study design: RCT Double-blind Double-dummy Duration:18 weeks (primary efficacy outcome at 6 weeks; step-down dose in next 2 6 week phases) N=280 Enrolled: NR/NR/280 ITT Analysis: Yes	: Male and female patients (aged 5–12 yr) with an asthma diagnosis for at least 3 months, PEF >/=60% of predicted normal (after withholding β2-agonist therapy for >/=4 h), suboptimal asthma control requiring the initiation of, or an increase in current ICS therapy (CFC-BDP 200 mcg/day or equivalent), currently using a short-acting β2-agonist on an as-required basis, and able to use a mini-Wright PEF meter correctly. Asthma severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
van Aalderen et al.{van Aalderen, 2007 #4844} 2007 Multinational (Belgium, Netherlands, UK) Multicenter (46 sites) writing support from Prime Medica...; Ivax pharmaceuticals	Nasal steroid therapy (equivalent to >/= 400 mcg.day BDP), provided that the dose remained constant for 4 weeks before study entry and throughout the study, and oral antihistamines (excluding astemizole) were permitted; inhaled b2-agonist therapy was continued throughout study on an as-required basis	Other? (Please list all): an acute upper respiratory tract infection within 2 weeks or a lowerrespiratory tract infection within 4 weeks of the screening visit or during the run-in period, or if they had other unstable or untreated chronic conditions; use of sodium chromones, theophylline, anticholinergics, long-acting b2-agonists (salmeterol and formoterol), leukotriene antagonists and 5-lipoxygenase inhibitors was not permitted in the 2 weeks before the screening visit, during the run-in period or during the double-blind treatment period; medications, such as oral or parenteral steroids, salmeterol in combination with FP, monoamine oxidase inhibitors, tricyclic antidepressants, b-blockers (including eye drops) and oral b2-agonists within 4 weeks of the screening visit or during the run-in period were also prohibited.	Yes- elucidate....: 2 week run-in period during which patients continued their current asthma therapy

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
van Aalderen et al.{van Aalderen, 2007 #4844} 2007 Multinational (Belgium, Netherlands, UK) Multicenter (46 sites) writing support from Prime Medica...; Ivax pharmaceuticals	Intervention: Drug 1: BDP Drug 2: FP Total daily dose: Drug 1: 200 mcg (dose could be stepped down after 6 weeks) Drug 2: 200 mcg (dose could be stepped down after 6 weeks) Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Delivery device: Drug 1: AeroChamber Plus Drug 2: Volumatic spacer Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 139 Drug 2: 141 Mean age (years): Drug 1: 8.3 Drug 2: 8.6 Sex (% female): Drug 1: 45 Drug 2: 38 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 6 wks/18 wks: 7.9%/62% Drug 2: 5.7%/59% Optional - Withdrew due to lack of efficacy (%): Drug 1: 6 wks/18 wks: 0.72%/37.4% Drug 2: 1.4%/41.1% Adverse events caused withdrawal (%): Drug 1: 3,6% (doesn't specify whether over 6 weeks or 18 weeks) Drug 2: <1%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
van Aalderen et al.{van Aalderen, 2007 #4844} 2007 Multinational (Belgium, Netherlands, UK) Multicenter (46 sites) writing support from Prime Medica...; Ivax pharmaceuticals	Intervention: Drug 1 Baseline: BDP Drug 1 Endpoint: BDP 6 wks Drug 2 Baseline: FP Drug 2 Endpoint: FP 6 wks Number in group (n): Drug 1- baseline: 139 Drug 2- baseline: 140	Rescue med use day: Drug 1- baseline: mean # puffs: 1.59 Drug 1 -endpoint: 0.73 Drug 2 - baseline: 1.40 Drug 2 - endpoint: 0.69 P = 0.505 Day time symptom control: % change from baseline in symptom-free days: D1 - end: 32.5% D2 - end: 32.5% P = 0.897 Night time symptom control: % change from baseline in nights without sleep disturbance: D1 - end: 17.5% D2 - end: 20.8% P = 0.561 Other Asthma QOL instrument: PAQLQ (% of pateints showing clinically significant improvement during 1st 6 wks): D1 end: 68% D2 end: 50% P=1.00 General QOL instrument: PACQLQ (% of pateints showing clinically significant improvement during 1st 6 wks): D1 end: 44% D2 end: 42% P = 0.369 Other: "Good asthma control": D1 end : 36% D2 end: 42% P = NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
van Aalderen et al.{van Aalderen, 2007 #4844} 2007 Multinational (Belgium, Netherlands, UK) Multicenter (46 sites) writing support from Prime Medica...; Ivax pharmaceuticals	Overall adverse events reported (%): Drug 1: 47% Drug 2: 49% P = NS Severe adverse events (%): Drug 1: 1% Drug 2: 0 Upper respiratory tract infection (%): Drug 1: 19% Drug 2: 21% Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: There were no clinically relevant trends in urinary free cortisol levels (measured in 59 patients in The Netherlands) Additional adverse events and comments: There were no clinically relevant trends in vital signs, or use of concomitant medication, and no clinically relevant changes were noted on physical examination.	Compliance Treatment compliance was assessed before and after each 6-week treatment period based on the weight difference between used and unused inhaler canisters of active study medication; this was then converted into the number of actuations. A patient was considered compliant if his/her total number of calculated actuations was between >70% and <130% of the predicted. Mean compliance in the ITT population during weeks 1–6 was 81.6% in the BDP extrafine aerosol group and 73.8% in the CFC-FP group. During the entire study period, compliance was 79.5% and 73.2%, respectively.	Fair- inadequate reporting; Attirtion was not high at 6 weeks; attrition was high at the end of 18 weeks. However, primary efficacy endpoint was at 6 weeks; patients were withdawn if asthma poorly or not controlled; patients with intermediate control continued at same dose; patients with good control had dose stepped down during next 2 phases of study

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1090	van der Molen et al.{van der Molen, 1997 #1090} 1997 Canada and the Netherlands Multicenter Astra Draco AB	Study design: RCT double-blind parallel-group study Duration: 24 weeks N=239 ITT Analysis: Yes	regular use of any dose of ICSs, the use of at least five inhalations of a short acting β2-agonist per week before entry visit, and >15% reversibility in baseline FEV1 after two inhalations of 250 lg terbutaline or the equivalent dose of salbutamol

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
van der Molen et al.{van der Molen, 1997 #1090} 1997 Canada and the Netherlands Multicenter Astra Draco AB	NA	use of oral corticosteroids at any time in the last month, smoking history of >20 pack years, FEV1 of <40% predicted, or an exacerbation of asthma symptoms during the previous month.	Wash out of 4 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
van der Molen et al.{van der Molen, 1997 #1090} 1997 Canada and the Netherlands Multicenter Astra Draco AB	Intervention: Drug 1: FM Drug 2: Placebo Total daily dose: Drug 1: 24 µg Drug 2: NA Steroid dosing range: NA Delivery device: Drug 1: Turbohaler Drug 2: Turbohaler Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 125 Drug 2: 114 Mean age (years): Drug 1: 40.5 Drug 2: 45.4 Sex (% female): Drug 1: 51.2 Drug 2: 50.2	Number (%) withdrawn: Drug 1: 15.8 Drug 2: 10.4 Adverse events caused withdrawal (%): Drug 1: 4 Drug 2: 1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
van der Molen et al.{van der Molen, 1997 #1090} 1997 Canada and the Netherlands Multicenter Astra Draco AB	Intervention: Drug 1: ICS + FM DPI (48) Drug 2: ICS + placebo DPI Number in group (n): Drug 1:125 Drug 2: 114	Symptoms: ICS + FM > ICS + placebo Improvement in symptom score from baseline: 1.28 vs 0.64, between group difference=0.64, P=0.039 Exacerbations: No difference [# (%) of subjects requiring courses of oral prednisolone: 33 (26.4%) vs 32 (28.1%), difference between groups P=NS; # of courses of prednisolone: 58 vs 55; P=NS] Rescue med use: ICS + FM > ICS + placebo [decrease in mean daytime # inhalations: 1.5 (from 2.4 at baseline to treatment mean 0.9) vs 0.4, between group difference= -1.1 (95% CI -1.4, -0.7; P<0.001); decrease in mean nighttime # inhalations: 0.9 (from 1.5 at baseline to treatment mean 0.6) vs 0.2 , between group difference== -0.8 (95% CI -1.1, -0.5; P<0.001)]

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
van der Molen et al.{van der Molen, 1997 #1090} 1997 Canada and the Netherlands Multicenter Astra Draco AB	Tremor (n): Drug 1: 3 Bronchospasm (n): Drug 1: 1 Rash (n): Drug 1: 1	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
931	van Noord et al.{van Noord, 1999 #931} 1999 The Netherlands Multicenter (27) Glaxo Wellcome	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=274 Enrolled: 369 recruited/274 eligiable after run in ITT Analysis: No another type of analysis was used (define): done in 14 day batches…	: Asthmatic patients aged at least 18 years and receiving 400–600 µg BDP or 800–1200 µg BUD daily; at end of run-in (1) FEV1 at least 50% of the predicted value at visit 3; (2) an increase in FEV1 of at least 10% predicted FEV1 from baseline after inhalation of 400 µg salbutamol from a metered dose inhaler or 800 µg from a dry powder inhaler at visit 1, 2 or 3, or during the month prior to the run in period; (3) either a total daytime plus night time symptom scoreof >1, or a diurnal variation in peak expiratory flow (PEF) of at least 15%, or use of rescue salbutamol on two or more occasions per 24 hours on at least four days of the last two weeks of the run in period. Asthma Severity: Mild Moderate Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
van Noord et al.{van Noord, 1999 #931} 1999 The Netherlands Multicenter (27) Glaxo Wellcome	Methylxanthines and anticholinergics were permitted in stable doses	Other: changed their asthma medication in the preceding six weeks; used oral steroids in the previous three months; upper or lower respiratory tract infection requiring antibiotic treatment;been admitted to hospital for their asthma in the previous month.	Yes: four week run in period of treatment with FP (100 ìg twice daily if pre-trial dose was 400–600 ìg inhaled corticosteroids or 250 ìg twice daily if pre-trial dose was 800–1200 ìg ICS); stratified into low and high dose ICS

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
van Noord et al.{van Noord, 1999 #931} 1999 The Netherlands Multicenter (27) Glaxo Wellcome	Intervention: Drug 1: FP + SM Drug 2: FP Total daily dose: Drug 1: 200 or 500 + 100 Drug 2: 400 or 1000 Steroid dosing range (Low, medium or high): Drug 1: Low or med Drug 2: med or high Delivery device: Drug 1: Diskhaler Drug 2: Diskhaler Is dosing comparable between treatment groups? NA: combo vs ICS alone	# in group (n): Drug 1: 139 Drug 2: 135 Mean age (years): Drug 1: 46 Drug 2: 47 Sex (% female): Drug 1: 53 Drug 2: 50 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 6 (4) Drug 2: 9 (7)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
van Noord et al.{van Noord, 1999 #931} 1999 The Netherlands Multicenter (27) Glaxo Wellcome	Intervention: Drug 1 Baseline: FP + SM Drug 1 Endpoint: FP + SM Drug 2 Baseline: FP Drug 2 Endpoint: FP Number in group (n): Drug 1: 139 Drug 2: 135	Other Relevant Health Outcome Results: odds ratios (OR) of FP versus SLM treatment night time use of rescue salbutamol, OR 1.47 (95% CI 1.04 to 2.10), p = 0.03; daytime use of rescue salbutamol, OR 2.19 (95% CI 1.42 to 3.40), p<0.001; days with symptoms, OR 1.52 (95% CI 1.01 to 2.28), p = 0.04; 16 patients (12%) in the SLM group and 15 patients (11%) in the FP group received a course of oral steroids (p NR)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
van Noord et al.{van Noord, 1999 #931} 1999 The Netherlands Multicenter (27) Glaxo Wellcome	Additional adverse events and comments: Reported adverse events at the scheduled visits were not significantly different in the two treatment groups. There were four withdrawals because of an adverse event, all in the FP group.	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4747	van Staa et al.{van Staa, 2001 #4747} 2001 UK Primary care database Proctor and Gamble	Study design: Observational Database analysis : retrospective cohort Duration: Mean duration of follow-up per subject (years): ICS 1.7; Bronchodilator: 1.1; Control: 2.7 N=450/422 Enrolled: NR ITT Analysis: Not applicable	: The ICS users were defined as permanently registered patients aged 18 years orolder who received one or more prescriptions for inhaled corticosteroids during the period of time from the enrollment date of their practice in the GPRD up to the end of data collection (December 1997). Asthma Severity: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
van Staa et al.{van Staa, 2001 #4747} 2001 UK Primary care database Proctor and Gamble	Controlled for anticonvulsants, methotrexate, thiazide diuretics, anxiolytics, antipsychotics, antidepressants, anti-Parkinson drugs, hormone replacement therapy, bisphosphonates, vitamin D, calcitonin	Inhaled corticosteroid users who received a prescription for oral corticosteroids in the period of time from 6 months before to 91 days after the last inhaled corticosteroid prescription were excluded from the analysis	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
van Staa et al.{van Staa, 2001 #4747} 2001 UK Primary care database Proctor and Gamble	Intervention: Drug 1: ICS Drug 2: Bronchodilator only Drug 3: Control Total daily dose: Drug 1: <300- 300-700 - >700 mcg Drug 2: N/A Drug 3: N/A Steroid dosing range (Low, medium or high): Drug 1: Low-Medium-High Delivery device: Drug 1: Any Drug 2: N/A Drug 3: N/A Is dosing comparable between treatment groups? Not applicable- Dosing was comparable within ICS group for BDP, BUD, and FP	# in group (n): Drug 1: 170,818 Drug 2: 108,786 Drug 3: 170,818 Mean age (years): Drug 1: 45 Drug 2: 49 Drug 3: 45 Sex (% female): Drug 1: 55 Drug 2: 61 Drug 3: 55 Current use of ICS at baseline (%): Drug 1: 100 Other: Drug 1: nonvertebral fracture in prior year (%): 1.2 Drug 2: 1.2 Drug 3: 1.1 Other: Drug 1: vertebral fracture in prior year (%): 0.05 Drug 2: 0.06 Drug 3: 0.04 Other: Drug 1: RA: 0.7 Drug 2: 1.1 Drug 3: 0.7	Number (%) withdrawn: Drug 1: N/A Drug 2: N/A Drug 3: N/A

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
van Staa et al.{van Staa, 2001 #4747} 2001 UK Primary care database Proctor and Gamble	Intervention: Drug 1: ICS Drug 2: Bronchodilator only Drug 3: Control Number in group (n): Drug 1: 170,818 Drug 2: 108,786 Drug 3: 170,818	Other Relevant Health Outcome Results: During follow-up, the incidence of nonvertebral fractures was 1.4 fractures per 100 person-years in the ICS group, 1.4 in the bronchodilator group, and 1.1 in the control group. After adjustment for potential confounding variables (coexisting disease, concomitant drug treatment, and a baseline history of fracture or back pain), the rate of nonvertebral fractures was significantly elevated among ICS users when compared with control patients (RR=1.15; 95% CI, 1.10–1.20). No difference was apparent in nonvertebral fracture risk between the ICS and bronchodilator groups (RR=1.00; 95% CI, 0.94–1.06). The crude RR in the ICS group compared with the bronchodilator group was 0.95 (95% CI, 0.90–1.01) and the RR adjusted for age and gender was 0.99 (95% CI, 0.94–1.05). ICS users also had a significantly higher rate of hip fracture than controls (RR=1.22; 95% CI,1.04–1.43); again the rate was similar to that of the bronchodilator group (RR=1.20; 95% CI, 0.99–1.45). The rate of nonvertebral fractures among users of budesonide (RR=0.95; 95% CI, 0.85–1.07) and FP (RR= 1.03; 95% CI, 0.71–1.49) was similar to that of BDP. Comparing the ICS users with the control group, a dose response was found for hip

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
van Staa et al.{van Staa, 2001 #4747} 2001 UK Primary care database Proctor and Gamble	Fractures (%): Drug 1: see above	NR	

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1018	Verberne et al.{Verberne , 1998 #1018} 1998 outpatient clinics of 9 hospitals, 6 university hospitals, and 3 general hospitals, unclear whether set only in the Netherlands or multinational Glaxo Wellcome BV	Study design: RCT Double-blind Duration: 1 year N=177 Enrolled: Nr/NR/177 ITT Analysis: Unable to determine: cannot tell, possibly LOCF	Age: 6-16 FEV1 expressed as a percent of the predicted value: 55-90 and/or FEV1: FVC 50-75% predicted Reversability of FEV1: 10% s/p 0.8mg salbutamol Previous use of corticosteroids: used ICS between 200 and 800mg daily for at least 3 mo before thestart of the study Other: airway hyper responsiveness to methacholine, i.e., a 20% fall in FEV1 after inhalation of 150mg or less methacholine (PD20 methacholine), which is more than two standard deviations below the mean value in healthy children; an ability to produce reproducible lung functiontests, i.e., a variation in three consecutive measurements of FEV1 of less than 5%; a history of stable asthma for at least 1 mo without exacerbations or respiratory tract infections Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Verberne et al.{Verberne , 1998 #1018} 1998 outpatient clinics of 9 hospitals, 6 university hospitals, and 3 general hospitals, unclear whether set only in the Netherlands or multinational Glaxo Wellcome BV	salbutamol 200mg on demand was allowed as rescue medication, with a maximum of 6 inhalations per day. standard course of prednisolone if maximum allowed salbutamol was ineffective		Yes: 6wk run-in period during which all patients received beclomethasone 200mg twice a day; salbutamol 200mg on demand was allowed as rescue medication, with a maximum of 6 inhalations per day

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Verberne et al.{Verberne , 1998 #1018} 1998 outpatient clinics of 9 hospitals, 6 university hospitals, and 3 general hospitals, unclear whether set only in the Netherlands or multinational Glaxo Wellcome BV	Intervention: Drug 1: BDP400/SM Drug 2: BDP800 Drug 3: BDP400 Total daily dose: Drug 1: 400mcg/100mcg Drug 2: 800mcg Drug 3: 400mcg Steroid dosing range (Low, medium or high): Drug 1: med to high Drug 2: high Drug 3: med to high Delivery device: Drug 1: Rotadisk/Diskhaler Drug 2: Rotadisk/Diskhaler Drug 3: Rotadisk/Diskhaler Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 60 Drug 2: 60 Drug 3: 57 Mean age (years): Drug 1: 10.8 Drug 2: 11.4 Drug 3: 11.1 Sex (% female): Drug 1: 33.3 Drug 2: 40 Drug 3: 36.8 Current smokers (%): Drug 1: NR Drug 2: NR Drug 3: NR Optional - Disease duration (years): Drug 1: 7.8 Drug 2: 9.0 Drug 3: 8.5 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Optional - Current use of Cromolyn Sodium (%): Drug 1: ICS dose, mcg 490 Drug 2: 503	Number (%) withdrawn: Drug 1: 5 Drug 2: 6 Drug 3: 4 Optional - Withdrew due to asthma exacerbations (%): Drug 1: 0 Drug 2: 0 Drug 3: 1.7 Adverse events caused withdrawal (%): Drug 1: 3.3 Drug 2: 1.7 Drug 3: 0 Optional - Other reasons for withdrawal (%): Drug 1: lost to f/u or noncompliance 5 Drug 2: 8.3 Drug 3: 5.3

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Verberne et al.{Verberne , 1998 #1018} 1998 outpatient clinics of 9 hospitals, 6 university hospitals, and 3 general hospitals, unclear whether set only in the Netherlands or multinational Glaxo Wellcome BV	Intervention: Drug 1 Baseline: BDP400/SM Drug 1 Endpoint: BDP400/SM Drug 2 Baseline: BDP800 Drug 2 Endpoint: BDP800 Drug 3 Baseline: BDP400 Drug 3 Endpoint: BDP400 Number in group (n): Drug 1- baseline: 60 Drug 1- endpoint: 60 Drug 2- baseline: 60 Drug 2- endpoint: 60 Drug 3- baseline: 57 Drug 3- endpoint: 57	Rescue med use during 24 hour period: Mmedian # of additional salbutamol inhalations: Drug 1-endpoint: 0.19 Drug 2-endpoint: 0.33 Drug 3- endpoint: 0.15 BDP800 vs BDP400 P = 0.06, other comparisons P = NR Symptom control during 24 hour period: D1 base: % of children reporting no symptoms during 2wk diary card periods, 3 D1 end: 34 D2 base: 13 D2 end: 39 D3 base: 11 D3 end: 35 P = NS Courses of steroids: Number prednisolone courses for exacerbations/number of patients: D1 end: 13/10 D2 end: 8/7 D3 end: 13/10 P = NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Verberne et al.{Verberne , 1998 #1018} 1998 outpatient clinics of 9 hospitals, 6 university hospitals, and 3 general hospitals, unclear whether set only in the Netherlands or multinational Glaxo Wellcome BV	Overall adverse events reported (%): Drug 1: 98 Drug 2: 87 Drug 3: 93 Growth: Drug 1: 5.1 (4.5, 5.7) Drug 2: 3.6 (3.0, 4.2) Drug 3: 4.5 (3.8, 5.2) Drug 5: 95%CI shown in ( ) Cough (%): Drug 1: 20 Drug 2: 27 Drug 3: 23 Headache (%): Drug 1: 42 Drug 2: 27 Drug 3: 41 Upper respiratory tract infection (%): Drug 1: 27 Drug 2: 25 Drug 3: 16 Respiratory infection (%): Drug 1: viral 28 Drug 2: 30 Drug 3: 25 Rhinitis (%): Drug 1: 35 Drug 2: 33 Drug 3: 25 Other (%): Drug 1: fever 20 Drug 2: 12 Drug 3: 14 Other (%): Drug 1: nausea&vomiting 18 Drug 2: 8 Drug 3: 13 Other (%): Drug 1: diarrhea 13 Drug 2: 3 Drug 3: 7 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: Heights were also expressed as standard deviation scores (SDS) using Dutch reference growth charts. A slightly greater proportion of patients were prepubertal in the BDP400 group (47%) than in the BDP 4001SM (43%) or BDP 800 (35%) groups. The reductions in	Compliance Compliance with study treatment was slightly better in the BDP400+SM group than in the BDP800 (p=0.01) and the BDP400 group (p=0.01). The median number of blisters of study medication used per day were 1.88, 1.77, and 1.75 in the BDP400+SM, BDP800, and BDP400 groups, respectively; i.e., 94%, 89%, and 88% of the prescribed study medication. Compliance with maintenance beclomethasone treatment was comparable to that with study medication; the median number of blisters per day were 1.89, 1.81, and 1.75, respectively.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1082	Verberne et al.{Verberne, 1997 #1082} 1997 Netherlands Hospital pediatric outpatient clinic Glaxo Wellcome B.V., Zeist, The Netherlands	Study design: RCT Double-blind Duration: 52 weeks N=67 Enrolled: NR/NR/67 ITT Analysis: Unable to determine	Age: 6-16 : (1) FEV1 that was 55–90% of predicted value and/or a ratio of FEV1 to FVC that was 50–75%; (2) an increase of at least 10% in FEV1 after inhalation of 0.8 mg salbutamol; (3) airway hyper responsiveness to methacholine, i.e., a 20% fall in FEV1 after inhalation of 150 mcg or less methacholine (PD20 methacholine); this being morethan 2 SD below the mean value in healthy children; (4) an ability to produce reproducible lung function tests, i.e., a variation in 3 consecutive measurements of FEV1 of less than 5%; (5) a history of stable asthma for at least 1 momth without exacerbations or respiratory tract infections; (6) not used ICS in the previous six mo or cromoglycate in the previous 2 wks. Asthma Severity: Mild Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Verberne et al.{Verberne, 1997 #1082} 1997 Netherlands Hospital pediatric outpatient clinic Glaxo Wellcome B.V., Zeist, The Netherlands	Salbutamol 2--mcg allowed with maximum dose of 6 inhalations/day. Asthma symptoms, which did not sufficiently improve with the maximum dose of rescue salbutamol, were treated with a standard course of prednisolone.		Yes.: 6 week run in period during which the only medication allowed was salbutamol 200 mcg on demand, with a maximum of six inhalations/day. In the first and the last week of the run-in period measurements of FEV1 and FVC before and after bronchodilatation and measurements of PD20 methacholine were performed. Lung function inclusion criteria had to be fullfilled at one of these visits.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Verberne et al.{Verberne, 1997 #1082} 1997 Netherlands Hospital pediatric outpatient clinic Glaxo Wellcome B.V., Zeist, The Netherlands	Intervention: Drug 1: SM Drug 2: BDP Total daily dose: Drug 1: 100 mcg Drug 2: 400 mcg Steroid dosing range (Low, medium or high): Drug 1: N/A Drug 2: medium Delivery device: Drug 1: Rotakisk in combination with Diskhaler Drug 2: Rotadisk in combination with Diskhaler Is dosing comparable between treatment groups? NA: LABA vs. ICS	# in group (n): Drug 1: 32 Drug 2: 35 Mean age (years): Drug 1: 10.6 Drug 2: 10.5 Sex (% female): Drug 1: 28 Drug 2: 37 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Previous ICS use (%): Drug 1: 16 Drug 2: 17 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Other: Drug 1: Atopy status=none (%): 0 Drug 2: 17 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 7 (22%) Drug 2: 3 (9%) Optional - Withdrew due to asthma exacerbations (%): Drug 1: 19 Drug 2: 3 Adverse events caused withdrawal (%): Drug 1: 3 Drug 2: 0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Verberne et al.{Verberne, 1997 #1082} 1997 Netherlands Hospital pediatric outpatient clinic Glaxo Wellcome B.V., Zeist, The Netherlands	Intervention: Drug 1 Baseline: SM Drug 1 Endpoint: SM Drug 2 Baseline: BDP Drug 2 Endpoint: BDP Number in group (n): Drug 1: 32 Drug 2: 35	Rescue med use during 24 hour period: Drug 1- baseline: median number of additional salbutamol inhalations per day: Drug 1-endpoint: 0.44 Drug 2-endpoint: 0.07 P = 0.0001 Symptom control during 24 hour period: D1 base: % of children reporting no symptoms during 2 week diary card period of run-in: 3% D1 end: during 2week diary card period after 1 year: 36% D2 base: 6% D2 end: 55% P = NR Courses of steroids: D1 base: # of steroid courses/ # of patients receiving a steroid course D1 end: 17/15 D2 end: 2/2 P = NR Other Relevant Health Outcome Results: Daytime and nighttime symptoms diminished in both treatment groups, with fewer symptoms in the patients treated with BDP. However, the difference between SM and BDP was only significant at some time points. The percentage of children in the BDP treated group reporting no symptoms during the 2-wk diary card periods increased from 6% in the run-in period to 55% after 1 yr of treatment. In comparison, 3% and 36% were asymptomatic during the corresponding periods in the SM treated group. The need for additional salbutamol during daytime and nightt

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Verberne et al.{Verberne, 1997 #1082} 1997 Netherlands Hospital pediatric outpatient clinic Glaxo Wellcome B.V., Zeist, The Netherlands	Overall adverse events reported (%): Drug 1: 94 Drug 2: 89 Cough (%): Drug 1: 9 Drug 2: 23 Sore throat (%): Drug 1: 6 Drug 2: 9 Headache (%): Drug 1: 19 Drug 2: 31 Upper respiratory tract infection (%): Drug 1: 9 Drug 2: 14 Rhinitis (%): Drug 1: 28 Drug 2: 14 Other (%): Drug 1: fever: 25 Drug 2: 11 Other (%): Drug 1: nausea/vomiting: 22 Drug 2: 11 Other (%): Drug 1: fatigue: 13 Drug 2: 29 Additional adverse events and comments: At no point during the treatment period were any significant changes in heart rate and systolic and diastolic blood pressure found in either treatment group. The mean increase in height was 6.1 cm (95% CI 5.3; 6.9) in the SM treated group, compared with 4.7 cm (95% CI 4.0; 5.3) in the BDP treated group (P=0.007). SDS showed a change of -0.03 SDS in the patients treated with SM compared to -0.28 SDS in the patients treated with BDP (P=0.001). No interaction was found with gender. A significant interaction (P=0.03) was found with puberty; the mean difference in SDS between groups was -0.10 (95% CI 20.29; 0.10) for patients with puberty stages 2 and more and	Compliance Compliance with study treatment did not differ between the groups: the median number of blisters used per day were 1.82 and 1.84 in the SM and BDP groups, respectively; i.e., 91 and 92%, respectively, of the prescribed study medication was used.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
953	Vermetten, 1999 #953} 1999 Netherlands Primary care NR: but correspondance is with author at Glaxo	Study design: RCT Double-blind Duration: 12 weeks N=233 Enrolled: 411 recruited, 233 randomized	: 18 to 66 years; on ICS for at least 6 weeks; and needed salbutamol as well; no recent exacerbations; Rev PEF at least 15%, and predicted value at least 60% Asthma Severity: Mild

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Vermetten, 1999 #953} 1999 Netherlands Primary care NR: but correspondance is with author at Glaxo	none that treated asthma	Other: asthma exacerbation during run-in. And only one was allowed during trial	Yes: 2 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Vermetten, 1999 #953} 1999 Netherlands Primary care NR: but correspondance is with author at Glaxo	Intervention: Drug 1: BDP + BDP Drug 2: BDP + SM Total daily dose: Drug 1: 200-400/400 Drug 2: 200-400/200 Steroid dosing range (Low, medium or high): Drug 1: low/med Drug 2: low Delivery device: Drug 1: diskhaler Drug 2: diskhaler Is dosing comparable between treatment groups? NA: ICS vs LABA	# in group (n): Drug 1: 120 Drug 2: 113 Mean age (years): Drug 1: 42 Drug 2: 42 Sex (% female): Drug 1: 62 Drug 2: 47 Current smokers (%): Drug 1: 33 Drug 2: 33 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? NR: sex, otherwise similar, difference not likely to affect results	Number (%) withdrawn: Drug 1: NR Drug 2: NR Overall: overall 31 (13) Adverse events caused withdrawal (%): Drug 1: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Vermetten, 1999 #953} 1999 Netherlands Primary care NR: but correspondance is with author at Glaxo	Intervention: Drug 1 Baseline: BDP Drug 1 Endpoint: BDP Drug 2 Baseline: SM Drug 2 Endpoint: SM **Check interventions** Number in group (n): Drug 1: 120 Drug 2: 113	Rescue med use day: (SE) Drug 1- baseline: average # of rescue blisters needed per day: 0.84 (0.09) Drug 1 -endpoint: 0.61 ().10)) Drug 2 - baseline: 0.88 (0.09) Drug 2 - endpoint: 0.48 (0.07) P < 0.05 Rescue med use at night (SE): Drug 1- baseline: 0.47 (0.05) Drug 1 - endpoint: 0.37 (0.06) Drug 2 - baseline: 0.47 (0.06) Drug 2 - endpoint: 0.30 (0.06) P = NS Asthma exacerbations: D1 end: 14 D2 end: 8 P = NS Day time symptom control: D1 - base: average proportion of days with symptoms (SE): 0.54 (0.03) D1 - end: 0.38 (0.04) D2 - base: 0.56 (0.04) D2 - end: 0.37 (0.04) P = NS Night time symptom control: (SE) D1 - base: 0.41 (0.03) D1 - end: 0.34 (0.04) D2 - base: 0.43 (0.04) D2 - end: 0.33 (0.04) P: P = NS Other Asthma QOL instrument: D1 base: overall Hyland Quality of life questionnaire: P= NS

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Vermetten, 1999 #953} 1999 Netherlands Primary care NR: but correspondance is with author at Glaxo	Headache (%): Drug 1: 14 Drug 2: 12 Other (%): Drug 1: Tremor 0 Drug 2: 3 Other (%): Drug 1: palpitation 0 Drug 2: 3 Other (%): Drug 1: medical/pulmonary problems 16/25 Drug 2: 32/32 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: None reported	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
2298	Vervloet et al.{Vervloet, 1998 #2298} (abstracted with #2272) Rutten-van Molken multinational, outpatient multicenter (41 centers in France, Italy, Spain, Sweden, Switzerland, and the UK) Funding?	Open-label RCT N=482	18 years or greater diagnosed more than 1 year before study entry who, according to their respiratory physician, could benefit from the regular use of long-acting b2-agonists were recruited. To be eligible, patients were required to have used inhaled corticosteroids at a constant dose ³400 mg/day (or 200 mg/day for fluticasone) for at least 1 month prior to the screeningvisit.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Vervloet et al.{Vervloet, 1998 #2298} (abstracted with #2272) Rutten-van Molken multinational, outpatient multicenter (41 centers in France, Italy, Spain, Sweden, Switzerland, and the UK) Funding?		other respiratory diseases, CVD, uncontrolled hypertension(diastolic blood pressure > 100mm Hg), hyperthyroidism, diabetes mellitus, neuromuscular disease, pregnant women, nursing mothers or women not practising a reliable form of contraception, not allowed to use tricyclic antidepressants or monoamine oxidase derivates, diuretics, b-blockers, drugs which prolong the QTcinterval (e.g. quinidine and other class I antiarrhythmics) or any investigational drug other than the trial medication.	None

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Vervloet et al.{Vervloet, 1998 #2298} (abstracted with #2272) Rutten-van Molken multinational, outpatient multicenter (41 centers in France, Italy, Spain, Sweden, Switzerland, and the UK) Funding?			Withdrawals: Drug 1: 21 (8.7%) Drug 2: 27 (11.2) Withdrawals due to AEs: Drug 1:4.6% Drug 2: 5.0%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Vervloet et al.{Vervloet, 1998 #2298} (abstracted with #2272) Rutten-van Molken multinational, outpatient multicenter (41 centers in France, Italy, Spain, Sweden, Switzerland, and the UK) Funding?	FM DPI (24) vs. SM DPI (100)	Rescue med us: puffs in 6 months D1: 199 D2: 203 P = 0.468 Symptom control: mean episode free days D1: 97 D2: 95 P = NS St George Respiratory Questionnaire: % of patients reaching clinically relevant improvement in QOL (4 or more points in total SGRQ score): D1: 64% D2: 62% ~~P = NS~~ Missed days of work D1: 3.19 D2: 2.64 P = 0.144 Hospitalizations (mean inpatient days): D1: 0.58 D2: 0.43 P=0.996

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Vervloet et al.{Vervloet, 1998 #2298} (abstracted with #2272) Rutten-van Molken multinational, outpatient multicenter (41 centers in France, Italy, Spain, Sweden, Switzerland, and the UK) Funding?	Drug related AEs (%) D1: 2 (13%) D2: 21 (9%) (headache most common)	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
3020	Vignola et al.{Vignola, 2004 #3020} SOLAR Multinational Multicenter Novartis Pharma AG and Genetech	RCT 28 wks N= 405	Age: 12–75 years; history of allergic asthma for > 1 yr with > 12% increase in FEV1after 400 mcg salbutamol; IgE level from > 30 to < 1300 IU/ml required, together with a positive skin-prick test to at least one indoor allergen; history of moderate-to-severe PAR symptoms for > 2 years; receiving > 400 mcg/day of ICS; had a history of > 2 unscheduled medical visits for their asthma during past year or > 3 in the past 2 years; total scores of >64/192 (32 items, amended to use a 0–6 scale) in AQLQ and >56/168 (28 items, 0–6 scale) in the RQLQ at baseline, which corresponds to a minimum QoL score worse than that of mild symptoms in both diseases

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Vignola et al.{Vignola, 2004 #3020} SOLAR Multinational Multicenter Novartis Pharma AG and Genetech	Long-acting b2-adrenoceptor agonists and nasal steroids was allowed if patients were on a stabilized regimen at screening. Asthma exacerbations could be treated with nebulized and/or inhaled b2-adrenoceptor agonists, a short course (3–10 days) of systemic corticosteroids or doubling of the inhaled BUD dose. Rhinitis exacerbations couldbe treated with oral antihistamine.	Use of systemic corticosteroids, long-acting antihistamines, cromolyn sodium, nedocromil sodium, oral b2-adrenoreceptor agonists, theophylline, leukotriene-receptor antagonists, inhaled anticholinergics, methotrexate, gold salts, cyclosporin and allergen-specific immunotherapy; active (in season) SAR at baseline, acute sinusitis, chest infection, persistent nonallergic rhinitis, pregnancy, or a platelet count < 130 x 10 9 /l.	4-wk run-in where ICS medication was standardized by switching patients to equivalent dose of BUD Turbuhaler (if not already taking this)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Vignola et al.{Vignola, 2004 #3020} SOLAR Multinational Multicenter Novartis Pharma AG and Genetech	≥ 0.016 mg/kg/IgE (IU/mL) per 4 weeks	Age: Drug 1: OM 43.4 Drug 2: Placebo 43.3 Sex (% female): Drug 1: OM 67.5 Drug 2: Placebo 65.7 Current smokers (%) 0 ICS use at baseline (%): Drug 1: OM 100 Drug 2: Placebo 100	Withdrawals: Drug 1: OM 5 (2.4%) Drug 2: Placebo 15 (7.7%) Withdrawals due to AEs: Drug 1: OM NR Drug 2: Placebo NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Vignola et al.{Vignola, 2004 #3020} SOLAR Multinational Multicenter Novartis Pharma AG and Genetech	Intervention: Drug 1: OM Drog 2: Placebo Number in group (n): Drug 1: Drug 2:	• Symptoms: Significant reduction in Wasserfallen asthma symptom score in OM patients at endpoint (treatment difference -1.8, P = 0.023) and total rhinitis symptom score (treatment difference -3.53, P < 0.001) vs. placebo • Exacerbations: Fewer OM patients experienced at least one exacerbation (20.6% vs. 30.1%; P = 0.02) • Mean rate of exacerbations lower with OM (0.25 vs. 0.40; P = 0.02) • Rescue med use: Use (mean puffs/day) of short-acting β2-agonists similar between groups during study (1.8 vs. 2.4; P = NR) • QoL: Clinically significant (≥ 1.0 point) improvement in AQLQ and RQLQ in 57.7% of OM patients vs. 40.6% placebo patients (P < 0.001) • AQLQ > 0.5 point improvement: 78.8% vs. 69.8%; P=0.50; > 1.0 improvement: 67.3% vs. 50.0%, P < 0.001 • RQLQ > 0.5 point improvement: 83.7% vs. 71.4%, P = 0.003; > 1.0 improvement: 67.3% vs. 52.1%, P = 0.001 • Overall change in AQLQ 1.4 vs. 1.1 at 28 weeks, P = NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Vignola et al.{Vignola, 2004 #3020} SOLAR Multinational Multicenter Novartis Pharma AG and Genetech	Overall OM 78.5 Placebo 68.9 Injection site reaction: OM 7.7 Placebo 4.6	NR	Fair

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
166	Vogelmeier, et al.{Vogelmeier, 2005 #166} 2005 Multicenter Primary care AstraZeneca	Study design: RCT open label parallel group Duration: 12 months N=2143 Enrolled: 2509 enrolled, 2143 randomised ITT Analysis: No another type of analysis was used (define): excluded 8 patients after randomization due to no data	Outpatients aged >/= 12 yrs with a diagnosis of asthma for >/= 6 months were eligible if they had used>/= 500 mg/day of budesonide or fluticasone (or >/= 1,000 mg of another ICS) for at least 1 month before study entry. Pre-terbutaline FEV1 40–90% of predicted and at least one severe exacerbation >2 weeks but >/= 12 months beforestudy entry. Patients had to have used as-needed medication on >/= 4 of the last 7 days of run-in. Asthma severity: Mild Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Vogelmeier, et al.{Vogelmeier, 2005 #166} 2005 Multicenter Primary care AstraZeneca	Addition of other asthma controller medication was allowed after randomisation, if necessary.	The use of either budesonide/formoterol or salmeterol/fluticasone during the previous 3 months excluded patients from the study	Yes- elucidate....: 2-week run-in period during which patients used their existing ICS (and LABA, if appropriate) and as-needed medication.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Vogelmeier, et al.{Vogelmeier, 2005 #166} 2005 Multicenter Primary care AstraZeneca	Intervention: Drug 1: FP/SM Drug 2: BUD/FM Total daily dose: Drug 1: 500mcg Drug 2: 640mcg Steroid dosing range (Low, medium or high): Drug 1: medium Drug 2: medium Delivery device: Drug 1: Diskus Drug 2: Turbuhaler Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 1076 Drug 2: 1067 Mean age (years): Drug 1: 45 (12-84) Drug 2: 45 (12-80) Sex (% female): Drug 1: 60.1 Drug 2: 57.7 Optional - Disease duration (years): Drug 1: 12 (0-74) Drug 2: 13 (1-75) Optional - Rescue medication use (puffs per day): Drug 1: 2.7 Drug 2: 2.6 Optional - Current use of LABA (%): Drug 1: 38 Drug 2: 38 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100	Number (%) withdrawn: Drug 1: 14 Drug 2: 11.2 Adverse events caused withdrawal (%): Drug 1: 2 Drug 2: 1.2 Optional - Lost to follow-up (%): Drug 1: 1.8 Drug 2: 1.4 Optional - Protocol violation (%): Drug 1: 4.3 Drug 2: 3.5 Optional - Other reasons for withdrawal (%): Drug 1: 5.9 Drug 2: 5.1

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Vogelmeier, et al.{Vogelmeier, 2005 #166} 2005 Multicenter Primary care AstraZeneca	Intervention: Drug 1 Baseline: FPSM Drug 1 Endpoint: FP/SM Drug 2 Baseline: BUD/FM Drug 2 Endpoint: BUD/FM Intervention: Drug 1- baseline: 1076 Drug 1- endpoint: 1076 Drug 2- baseline: 1067 Drug 2- endpoint: 1067	Rescue med use during 24 hour period: Drug 1- baseline: 2.7 Drug 1-endpoint: 0.93 Drug 2-baseline: 2.6 Drug 2-endpoint: 0.58 P < 0.001 Asthma exacerbations: D1 end: all severe exacerbations = 204 (19%) D2 end: 159 (15%) P: 0.0076 (based on instantaneous risk of experiencing at least one severe exacerbation) Symptom control during 24 hour period: D1 base: 1.87 D1 end: change in ACQ5 score from baseline = -0.58 D2 base: 1.86 D2 end: -0.64 P =:0.069 AQLQ - overall: D1 base: 4.95 D1 end: change from baseline = 0.57 D2 base: 4.97 D2 end: 0.60 P = 0.51 Hospitalizations: D1 end: severe exacerbations due to ER visits/hospitalizations = 46 (4%) D2 end: 31 (3%) P = 0.18 instantaneous risk of at least one severe exacerbation Other: D1 end : severe exacerbations excluding unscheduled clinic visits = 167 (6%) D2 end: 132 (12%) P = 0.025 instantaneous risk of at least one severe exacerbation

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Vogelmeier, et al.{Vogelmeier, 2005 #166} 2005 Multicenter Primary care AstraZeneca	Serious adverse events (%): Drug 1: 8.2 Drug 2: 7.5 Death (%): Drug 1: 0.1 (2 people) Drug 2: 0 Additional adverse events and comments: Although a comparable number of patients discontinued the study due to AEs (27 budesonide/formoterol patients versus 28 salmeterol/fluticasone patients), a greater number of salmeterol/fluticasone patients withdrew owing to asthma versus budesonide/formoterol patients (11 versus three patients, respectively).	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
843	Volmer et al.{Volmer, 1999 #843} 1999 Germany Multicenter GlaxoSmithKline	Study design: RCT Double-blind : 2 studies one blinded and one open; results reported within cost-effectiveness analysis. Duration: 6 weeks; 8 weeks (RCT) N=randomized open-label trial 332; RCT 321 Enrolled: NR ITT Analysis: Yes	: steroid-naive patients with moderate asthma; 18-70 tears old Asthma Severity: Moderate

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Volmer et al.{Volmer, 1999 #843} 1999 Germany Multicenter GlaxoSmithKline	NR	serious coexisting disease or those requiring drugs likely to interact with the study drugs	Yes: 2 week run-in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Volmer et al.{Volmer, 1999 #843} 1999 Germany Multicenter GlaxoSmithKline	Intervention: Drug 1: Open FP/FL Drug 2: RCT FP/FL Total daily dose: Drug 1: 500/1000 Drug 2: 500/1000 Delivery device: Drug 1: metered inhaler Drug 2: metered inhaler Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 172/160 Drug 2: 161/147 Mean age (years): Drug 1: 48.4/46.1 Drug 2: 49.3/51.2 Sex (% female): Drug 1: 47/44 Drug 2: 58/55 Current smokers (%): Drug 1: 21/18 Drug 2: 25/31 Optional - Previous ICS use (%): Drug 1: 0/0 Drug 2: 0/0 Current use of ICS at baseline (%): Drug 1: o/o Drug 2: o/o	Number (%) withdrawn: Drug 1: NR Drug 2: NR Adverse events caused withdrawal (%): Drug 1: 6.9/4.0 Drug 2: 2.5/0.7

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Volmer et al.{Volmer, 1999 #843}	Intervention:	Other:
1999	Drug 1 Baseline	D1 base: Symptom free dayss, change from baseline
	Drug 1 Endpoint: Open FP/FL	D1 end : 30.2/21.1
Germany	Drug 2 Baseline	D2 end: 25.7/20.0
Multicenter	Drug 2 Endpoint: RCT FP/FL	P: NR
GlaxoSmithKline	Number in group (n):	Other:
	Drug 1- endpoint: 172/160	D1 base: proportion of SFD at study end
	Drug 2- endpoint: 161/147	D1 end : 36.4/28.5
		D2 end: 35.1/31.1
		P: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Volmer et al.{Volmer, 1999 #843} 1999 Germany Multicenter GlaxoSmithKline	Overall adverse events (%): Drug 1: 6.9/4.0 Drug 2: 2.5/0.7	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
4793 LTRAs	Watkins et al.{Watkins, 2007 #4793} 2007 US Multicenter (233) allergy and pulmonary clincis, private offices, and academic/research centers Abbott Laboratories	Study design: RCT Other- open label study of zileuton plus usual care vs usual care Other-open label randomized prospective study Duration: 12 months N=2947 Enrolled: NR ITT Analysis: Unable to determine	Age: >=16 FEV1 expressed as a percent of the predicted value: see reversibility Reversability of FEV1: baseline FEV1 of ≥35% of the predicted value, measured at least 4 hours after salbutamol (albuter-ol) inhalation or 12 hours after SM inhalation.Patients had a ≥15% increase in FEV1 salbutamol at screening, or a documented history of positive response to either a methacholine or hista-mine challenge, and could have no clinically signifi-cant abnormalities other than asthma. . Other: Women were required to be either postmenopausal, surgically sterile or using an effective method of contracep-tion. Patients agreed to limit their alcohol consumption to ≤2 ounces per day during the study. Patients were allowed to continue their current asthma medi-cations and other concomitant medications, excluding isotretinoin, methotrexate, systemic corticosteroids, gold salt, terfenadine, astemizole, carba-mazepine and lipid-lowering agents, all of which had to be discontinued 2-4 weeks prior to starting zileuton Asthma severity: NR

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Watkins et al.{Watkins, 2007 #4793} 2007 US Multicenter (233) allergy and pulmonary clincis, private offices, and academic/research centers Abbott Laboratories	Patients were allowed to continue their current asthma medications, excluding isotretinoin, methotrexate, systemic corticosteroids, gold salt, terfenadine, astemizole, carba- treatment.	Smoking - current or former: none for at least 6 mo	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Watkins et al.{Watkins, 2007 #4793} 2007 US Multicenter (233) allergy and pulmonary clincis, private offices, and academic/research centers Abbott Laboratories	Intervention: Drug 1: zileuton plus usual care Drug 2: usual care only Total daily dose: Drug 1: 2400 mg Drug 2: none Steroid dosing range (Low, medium or high): Drug 1: NA Delivery device: Drug 1: NA Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 2458 Drug 2: 489 Mean age (years): Drug 1: 43.3 Drug 2: 42.7 Sex (% female): Drug 1: 60.6 Drug 2: 63.0 Current smokers (%): Drug 1: 0 (exclusion) Drug 2: 0 Current use of ICS at baseline (%): Drug 1: NR Drug 2: NR Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 1069 (43.5%) Drug 2: 127 (26.0%) Overall: 40.6% Adverse events caused withdrawal (%): Drug 1: 486 (19.8%) Drug 2: 11 (2.3%)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Watkins et al.{Watkins, 2007 #4793} 2007 US Multicenter (233) allergy and pulmonary clincis, private offices, and academic/research centers Abbott Laboratories	Intervention: Drug 1: zileuton plus usual care Drug 2: usual care only Number in group (n): Drug 1: 2458 Drug 2: 489	Rescue medication: Drug 1: 23.0% vs 30.3%; p ≤ 0.001 Emergency care: Drug 1: 7.7% vs 11.5%; p ≤ 0.05 Hospitalization Drug 1: 3.2% vs 4.1%, not significant

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Watkins et al.{Watkins, 2007 #4793} 2007 US Multicenter (233) allergy and pulmonary clincis, private offices, and academic/research centers Abbott Laboratories	Additional adverse events and comments: 109 patients (4.4%) receiving zileuton treatment had ALT levels to >3xULN, including 31 patients (1.3%) who had levels >8x ULN, compared with 5 of 480 patients in the usual care alone group (1.0%; p<0.001) who had levels to >3 xULN, of whom 1 (0.2%) had levels elevated to >8x ULN. ALT levels weregenerally not associated with increases in alkaline phosphatase and/or total bilirubin levels. injury was predominantly hepatocellular). Most elevations in ALT>3 xULN (64.2%) in the zileutontreated group occurred first 3 months of treatment.There was no difference in elevations in ALT level to 3x ULN between men (4.5%) and women (4.7%), but more women than men experienced an ALT level>8 x ULN (1.8% vs 0.5%). Women aged >65 years appeared to be at higher risk of elevated ALT levels than those aged <65 years (a rate of 10.1% compared with 4.1%). Patients who experienced ALT levels of >3 x ULN but <5 ULN were allowed to remain on treatment and 52.5% of these patients were able to continue zileuton therapy and experienced resolution of the elevation (a reduction in level to <2x ULN). In each of the patients wh	NR	Fair: although attrition is high and there was differential attrition, the direction of attrition would bias the results toward not finding AEs on liver in the zileuton group, thus the result is likely valid and even possibly an underestimate Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
354	Weiss et al.{Weiss, 2004 #354} 2004 US Multicenter (enrollees in 25 health plans) AstraZeneca LP, Wilmington, Delaware	Study design: RCT Duration: 52 weeks N=945 Enrolled: NR/NR/945 ITT Analysis: Yes	: patients aged >/=18 years from 25 US health plans with a history of asthma requiring daily prescription asthma medication. Patient requirements included a baseline FEV1 >/=40% and </=90% of predicted and >/=12% reversibility following a standard beta-agonist dose. Premenopausal women were required to use an acceptable method of birth control. Asthma Severity: Mild Moderate Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Weiss et al.{Weiss, 2004 #354} 2004 US Multicenter (enrollees in 25 health plans) AstraZeneca LP, Wilmington, Delaware	The only inhaled corticosteroids allowed during the treatment phase were the study medications; however, the concomitant use of other medications (eg, albuterol pMDI, PO or IV corticosteroids, theophylline) was allowed at the discretion of the investigator. (Other ICS discontinued at randomization.) All concomitant medication use was recorded in case-report forms as well as in patient diaries.	Patients with clinically significant irreversible airway obstruction or any medical or psychological condition that would affect study participation were excluded. Pregnant and breastfeeding women were excluded.	Yes: 2 week

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Weiss et al.{Weiss, 2004 #354} 2004 US Multicenter (enrollees in 25 health plans) AstraZeneca LP, Wilmington, Delaware	Intervention: Drug 1: BUD Drug 2: TAA Total daily dose: Drug 1: mean daily dose at start and end: 941.9/956.8 mcg Drug 2: 1028.21/1042.95 mcg Steroid dosing range (Low, medium or high): Drug 1: on average: medium; range low-high Drug 2: medium; low-high Delivery device: Drug 1: DPI Drug 2: pMDI Current use of ICS at baseline (%): Drug 1: NR Drug 2: NR Is dosing comparable between treatment groups? NA: difficult to assess clearly, starting doses and dose adjustments of both medications were left to the discretion of the clinical investigator	# in group (n): Drug 1: 631 Drug 2: 314 Mean age (years): Drug 1: 46.5 Drug 2: 47.3 Sex (% female): Drug 1: 63.9 Drug 2: 63.1 Optional - Race (% white): Drug 1: 83.4 Drug 2: 85.7 Current smokers (%): Drug 1: NR Drug 2: NR Current use of ICS at baseline (%): Drug 1: NR Drug 2: NR	Number (%) withdrawn: Drug 1: 93 (14.7) Drug 2: 42 (13.4) Adverse events caused withdrawal (%): Drug 1: 3.0 Drug 2: 2.5

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Weiss et al.{Weiss, 2004 #354} 2004 US Multicenter (enrollees in 25 health plans) AstraZeneca LP, Wilmington, Delaware	Intervention: Drug 1 Baseline: BUD Drug 1 Endpoint: BUD Drug 2 Baseline: TA Drug 2 Endpoint: TA Number in group (n): Drug 1- baseline: 631 Drug 1- endpoint: 631 Drug 2- baseline: 314 Drug 2- endpoint: 314	Symptom control during 24 hour period: Symptom-free days/mo, no. (95% CI): D1 end: 7.74 (6.81 to 8.66) D2 end: 3.78 (2.47 to 5.09) P < 0.001 Day time symptom control: Daytime asthma symptom score (95% CI): D1 - end: -0.37 (-0.43 to -0.31) D2 - end: -0.20 (-0.29 to -0.12) P: P=0.001 Night time symptom control: Nighttime asthma symptom score (95%CI): D1 - end: -0.32 (-0.38 to -0.26) D2 - end: -0.12 (-0.21 to -0.03) P < 0.001 AQLQ - overall: D1 base: 4.6 (1.1) D1 end: 0.99 (0.91 to 1.07) D2 base: 4.5 (1.1) D2 end: 0.72 (0.61 to 0.83) P < 0.001 AQLQ - symptoms: D1 end: 0.99 (0.91 to 1.08) D2 end: 0.69 (0.56 to 0.81) P < 0.001 AQLQ - environment: D1 end: 0.81 (0.72 to 0.91) D2 end: 0.60 (0.46 to 0.74) P = 0.009 AQLQ - emotions: D1 end: 1.12 (1.03 to 1.22) D2 end: 0.80 (0.66 to 0.94) P < 0.001

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Weiss et al.{Weiss, 2004 #354} 2004 US Multicenter (enrollees in 25 health plans) AstraZeneca LP, Wilmington, Delaware	Overall adverse events reported (%): Drug 1: 85 Drug 2: 86 Additional adverse events and comments: The distribution and incidence of AEs were similar between the study groups, with approximately 86% of patients (539 receiving BUD and 269 receiving TA in each group reporting >/=1 AE during the study The most frequently reported AEs were respiratory tract infection, sinusitis, bronchitis, and accident/injury. A total of 173 patients (18.3%) reported AEs considered possibly or probably related to treatment--2 1.4% (135/63 1) from the BUD group and 12.1% (38/3 14) from the TA group. Most patients in both treatment groups experienced no clinically significant changes in laboratory values during the course of the study Many of the clinically relevant abnormalities were associated with preexisting conditions (eg, atopic allergy, diabetes mellitus, rhinitis) or concomitant medications (eg, oral corticosteroids, antiseizure medications) that did not exclude the patient from participation in the study. There were no apparent differences between treatments in mean or individual patient changes	Compliance Assessment of medication compliance demonstrated significantly greater compliance in patients using BUD throughout the study, with scores at study end of 89.2 and 82.8 for patients receiving BUD and TA, respectively (P < 0.001).	Fair: open-label Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
1150	Woolcock et al.{Woolcock, 1996 #1150} 1996 Multinational (14 countries) Multicenter (72) Glaxo	Study design: RCT Double-blind Duration: 24 weeks N=738 Enrolled: 990/NR/738 ITT Analysis: Yes	: At least 17 years old and taking 400-500 BDP: 15% reversability in FEV with salbutamol: symptom score greater than 1: FEV or PEFR at >50% predicted Asthma Severity: Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Woolcock et al.{Woolcock, 1996 #1150} 1996 Multinational (14 countries) Multicenter (72) Glaxo	yes- but must be kept constant dose	Other: Change in asthma meds, hospitalized for asthma, lower or upper respiratory infection requiring antibiotics within last month; require trmt with ccs (oral or parental)	Yes: 1 to 4 weeks

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Woolcock et al.{Woolcock, 1996 #1150} 1996 Multinational (14 countries) Multicenter (72) Glaxo	Intervention: Drug 1: SM 50 + BDP Drug 2: SM 100 + BDP Drug 3: BDP Total daily dose: Drug 1: 100 + 1000 Drug 2: 200 + 1000 Drug 3: 2000 Steroid dosing range (Low, medium or high): Drug 1: high Drug 2: high Drug 3: high Delivery device: Drug 1: MDI Drug 2: MDI Drug 3: MDI Is dosing comparable between treatment groups? NA	# in group (n): Drug 1: 243 Drug 2: 244 Drug 3: 251 Mean age (years): Drug 1: 44 Drug 2: 46 Drug 3: 42 Sex (% female): Drug 1: 49 Drug 2: 49 Drug 3: 46 Current smokers (%): Drug 1: 19 Drug 2: 16 Drug 3: 13 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 25 (10.3) Drug 2: 29 (11.9) Drug 3: 35 (13.9) Adverse events caused withdrawal (%): Drug 1: 5.8 Drug 2: 5.7 Drug 3: 6.0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Woolcock et al.{Woolcock, 1996 #1150} 1996 Multinational (14 countries) Multicenter (72) Glaxo	Intervention: Drug 1 Baseline: SM 50 + BDP Drug 1 Endpoint: SM 50 + BDP Drug 2 Baseline: SM 100+ BDP Drug 2 Endpoint: SM 100+ BDP Drug 3 Baseline: BDP Drug 3 Endpoint: BDP P-values (Define comparison): SM 50 and SM 100 vs BDP Number in group (n): Drug 1- baseline: 243 Drug 2- baseline: 244 Drug 3- baseline: 251	Asthma exacerbations: D1 end: 20% D2 end: 16% D3 end: 20% P = NS among all groups Symptom control during 24 hour period: D1 base: median % symptom-free days: 0 D1 end: NR, shown in figure only D2 base: 0 D2 end: NR, shown in figure only D3 base: 0 D3 end: NR, shown in figure only P: better in both SM groups than BDP (P < 0.001 for both comparisons with BDP) Nocturnal awakenings: D1 base: % of nights NOT awakened by asthma: 43% D1 end: after 4 weeks: 100% D2 base: 43% D2 end: 100% D3 base: 29% D3 end: 86% P < 0.001 and P = 0.001 (both SM groups vs BDP, respectively)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Woolcock et al.{Woolcock, 1996 #1150} 1996 Multinational (14 countries) Multicenter (72) Glaxo	Oral candidiasis- thrush (%): Drug 1: 2 Drug 2: <1 Drug 3: 2 Cough (%): Drug 1: Bronchitis 7 Drug 2: 10 Drug 3: 9 Headache (%): Drug 1: 11 Drug 2: 16 Drug 3: 17 Other (%): Drug 1: nasopharyngitis 10 Drug 2: 11 Drug 3: 10 Other (%): Drug 1: tremors 2 Drug 2: 8 Drug 3: <1 Other (%): Drug 1: palpitations 2 Drug 2: 2 Drug 3: 2 Outcomes concerning tests evaluating suppression of HPA axis, i.e. cortisol levels: Depression was seen in BDP group but not Salm groups	NR	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
634	Worth et al.{Worth, 2001 #634} 2001 Germany, France, and The Netherlands Multicenter - 39 sites 3M Pharmaceuticals	Study design: RCT open label, parallel group Duration: 8 weeks N=209 Enrolled: NR, NR, 209 ITT Analysis: Yes	: Male and female patietns aged 18-75 with moderate to severe asthma, FEF 50-80% after withholding beta agoinst for 4 hours. Had to have been using ICS at an equivalent dosage to BUD 500-1000 mcg/day and a short-acting beta agonist on an "as needed" basis during the 4 weeks prior to enrollment. Asthma Severity: Moderate Severe Not or poorly controlled

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Worth et al.{Worth, 2001 #634} 2001 Germany, France, and The Netherlands Multicenter - 39 sites 3M Pharmaceuticals	The use of LABA, anticholinergics, theophyllines, and cromones was premitted provided that the dose was kept stable throughout the study.	Pregnancy or a likelihood of becoming pregnant, evidence of clinically unstable or untreated significant immunological, neoplastic, endocrine, hematological, hepatic, renal, GI, neurological disease, psychiatric abnormalities or significant respiratory disorders other than asthma; acute upper or lower RTI within the past 2 weeks, diagnosis of cardiac disease, immobilization for any reason; past use of intraarticular, IM or IV steroids within 8 weeks, or oral steroids, fluticasone, MAOIs, TCA, beta blockers, oral beta agonists, or any investiational drug within 4 weeks; current use of nasal steroid > 400 mcg BDP, or equivalent, or varying doses of nasal steroids; and hypersensitivity or reaction to sympathomimetic drugs or inhaled steroids.	Yes: 5 to 14 day run-in period, during which patients continued to use their normal ICS therapy. Each day, participants recorded mean PEF in Am, daily asthma symptom scores for wheezing, coughing, SOB, and chest tightness on a scale of 0 - 5.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Worth et al.{Worth, 2001 #634} 2001 Germany, France, and The Netherlands Multicenter - 39 sites 3M Pharmaceuticals	Intervention: Drug 1: BDP Drug 2: BUD Total daily dose: Drug 1: 800mcg Drug 2: 1600mcg Steroid dosing range (Low, medium or high): Drug 1: high Drug 2: high Delivery device: Drug 1: MDI Drug 2: DPI Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 111 (ITT population) Drug 2: 98 (ITT population) Mean age (years): Drug 1: 49.2 Drug 2: 47.8 Overall: 0.46 Sex (% female): Drug 1: 56.8 Drug 2: 54.1 Overall: 0.68 Current smokers (%): Drug 1: NR Drug 2: NR Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Other: Drug 1: daily asthma symptoms (%) = 8.7 Drug 2: 14.5 Overall: 0.14 Other: Drug 1: shortness of breath (%) = 31.2 Drug 2: 40.5 Overall: 0.11	Number (%) withdrawn: Drug 1: 8 (7%) Drug 2: 15 (15%) Overall: 23 (11%) Adverse events caused withdrawal (%): Drug 1: 3 Drug 2: 5

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Worth et al.{Worth, 2001 #634} 2001 Germany, France, and The Netherlands Multicenter - 39 sites 3M Pharmaceuticals	Intervention: Drug 1 Baseline: BDP Drug 1 Endpoint: BDP Drug 2 Baseline: BUD Drug 2 Endpoint: BUD Number in group (n): Drug 1- endpoint: 111 Drug 2- endpoint: 98	Rescue med use during 24 hour period: % of days on which rescue was use: Drug 1-endpoint: reduction in % of days on which rescue was use: = -23.76 Drug 2-endpoint: -17.13 P = NS Other: D1 base: Asthma symptoms (0-5 scale): SOB score = 1.38 D1 end : 0.85 D2 base: 1.22 D2 end: 0.90 P = 0.04 for BDP vs BUD change from baseline Other: D1 base: Asthma symptoms: Sleep disturbance score = 0.84 D1 end : 0.49 D2 base: 0.82 D2 end: 0.61 P = 0.04 for BDP vs BUD change from baseline

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Worth et al.{Worth, 2001 #634} 2001 Germany, France, and The Netherlands Multicenter - 39 sites 3M Pharmaceuticals	Overall adverse events reported (%): Drug 1: 24.3 Drug 2: 26.5 P = NS Dysphonia (%): Drug 1: 5.4 Drug 2: 4.08 Other (%): Drug 1: number of AD possibly or probably related to study med: 10 Drug 2: 14 Other (%): Drug 1: fungal infection = 2.7 Drug 2: 4.08 Other (%): Drug 1: gingivitis = 0.9 ; weight increase = 0.90 ; increased asthma symptoms, bronchitis, acute asthma episode, inhalation site sensation, stomatitis = all 0 Drug 2: 0 ; 0 ; all 1.02	Compliance All study inhalers were weighted on dispatch and return. Predicted and actual weights of the inhaler canisters were converted tothenumber of actuation administered using mean shot weights. Patients were considered to be com[pliant if the total nubmer of actuations from the inhalers was +/- 40% of predicted for weeks 1 - 8. However, it was not possible to assess the weight of the remaining BUD due to the rising moisture content which resulted in increasing wight of the contained powder.	Fair Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
375	Yurdakul et al.{Yurdakul, 2003 #375} 2003 Turkey Research Hospital NR	Study design: RCT open label Duration: 12 weeks N = 74 Number screened: NR ITT Analysis: Unable to determine	Other: aged 23–45 years with mild persistent asthma according to the criteria of GINA, FEV1 at baseline had to be at least 80% of the predicted normal value, with an increase of at least 15% in FEV1 from the baseline value after the inhalation of 400 mg of salbutamol. All of the patients were previously using inhaled BUD at a dose of 200 mg a day or equivalent doses of BDP or FP and short-acting β2-agonist irregularly for at least 2 months prior to study. Asthma Severity: Mild

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Yurdakul et al.{Yurdakul, 2003 #375} 2003 Turkey Research Hospital NR	all patients were given short-acting b2-agonist (terbutaline) inhaler as needed.	Other: Patients were excluded if they had respiratory tract infection, smoked cigarettes or had a respiratory disorder other than asthma disease, had asthma exacerbations within the preceding 2 months, pregnant or lactating women or with hypersensitivity to sympathomimetic amines and women of child bearing potential who did not use a reliable contraceptive method. Concurrent use of any medications that could interact with the drugs used in the groups was not allowed.	Yes: The study had a 3-week run-in period, followed by 3 months of randomized treatment. All patients entering the run-in period received inhaled BUD at a dose of 200 mg twice daily, plus 250 mg of inhaled terbutaline as needed.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Yurdakul et al.{Yurdakul, 2003 #375} 2003 Turkey Research Hospital NR	Intervention: Drug 1: BUD Drug 2: ML Drug 3: theophylline Total daily dose: Drug 1: 400mcg Drug 2: 10mg Drug 3: data not abstracted Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: NA Delivery device: Drug 1: DPI Drug 2: tablet Is dosing comparable between treatment groups? Not applicable- why not?: ICS versus ML	# in group (n): Drug 1: 25 Drug 2: 25 Mean age (years): Drug 1: 36 Drug 2: 34 Sex (% female): Drug 1: 80 Drug 2: 84 Current smokers (%): Drug 1: 0 Drug 2: 0 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 0 Drug 2: 0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Yurdakul et al.{Yurdakul, 2003 #375} 2003 Turkey Research Hospital NR	Intervention: Drug 1 Baseline: BUD Drug 1 Endpoint: BUD at 3 month follow-up Drug 2 Baseline: ML Drug 2 Endpoint: ML at 3 month follow-up Number in group (n): Drug 1- baseline: 25 Drug 1- endpoint: 25 Drug 2- baseline: 25 Drug 2- endpoint: 25	Rescue med use during 24 hour period: Drug 1- baseline: mean # puffs/d: 0.7 (0.1) Drug 1-endpoint: 0.1 (0.1); mean change from baseline: 0.6 (0.2) Drug 2-baseline: 0.7 (0.2) Drug 2-endpoint: 0.1 (0.1); 0.6 (0.2) P > 0.05 between groups Asthma exacerbations: # (%) of patients with exacerbations over course of study: D1 end: 0 D2 end: 4 (16%) P = NR Day time symptom control: D1 - base: mean daytime symptom score: 1.9 (0.4) D1 - end: 0.5 (0.5); mean change from baseline: 1.5 (0.7) D2 - base: 1.8 (0.5) D2 - end: 0.6 (0.5); 1.3 (0.6) P > 0.05 between groups Night time symptom control: D1 - base: mean daytime symptom score: 1.5 (0.5) D1 - end: 0.2 (0.4); mean change from baseline: 1.3 (0.6) D2 - base: 1.6 (0.4) D2 - end: 0.3 (0.5); 1.3 (0.5) P > 0.05 between groups

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Yurdakul et al.{Yurdakul, 2003 #375} 2003 Turkey Research Hospital NR	Overall adverse events reported (%): Drug 1: 12 Drug 2: 16 Dysphonia (%): Drug 1: 4 Drug 2: 0 Cough (%): Drug 1: 8 Drug 2: 0 Headache (%): Drug 1: 0 Drug 2: 4 Other (%): Drug 1: 0 Drug 2: dyspeptic complaints = 12	NR	Fair Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
219	Zeiger et al.{Zeiger, 2005 #219} 2005 Rand at al.{Rand, 2005 #16} 2005 MIAMI Trial USA Multicenter (39) Merck	Study design: RCT Double-blind parallel-group Duration: 16wk total 12 weeks then 36 week open label extension N = 400 Number screened: 901/735/400 ITT Analysis: No another type of analysis was used (define): ITT with some post randomisation exclusions (had to have data for at least 7 days)	Age: 15-85 FEV 1 expressed as a percent of the predicted value: >= 80% Reversability of FEV1: >=12% Days with asthma symptoms: 2-6 days per week during 2 weeks before randomization Duration of condition: at least 4 months Other: treatment with only as needed albuterol Asthma Severity: Mild Other: persistant

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Zeiger et al.{Zeiger, 2005 #219} 2005 Rand at al.{Rand, 2005 #16} 2005 MIAMI Trial USA Multicenter (39) Merck	Yes- as needed albuterol	Other: used other asthma controller medications or systemic corticosteroids within the past month or required recent hospital or urgent care for asthma.	Yes: 2 week placebo run-in

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Zeiger et al.{Zeiger, 2005 #219} 2005 Rand at al.{Rand, 2005 #16} 2005 MIAMI Trial USA Multicenter (39) Merck	Intervention: Drug 1: ML Drug 2: FP Total daily dose: Drug 1: 10 mg Drug 2: 176mcg Steroid dosing range (Low, medium or high): Drug 1: N/A Drug 2: low Delivery device: Drug 1: tablet Drug 2: MDI Is dosing comparable between treatment groups? NA: ICS versus LTRA	# in group (n): Drug 1: 189 Drug 2: 191 Mean age (years): Drug 1: 33.9 Drug 2: 36.5 Sex (% female): Drug 1: 70 Drug 2: 69 Optional - Race (% white): Drug 1: 78 Drug 2: 83 Current smokers (%): Drug 1: NR Drug 2: NR Optional - Disease duration (years): Drug 1: age of 1st trmt = 20.3 Drug 2: 20.8 Current use of ICS at baseline (%): Drug 1: 0 Drug 2: 0 Groups similar at baseline? Yes	Number (%) withdrawn: Drug 1: 12 (6) Drug 2: 18 (9.4) Adverse events caused withdrawal (%): Drug 1: 0.5 Drug 2: 2.1 Optional - Lost to follow-up (%): Drug 1: 0.5 Drug 2: 3.7

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Zeiger et al.{Zeiger, 2005 #219} 2005 Rand at al.{Rand, 2005 #16} 2005 MIAMI Trial USA Multicenter (39) Merck	Intervention: Drug 1 Baseline: ML Drug 1 Endpoint: ML Drug 2 Baseline: FP Drug 2 Endpoint: FP Number in group (n): Drug 1- baseline: 189 Drug 1- endpoint: 176 Drug 2- baseline: 191 Drug 2- endpoint: 178	Rescue med use during 24 hour period: Drug 1- baseline: 0.8 Drug 1-endpoint: -0.4 Drug 2-baseline: 0.9 Drug 2-endpoint: -0.4 P = 0.32 Day time symptom control: D1 - base: asthma symptoms frequency during daytime (scale 3-15) = 7.4 D1 - end: -1.3 D2 - base: 7.2 D2 - end: -1.5 P = 0.27 Night time symptom control: D1 - base: asthma symptoms frequency during nighttime (scale 4-20) = 8.9 D1 - end: -1.4 D2 - base: 8.6 D2 - end: -2.0 P = 0.04 AQLQ - overall: D1 base: scale 1-7 = 5 D1 end: 0.7 D2 base: 5.1 D2 end: 0.8 P = 0.20 Other: D1 base: Symptom free days (0-28) = 10 D1 end : 6.3 D2 base: 10.7 D2 end: 7.3 P = 0.24 Other: D1 base: Asthma control scale (0-4) = 1.0 D1 end : -0.4 D2 base: 1.0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Zeiger et al.{Zeiger, 2005 #219} 2005	NR	Adherence	Fair Poor
Rand at al.{Rand, 2005 #16} 2005 MIAMI Trial USA Multicenter (39) Merck		Patient-reported adherence to study medication was high in both treatment groups (mont 98.4%, FP 94.7%)	No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
139	Zeiger et al.{Zeiger, 2006 #139} 2006 CARE Network trial US Multicenter NHLBI, National Jewish Medical and Research Center, General clinical Research Centers at Washington University School of Medicine.	Study design: RCT Double-blind Double-dummy Other: 2x2 crossover design Duration: 16wk total (8wk, crossover, 8wk); additionally, only included data from the last 4wk of each treatment period N = 144 (127 included in analysis) Number screened: NR ITT Analysis: No another type of analysis was used (define): patients who completed both treatment periods	Age: 6-17 FEV 1 expressed as a percent of the predicted value: >=70 Reversability of FEV1: >=12% s/p maximmum bronchodilation or methacholine dose required to reduce baseline FEV1 by 20% Days with asthma symptoms: or rescue bronchodilator use on average of 3 or more d/wk for 4wk before enrollment Asthma Severity: Mild Moderate Not or poorly controlled Other: persistent

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Zeiger et al.{Zeiger, 2006 #139} 2006 CARE Network trial US Multicenter NHLBI, National Jewish Medical and Research Center, General clinical Research Centers at Washington University School of Medicine.	rescue medication	Concommitant diseases: respiratory tract infection within 4wk of enrollment Current treatment: corticosteroids within 4wks and LT modifier agents within 2wks of study	Yes: 5-10d; run-in used to characterize asthma; patients stratified based on clinical center, age, and % predicted FEV1. Additionally, a placebo washout period between treatment sequences was not implemented at the request of 2 institutional review boards. Previous studies have indicated that the first 4 weeks of the second treatment period was a sufficient time for study medication washout. As such, the first 4 weeks of each treatment period served as pseudo washout periods and were not included in the statistical analyses.The second 4 weeks of each treatment period were used to compare responses to treatments.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Zeiger et al.{Zeiger, 2006 #139} 2006 CARE Network trial US Multicenter NHLBI, National Jewish Medical and Research Center, General clinical Research Centers at Washington University School of Medicine.	Intervention: Drug 1: FP Drug 2: ML Overall: Baseline reported, mean (95%CI) where applicable Total daily dose: Drug 1: 200mcg Drug 2: 5mg ages 6-14, 10mg ages 15-18 Steroid dosing range (Low, medium or high): Drug 1: low Drug 2: NA Delivery device: Drug 1: DPI Drug 2: tablet Is dosing comparable between treatment groups? NA: steroid vs leukotriene antagonist	# in group (n): Overall: varies, 120-127 Mean age (years): Overall: 33% between 6 and 9 years Sex (% female): Overall: 41% Optional - Race (% white): Overall: 48% minority Optional - Rescue medication use (puffs per day): Overall: 7.5 (6.4, 8.6) Current use of ICS at baseline (%): Drug 1: 0 Overall ACQ = 0.96 (0.89, 1.03) Asthma Control Days/wk = 2.2 (1.9, 2.5) Groups similar at baseline? NA cross-over design	Number (%) withdrawn: Drug 1: NR Overall: 12%

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Zeiger et al.{Zeiger, 2006 #139} 2006 CARE Network trial US Multicenter NHLBI, National Jewish Medical and Research Center, General clinical Research Centers at Washington University School of Medicine.	Intervention: Drug 1 Baseline: FP Drug 1 Endpoint: FP Drug 2 Baseline: ML Drug 2 Endpoint: ML P-values (Define comparison): Difference (FP-ML) (95%CI), p-value Number in group (n): Drug 1- endpoint: Varies 120-127 Drug 2-endpoint: Varies 120-127	Other Asthma QOL instrument: D1 base: Baseline ACQ mean (95%CI) 0.96 (0.89, 1.03) D1 end: 0.59 (0.50, 0.69) D2 base: Baseline = 0.96 (0.89, 1.03) D2 end: 0.76 (0.66, 0.87) -0.17 (-0.27, -0.07), 0.0009; changes from baseline: FP P < 0.0001, ML P < 0.001 Other: D1 base: rescue med use puffs/wk, mean (95%CI) 7.5 (6.4, 8.6) D1 end : 3.1 (1.9, 4.2) D2 base: 7.5 (6.4, 8.6) D2 end: 4.4 (3.1, 5.6) -1.3 (-2.4, -0.1), 0.0305; Both FP and ML change from baseline P < 0.0001 Other: D1 base: asthma control days/wk mean (95%CI) 2.2 (1.9, 2.5) D1 end : 5.0 (4.6, 5.4) D2 base: 2.2 (1.9, 2.5) D2 end: 4.3 (3.9, 4.8) 0.7 (0.4, 1.0), <0.0001; Both FP and ML change from baseline P < 0.0001

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Zeiger et al.{Zeiger, 2006 #139} 2006 CARE Network trial US Multicenter NHLBI, National Jewish Medical and Research Center, General clinical Research Centers at Washington University School of Medicine.	NR	Adherence >85% for all arms	Fair: not ITT, methods not adequately reported Poor No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
664	Zetterstrom et al.{Zetterstrom, 2001 #664} 2001 Multicenter/Multinational - 59 centers in Finland, Germany, Ireland, Norway, Spain, and Sweden University hospitals AstraZeneca	Study design: RCT Double-blind Double-dummy Duration: 12 weeks N=362 Enrolled: 405 enrolled, 362 randomised ITT? Yes	Male and female asthma patients aged >/=18 yrs were eligible for inclusion in the study if: 1) they were using inhaled glucocorticosteroids at a constant daily dose of >/=500 mg for >/=30 days before entry; 2) they had a baseline FEV1 of 50–90% predicted; and 3) they had a reversibility from baseline of ¢15% after inhalation of terbutaline sulphate 1 mg or salbutamol 0.4 mg. Asthma Severity: Mild Moderate Severe

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Zetterstrom et al.{Zetterstrom, 2001 #664} 2001 Multicenter/Multinational - 59 centers in Finland, Germany, Ireland, Norway, Spain, and Sweden University hospitals AstraZeneca	No concomitant asthma medication, except rescue medication with terbutaline sulphate or salbutamol, was allowed during the study.	Use of oral, parenteral or rectal glucocorticosteroids within 30 days beforestudy entry; respiratory infection; seasonal asthma; severe cardiovascular disorder; beta-blocker therapy; a history of heavy smoking (>/=10 pack-yrs); pregnancy or failure to use acceptable contraceptives in women of childbearing potential.	Yes- 2-week run-in period, during which the patients continued with their usual inhaled glucocorticosteroid therapy.

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Zetterstrom et al.{Zetterstrom, 2001 #664} 2001 Multicenter/Multinational - 59 centers in Finland, Germany, Ireland, Norway, Spain, and Sweden University hospitals AstraZeneca	Intervention: Drug 1: BUD/FM single inhaler Drug 2: BUD/FM separate inhalers Drug 3: BUD Total daily dose: Drug 1: 640mcg - reported as dose delivered Drug 2: 800mcg - reported as MD Drug 3: 800mcg Steroid dosing range: Drug 1: medium Drug 2: medium Drug 3: medium Delivery device: Drug 1: Turbuhaler Drug 2: Turbuhaler Drug 3: Turbuhaler Is dosing comparable between treatment groups? Yes	# in group (n): Drug 1: 123 Drug 2: 115 Drug 3: 124 Mean age (years): Drug 1: 47 Drug 2: 45 Drug 3: 49 Sex (% female): Drug 1: 47 Drug 2: 50 Drug 3: 50 Current smokers (%): Drug 1: 9 Drug 2: 11 Drug 3: 6 Optional - Previous ICS use (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Current use of ICS at baseline (%): Drug 1: 100 Drug 2: 100 Drug 3: 100 Groups similar at baseline? No- lower % of current smokers in BUD group	Number (%) withdrawn: Drug 1: 20 (16) Drug 2: 17 (15) Drug 3: 16 (13) Adverse events caused withdrawal (%): Drug 1: 7 Drug 2: 4 Drug 3: 5

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Zetterstrom et al.{Zetterstrom, 2001 #664} 2001 Multicenter/Multinational - 59 centers in Finland, Germany, Ireland, Norway, Spain, and Sweden University hospitals AstraZeneca	Intervention: Drug 1: BUD/FM single inhaler Drug 2: BUD/FM separate inhalers Drug 3: BUD Number in group (n): Drug 1: 123 Drug 2: 115 Drug 3: 124	Rescue med use during 24 hour period: Drug 1: -0.99 (-1.29, -0.69) Drug 2t: -1.13 (-1.43, -0.28) Drug 3: -0.44 (-0.74, -0.13) P < 0.01 for both versus BUD Rescue med use day: Drug 1 rescue-use - free days % change from baseline = +31.9 (26.3, 37.5) Drug 2 +31.9 (26.2, 37.6) Drug 3: +12.8 (7.1, 18.4) P < 0.001 for both versus BUD Asthma exacerbations: D1 : severe asthma exacerbations = 8 (6.5%) D2: 11 (9.6%) D3: 11 (8.9%) P: too few event to detect a difference -NR Symptom control during 24 hour period: D1 : Total asthma symptom score (0-6) = -0.52 (-0.065, -0.39) D2: -0.44 (-0.57, -0.31) D3: -0.2 (-0.33, -0.7) P < 0.01 for both versus BUD Day time symptom control: D1: symptom free days % change from baseline = +25 (19.5, 30.6) D2: +22.3 (16.6, 28.0) D3: +8 (2.4, 13.6) P < 0.001 for both versus BUD Night time symptom control: D1: night-time awakenings due to asthma % change from baseline = -8.4 (-8.7, -2.5) D2: -5.6 (-8.7, -2.5) D3: -5.8 (-8.8, -2.7) P = NS Asthma Control Score: D1: Asthma control days % change from baseline = +28.5 (22.8, 34.2)

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Zetterstrom et al.{Zetterstrom, 2001 #664} 2001 Multicenter/Multinational - 59 centers in Finland, Germany, Ireland, Norway, Spain, and Sweden University hospitals AstraZeneca	Overall adverse events reported (%): Drug 1: 65 - NR - I calculated this Drug 2: 63 - NR - I calculated this Drug 3: 70 - NR - I calculated this Serious adverse events (%): Drug 1: 3 Drug 2: 0 Drug 3: 0.8 Drug 5: NS (NR) Dysphonia (%): Drug 1: 0 Drug 2: 4 Cough (%): Drug 1: 4 Drug 2: 1 Drug 3: 2 Headache (%): Drug 1: 2 Drug 2: 3 Drug 3: 4 Respiratory infection (%): Drug 1: 24 Drug 2: 22 Drug 3: 26 Rhinitis (%): Drug 1: 2 Drug 2: 4 Drug 3: 3 Other (%): Drug 1: aggravated asthma = 6 Drug 2: 8 Drug 3: 4	Adherence Adherence to therapy was assessed by reviewing patient diary cards. Self-erported adherence to study medication was high (mean > 98%) in all three treatment groups.	Good Fair No

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

	Author Year Trial name Country and setting Funding	Study design/details Duration N = Number screened/eligible /enrolled	Inclusion criteria
366	Zimmerman et al.{Zimmerman, 2004 #366} 2004 Canada Multicenter NR	Study design: RCT double-blind parallel-group study Duration: 12 weeks N=302 ITT Analysis: Yes	Children aged 6–11 years who had a clinical diagnosis of asthma or at least 6 months were eligible for the study if they had: FEV1 of 50–90% of predicted normal; documented postbronchodilator reversibility of at least 15%, or at least 9% of predicted normal; and treatment with regular ICSs for at least 3 months; asthma symptoms sufficient to suggest that additional therapy might be needed

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Other medications or interventions allowed:	Exclusion criteria	Was there a run-in or washout period at the beginning of the study? Please describe briefly if so.
Zimmerman et al.{Zimmerman, 2004 #366} 2004 Canada Multicenter NR	Nasal corticosteroids and immunotherapy were permitted, provided the dose had been constant for at least 30 days and 90 days	known or suspected hypersensitivity to formoterol or inhaled lactose; deteriorating asthma or a respiratory infection; clinically significant concurrent disease; significant seasonal allergy; or if they smoked; disallowed asthma medications before trial entry: oral corticosteroids or antileukotrienes within 30 days; astemizole within 60 days; sodium cromoglycate or ketotifen within 7 days; salmeterol or formoterol within 72 hr; or xanthines or antihistamines within 48 hr.	

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention	Baseline	Withdrawals
Zimmerman et al.{Zimmerman, 2004 #366} 2004 Canada Multicenter NR	Intervention: Drug 1: FM 9 Drug 2: FM 4.5 Drug 3: Placebo Total daily dose: Drug 1: 18 µg Drug 2: 9 µg Drug 3: NA Steroid dosing range: NA Delivery device: Drug 1: Turbuhaler Drug 2: Turbuhaler Drug 2: Turbuhaler Is dosing comparable between treatment groups? No	# in group (n): Drug 1: 95 Drug 2: 101 Drug 3: 106 Mean age (years): Drug 1: 9 Drug 2: 8 Drug 3: 9 Sex (% female): Drug 1: 39 Drug 2: 37 Drug 3: 36	Number (%) withdrawn: Drug 1: 16 (16.8%) Drug 2: 7 (7%) Drug 3: 11 (10.4% Overall: 11.6% Adverse events caused withdrawal (%): Drug 1: 2 Drug 2: 0.9 Drug 3: 0

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Intervention Number in group (n)	Outcomes
Zimmerman et al.{Zimmerman, 2004 #366} 2004 Canada	Intervention: Drug 1: FM 9 Drug 2: FM 4.5 Drug 3: Placebo	Symptoms: No difference [Total symptom score: baseline mean (range): 1.32 (0.0–4.0) vs 1.58 (0.1–4.2) vs 1.50 (0.0–4.0); treatment mean (range): 1.02 (0.0–3.3) vs 1.28 (0.0–4.2) vs 1.23 (0.0–4.4); adjusted mean change from baseline: -0.37 vs -0.28 vs -0.27, P=NS]
Multicenter NR	Subjects continued their current ICS and were randomized to FM (18) vs. FM (9) vs. placebo Number in group (n): Drug 1: 95 Drug 2: 101 Drug 3: 106	Rescue med use: No difference [mean #inhalations/day: baseline mean (range): 0.74 (0.0–5.6) vs 1.04 (0.0–5.4) vs 1.36 (0.0–9.2); treatment mean (range): 0.72 (0.0–5.2) vs 0.73 (0.0–8.4) vs 0.95 (0.0–7.7); adjusted mean change from baseline: -0.13 vs -0.27 vs -0.21, P=NS] Quality of life: No difference [PAQLQ total score: baseline mean (range): 5.33 (2.4–6.9) vs 5.13 (2.5–7.0) vs 5.09 (1.6–6.9); treatment mean (range): 5.80 (3.4–7.0) vs 5.72 (2.7–7.0) vs 5.76 (2.2–7.0); adjusted mean change from baseline: 0.49 vs 0.52 vs 0.57]

Evidence Table 1. Randomized controlled trials and observational studies of controller medications of asthma

Author Year Trial name Country and setting Funding	Adverse events:	Is adherence or compliance reported? Rate of adherence or compliance that is given in the article and any differences between treatment groups?	Quality rating for efficacy/effectiveness Adverse events assessment Effectiveness Trial
Zimmerman et al.{Zimmerman, 2004 #366} 2004 Canada Multicenter NR	Respiratory infection: Drug 1: 31 (33) Drug 2: 45 (43) Drug 3: 36 (36) Headache: Drug 1: 10 (11) Drug 2: 13 (12) Drug 3: 14 (14) Pharyngitis: Drug 1: 6 (6) Drug 2: 11 (10) Drug 3: 11 (11) Asthma aggravated: Drug 1: 6 (6) Drug 2: 5 (5) Drug 3: 11 (11) Rhinitis: Drug 1: 8 (8) Drug 2: 4 (4) Drug 3: 10 (10) Fever: Drug 1: 3 (3) Drug 2: 3 (3) Drug 3: 7 (7) Infection, viral: Drug 1: 7 (7) Drug 2: 4 (4) Drug 3: 5 (5) Abdominal pain: Drug 1: 1 (1) Drug 2: 6 (6) Drug 3: 5 (5)		Fair Fair No

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
594	Adams, N et al 2000 Cochrane Database Systematic Review NHS Research and Development UK and Garfield Weston Foundation UK	systematic review with meta-analysis	1174 subjects (24 studies)	To assess clinical outcomes in studies which have compared inhaled BDP and BUD in the treatment of chronic asthma.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Adams, N et al 2000 Cochrane Database Systematic Review NHS Research and Development UK and Garfield Weston Foundation UK	24 studies met the criteria for inclusion: Baran D. Brit J Diseases of the Chest 1987;81(2):170–5.; Bisgaard J All & Clin Immunol 1988;81(6):1088–95.; Bjorkander J, Euro J Resp Dis - Supplement 1982;122:108–17.; Boe J, Allergy: Euro J All & Clin Immunol 1989;44(5):349–55.; Brambilla C, Drug Investigation 1994;8(1): 49–56.; Dal Negro R, Euro Resp J. 1997:351S.; Ebden P, Thorax 1986;41(11):869–74.; Field HV, Arch Dis Childhood 1982;57(11): 864–6.; Greefhorst APM. Euro Resp J. 1992; Vol. 5, issue Suppl 15:360S.; Hamalainen KM, Euro Resp J 1998:61S.; Keelan P, Irish Medical Journal 1984;77(8): 244–7.; Micheletto C, Euro Resp J. 1997:351S.; Nicolaizik WH, Am J Respir & Crit Care Medicine 1994;150 (3):624–8.; Pedersen S, Euro Respir J 1988;1(5): 433–5.; Petrie GR, Drug Investigation 1990;2(2):129–31.; Rafferty P, Bri J Dis of the Chest 1985;79(3):244–50.; Selroos O, Allergy: Eu J All & Clin Immunol 1994;49(10):833–6.; Springer C, Arch Dis in Childhood 1987;62(8):815–9.; Stiksa G, Euro J Respir Dis - Supplement 1982;122:266–7.; Stiksa G, Euro J Resp Dis - Supplement 1982;122:266–7.; Stiksa G, Annals of Allergy 1985;55(1):49–51.; Svendsen 1992: [[Svendsen UG, Ugeskrift for Laeger 1993;155(28):2197-

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Adams, N et al 2000 Cochrane Database Systematic Review NHS Research and Development UK and Garfield Weston Foundation UK	Five studies (Bisgaard 1988, Brambilla 1994, Dal Negro 1997, Micheletto 1997, Selroos 1994) were parallel group studies. Nineteen studies (79%) were of crossover design. The length of treatment period varied. Twelve studies (50%) had treatment periods of between two and four weeks, 10 studies (42%) had treatment periods of between six and 12 weeks. The longest study (Selroos 1994) had an effective treatment period of two years. Methodological quality of included studies was variable. Only 10 studies (42%) were double blind. 19 studies (79%) provided adequate descriptions of numbers of patients withdrawn and the reasons for withdrawal. As assessed by the Jadad scoring method 15 studies (63%) achieved a score of 3 or 4; no studies achieved a maximum score of 5. In only four studies (17%) was allocation concealment clearly employed. In all other studies allocation concealment was unclear.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Adams, N et al 2000 Cochrane Database Systematic Review NHS Research and Development UK and Garfield Weston Foundation UK	Symptoms: No difference [symptom score (6 cross-over studies): SMD 0.06, 95% CI: -0.18 to 0.31, 6 studies; night-time breathlessness (three cross-over studies): SMD -0.09 (95% CI -0.43 to 0.25)] Rescue medicine use: No difference [qualitative summary, no meta-analysis]

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Adams, N et al 2000 Cochrane Database Systematic Review NHS Research and Development UK and Garfield Weston Foundation UK	ASTHMA NOT TREATED WITH ORAL STEROIDS CROSSOVER STUDIES Hypothalamo-pituitary adrenal axis (HPA) function Three studies (118 subjects) reported morning plasma cortisol. Two studies (76 subjects) reported plasma cortisol following a short cosyntropin test. No significant differences between BDP and BUD treatment groups were evident. In a single crossover study (Pedersen 1988), conducted in children and of fair methodological quality (Jadad score 3) 24 hour urinary free cortisol excretion was assessed. In this study subjects treated with BDP 800-1200 mcg/d had significantly lower 24 hour urinary cortisol levels compared to BUD 800-1200 mcg/d: BDP 7.6 nmol cortisol/ mmol creatinine/day v BUD 10.2 nmol cortisol/mmol creatinine/day p<0.01. Local oral side effects The incidence of local oral side effects was reported in a number of crossover studies (Baran 1987, Boe 1989, Ebden 1986, Petrie 1990, Svendsen 1992). However, interpretation of the results is extremely difficult. In each study, the incidence of side effects was reported by treatment (BDP or BUD), rather than by individual treatment perio experiencing an adverse event during the first period of the trial when receivi Because none of the studies incorporated washout periods, this was especial side effects from the crossover studies comparing BDP to BUD are uninterpre PARALLEL GROUP STUDIES: DOSE-DOWN TITRATION DESIGN There were no significant differences between treatments with regard to the i PARALLEL GROUP STUDIES: DOSE ESCALATION DESIGN Outcomes reported included 24-hour urinary free cortisol excretion and plasm ASTHMATICS TREATED WITH ORAL STEROIDS CROSSOVER STUDIES: OCS-SPARING STUDY DESIGN: NR CROSSOVER STUDIES: NON OCS-SPARING STUDY DESIGN: NR 	Good

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Study design:	Number of patients:	Aims of review:
Adams, N et a., 2007□ Cochrane Database Systematic Review□ NHS Research and Development UK	systematic review with meta-analysis	71 trials (14,602 participants),	Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Adams, N et a., 2007 Cochrane Database Systematic Review NHS Research and Development UK	FP vs. BDP (33 trials) FP vs. BUD (37) FP vs. BDP/BUD (2) 38 studies had FP:BDP/BUD dose ratio of 1:2; 22 had dose ratio 1:1; remainder had multiple dose ratio comparisons or ratio was unclear

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Adams, N et a., 2007 Cochrane Database Systematic Review NHS Research and Development UK	RCTs

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Adams, N et a., 2007 Cochrane Database Systematic Review NHS Research and Development UK	Dose ratio 1:2: Symptoms: FP > BDP/BUD [Change in symptom scores: SMD: -0.19 (95% CI -0.31 to -0.07) 6 studies, N = 1035. Absolute percentage of symptom free days: MD 4.9% (95% CI -1 to 11), two studies, N = 699. Change in percentage of symptom free days: MD 6.43% (95% CI 0.47 to 12.39), two studies, N = 399.] Nocturnal awakenings: No difference [Change in number of awakenings per night: MD: 0.01 (95% CI -0.04 to 0.06), two studies, N = 282] Exacerbations: No difference [Withdrawal due to asthma exacerbation: Peto OR 0.77 (95% CI 0.54 to 1.1), 11 studies N = 2824; Participants with an exacerbation: Peto OR 0.74 (95% CI 0.53 to 1.03), four studies N = 1213; Withdrawal due to lack of efficacy: Peto OR 0.6 (95% CI 0.33 to 1.07), seven studies, N = 1781] Rescue med use: FP > BDP/BUD [Change in percentage of rescue-free days: MD 6.89% (95% CI 0.32 to 13.46), two studies, N = 399; Change in rescue usage (puffs/day): MD -0.35 puffs (95% CI -0.63 to -0.07), four studies, N = 763; # of participants experiencing rescue-free days and nights: no significant differences were reported, 6 studies reported (data not pooled for several reasons)] Dose ratio 1:1: Symptoms: No diff

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Adams, N et a., 2007 Cochrane Database Systematic Review NHS Research and Development UK		

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
3762	Ducharme, F et al. □ 2004□ Cochrane Review□ Canadian Cochrane Network CANADA and Fonds de la Santé du Québec CANADA	systematic review and meta-analysis	5871 (27 studies)	In patients who were symptomatic, despite use of maintenance ICS, to determine whether the addition of anti-leukotriene agents reduced the frequency and severity of exacerbations and improved chronic asthma control while maintaining a good safety profile. The addition of anti-leukotriene agents to inhaled corticosteroids was compared to either the use of the same or double dose of ICS. Also, in patients who were well controlled on their baseline dose of ICS, we wished to quantify the magnitude of dose reduction in inhaled glucocorticoids (glucocorticoid-sparing effect) that could be achieved with the addition of antileukotrienes.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Ducharme, F et al. □ 2004□ Cochrane Review□ Canadian Cochrane Network CANADA and Fonds de la Santé du Québec CANADA	Baba 1999 {published data only}, Baba, K et al. The usefulness of pranlukast or seratrodast for step-down of inhaled corticosteroid therapy in adult chronic asthma. American Journal of Respiratory & Critical Care Medicine 1999;159(3 (Part 2 of 2)):A 626. Bateman 1995 {published and unpublished data} Bateman, ED et al. A multicentre study to assess the steroid-sparing potential of Accolate (zafirlukast; 20 mg bd). Allergy 1995;50(Suppl 26):320, Abs. P-0709. Finn 2000 {published data only} Finn, AF et al. Zaifirlukast improves asthma control in children treated with and without inhaled corticosteroids. European Respiratory Journal 2000;16(Supplement 31):307. Green (abs) 2002 {published data only} Green, RH et al. A placebo controlled comparison of formoterol, montelukast or higher dose of inhaled corticosteroids in subjects with symptomatic asthma despite treatment with low dose inhaled corticosteroids. Thorax 2002;57(Supp III):iii11 (S31). Hultquist 2000 {unpublished data only} Hultquist, C et al. Oxis turbuhaler (formoterol), accolate (zafirlukast) or placebo as add-on treatment to pulmicort turbuhaler (budesonide) in asthmatic patients on inhaled steroids. Astra-Z in asthmatic patients symptomatic on low-dose inhaled corticosteroids. Journal of Allergy & Clinical Immunology 1998;101(1 part 2):S233, Abs 965. Nis

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Ducharme, F et al. □ 2004□ Cochrane Review□ Canadian Cochrane Network CANADA and Fonds de la Santé du Québec CANADA	RCTs only; A total of 27 (2 paediatric and 25 adult) trials, 16 of which were published in full text at the time of this report (Kanniess 2002; Laviolette 1999;O'Sullivan 2003;Price 2003;Riccioni 2001;Riccioni 2002;Shingo 2002;Simons 2001; Tamaoki 1997; Tohda 2002;Tomari 2001;Tomita 1999;Vaquerizo 2003 ;Virchow 2000; Wada 1999),met the inclusion criteria for this review. We grouped these 27 trials according to one of three protocols defining their specific objective and design. □ □ Randomised placebo controlled trials in adults and children in which anti-leukotriene agents were added to inhaled glucocorticoid were considered for inclusion. Sensitivity analyses were performed based on the reported quality of randomisation, concealment of allocation, blind assessment of outcomes, and description□ of withdrawals and dropouts.□ □ Anti-leukotrienes + ICS versus SAME dose of inhaled corticosteroids (ICS): □ Thirteen trials, including 10 full-text publications (Laviolette 1999; O'Sullivan 2003;Riccioni 2001;Riccioni 2002;Simons 2001;Tamaoki 1997;Tomita 1999;Vaquerizo 2003 ;Virchow 2000;Wa study to determine the impact on inflammatory markers □ Anti-leukotrienes + ICS versus INCREASED dose of IC Seven trials, (Green RH 2002; Nayak 1998;Nsouli 200 trials, placebo-controlled. In two trials (Nayak 1998;Rin □ Anti-leukotrienes + ICS versus SAME dose of ICS (TA Seven trials included participantswhowerewell controlle

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Ducharme, F et al. 2004 Cochrane Review Canadian Cochrane Network CANADA and Fonds de la Santé du Québec CANADA	LTRA+ICS vs. Same ICS: Symptoms: No difference [change in symptom score (WMD = -0.10, 95% CI -0.24 to 0.03) or nocturnal awakenings (WMD -6.25, 95% CI -12.72 to 0.23) with licensed doses of LTRAs] Exacerbations: LTRA+ICS >ICS trend [reduction in the risk of exacerbations requiring systemic steroids: RR 0.64, 95% CI 0.38 to 1.07] Rescue medicine use: LTRA+ICS > ICS [change from baseline in beta-agonists use (SMD -0.15, 95% CI -0.24 to -0.05)] QOL: No difference [(WMD 0.08, 95% CI -0.03 to 0.20)] LTRA+ICS vs. Increased ICS : Symptoms: No difference [change from baseline in symptoms score (WMD 0.01, 95%CI -0.09 to 0.10)] Exacerbations: No difference [risk of exacerbation requiring systemic steroids: RR 0.92, 95% CI 0.56 to 1.51; withdrawals due to poor asthma control: RR 0.49, 95% CI 0.15 to 1.63] Rescue medicine use: No difference [change from baseline in use of rescue beta-agonists: WMD -0.03 95% CI -0.24 to 0.18]

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Ducharme, F et al. □ 2004□ Cochrane Review□ Canadian Cochrane Network CANADA and Fonds de la Santé du Québec CANADA	Anti-leukotrienes + ICS vs. SAME dose of ICS:□ No significant group differences were observed in the risk of overall withdrawals (3 trials, RR 0.97, 95% CI 0.69 to 1.37), withdrawal due to poor asthma control (3 trials, RR 0.46, 95% CI 0.16 to 1.31), withdrawals due to adverse effects (3 trials, RR 0.63, 95% CI 0.29 to 1.37), overall adverse effects (2 trials, RR 1.01, 95% CI 0.88 to 1.15), elevated liver enzymes (2 trials, RR 1.02, 95% CI 0.36 to 2.88), headache (3 trials, RR 1.15, 95% CI 0.89 to 1.49), and nausea (2 trials, RR 0.45, 95%CI 0.19 to 1.07),. There was no death. For pooling of two trials that used higher than licensed odses of pranlukast or zafirlukast: There was no significant group difference in the risk of overall withdrawals (2 trials, RR 0. 74 95%CI 0.39 to 1.39), withdrawals due to adverse effects (RR 0.73, 95% CI: 0.28 to 1.88), overall adverse effects (RR 1.02, 95% CI: 0.81 to 1.27) and nausea (RR 1.48, 95% CI 0.45 to 4.87).□ □ Anti-leukotrienes + ICS vs. INCREASED dose of ICS:□ Safety measures also show no significant group difference□ for overall withdrawals (2 trials, RR 0.99, 95% CI 0.63 to 1.55), withdrawals d □ When comparing the combination of two to four-fold the licensed doses of leu □ Anti-leukotrienes + ICS vs. SAME dose of ICS (TAPERING ICS dose):□ Less withdrawals due to any cause were observed in the leukotriene receptor 1.08, randomeffectmodel), elevated liver enzymes (RR1.67, 95% CI 0.86 to 3	good

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
3764	Ducharme, F et al. 2004 Cochrane Review Fonds de la Santé du Québec CANADA	systematic review and meta-analysis	9100 (27 trials)	The aim of this systematic review was (1) to compare the safety and efficacy of daily oral anti-leukotrienes with that of ICS in the management of children and adults with chronic asthma and (2) to determine the minimal required dose of maintenance ICS equivalent to the effect of anti-leukotriene agents. We also sought to determine whether the anti-leukotriene and inhaled steroid used, intervention duration, disease severity, patients' age, methodological quality, publication status and sponsorship influenced the magnitude of effect attributable to antileukotrienes.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Ducharme, F et al. 2004 Cochrane Review Fonds de la Santé du Québec CANADA	Basyigit 2001 {published data only} Basyigit IE, Yildiz F, Ozkara SK, Boyaci H, Ilgazli A, Ozkarakas O. The effects of inhaled steroids, leukotriene receptor antagonists and theophylline on induced sputumcell counts, serumand sputum ECP levels in mild persistent asthma. Eur Resp J 2001;18(supp 33):2615. Baumgartner 2003 {unpublished data only} Baumgartner RA, Martinez G, Edelma JM, Rodriguez Gomez GG, BersteinM, Bird S, Angner R, Polis A, Dass SB, Lu, Reiss TF. Distribution of therapeutic response in asthma control between oral montelukast and inhaled beclomethasone. Eur Respir J 2003; Vol. 21: 123–128. Bleecker 2000 {unpublished data only} Bleecker ER, Welch MJ, Weinstein SF, Kalberg C, Johnson M, Edwards L, et al. Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. Journal of Allergy & Clininal Immunology 2000;105(6):1123–9. Brabson 2002 {published data only} Brabson JH, Clifford D, Kerwin E, Raphael G, Pepsin PJ, Edwards LD, Srebro S, Rickard K. Efficacy and safety of low-dose fluticasone propionate compared with zafirlukast in patients with persistent asthma. Am J Med 2002;113:15–21. Busse 2001 {unpublished data only} BusseW, Raphael GD, Galant S, Kalberg C, Goode-Sellers S, Srebro S, et al. Low-dose fluticasone propionate con of Respiratory & Critical Care Medicine 1999;159:A641. Hughes 1999 (FP) {unpublished data only} Hughes GL, Edelman JM, Turpin JA, Liss C, Weeks Laitinen 1997 {unpublished data only} Laitinen LA, Naya IP, Binks S, Harris A. Comparative efficacy of zafirlukast & low dose steroids in asthmatics on p 1999;160(6):1862–8. Malmstrom 1999 {published and unpublished data} Malmstrom K, Rodriguez-Gomez G, Guerra J, Villaran C, Pineiro A, Lynn X, et function on treatment response: low-dose fluticasone versus zafirlukast. Am Allergy Asthma Immunol 2001;86:2001. Sheth 2001 (Abs) B {published data Twenty seven, including 14 new, trials met the inclusion criteria for this review. Of these, 20 were published in full text (Baumgartner 2003;Bleecker 200 report provided by the authors (Hughes 1999 (BDP);Laitinen 1997;Zieger (Abs)) and the remaining 4 citations were available only in abstract form (Basy

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Ducharme, F et al. 2004 Cochrane Review Fonds de la Santé du Québec CANADA	RCTs conducted in adults and/or in children in which leukotriene antagonists were compared to ICS were included.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Ducharme, F et al. 2004 Cochrane Review Fonds de la Santé du Québec CANADA	Symptoms: ICS > LTRA [symptom scores: 6 trials, SMD=0.29, 95% CI: 0.21 to 0.37; symptom-free days: 3 trials, WMD= -12, 95%CI: -16 to -7; and nocturnal awakenings: 6 trials, SMD=0.21, 95% CI: 0.13 to 0.30]. Exacerbations: ICS > LTRA for some [65% increased risk of exacerbation requiring systemic steroids for any LTRA: relative risk 1.65 (1.36 - 2.00); No significant difference in exacerbations requiring hospitalization [relative risk 1.62 (0.64 – 4.15)] Rescue medicine use: ICS > LTRA [daily use of B2-agonists: 6 trials, WMD= 0.28 puffs/day, 95% CI: 0.20 to 0.36; rescue-free days: 3 trials, WMD= -14%, 95% CI: -18 to -10] Quality of Life: ICS > LTRA [quality of life: 2 trials: WMD= -0.3, 95% CI: -0.4 to -0.2]. Missed work or school: No difference [days off from school/work: 2 trials, WMD= 0.06 days, -0.03 to 0.15].

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Ducharme, F et al. 2004 Cochrane Review Fonds de la Santé du Québec CANADA	WITHDRAWALS: Anti-leukotriene therapy was associated with a 30% increased risk of overall withdrawals [N=19 trials, RR=1.3, 95% CI: 1.1 to 1.6, random effect model]. The withdrawals appeared to be attributable to a marked increased risk of withdrawals due to poor asthma control [N=17 trials, RR=2.6, 95% CI: 2.0 to 3.4, fixed effect model] and not due to adverse effects [N=14 trials, RR= 1.2, 95% CI: 0.9 to 1.6, fixed effect model]. If 29 patients are treated with anti-leukotrienes rather than inhaled corticosteroids there will be one extra withdrawal due to poor asthma control , NNH 29 (95% CI 20 to 48). ADVERSE EFFECTS: There was no significant group difference in the number of patients who experienced “any adverse effects,” [N=15 trials, RR= 0.99, 95% CI: 0.93 to 1.04, fixed effect model], which met our definition of equivalence. There was also no significant difference in elevation of liver enzymes, [N=6 trials, RR=1.3, 95% CI: 0.7 to 2.3], headaches [N=16 trials, RR=0.9, (95% CI: 0.8 to 1.1], nausea [N=12 trials, RR=1.0, 95% CI: 0.7 to 1.5)], oral candidiasis [N=2 trials, RR=0.15, 95% CI: 0.02 to, 1.18], or death which was reported in c	good

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
2648	Ducharme, F.□ 2002□ Salary award of the Fonds de la Recherche en Santé du Québec. Ritz Kakuma was supported by the Canadian Cochrane Network.	systematic reivew and meta-analysis	2967 (13 studies)	Examined the safety and efficacy of oral anti-leukotrienes as add- on therapy to inhaled glucocorticoids in children and adults with asthma to quantify the improvement in asthma control achieved over inhaled steroids alone (at the same or double the dose) and the glucocorticoid sparing effect when inhaled steroids are tapered.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Ducharme, F. 2002 Salary award of the Fonds de la Recherche en Santé du Québec. Ritz Kakuma was supported by the Canadian Cochrane Network.	Lofdahl, C et al. BMJ 1999;319:87. Tamaoki, J et al. Am J Respir Crit Care Med 1997;155:1235. Virchow, J et al. Am J Respir Crit Care Med 1997;156:578. Laviolette, M et al. Am J Respir Crit Care Med 1999;160:1862. Simons, F et al. J Pediatr 2001;138:694. Wada, K et al. Allergol INt 2000;49:63. Ringdal, N et al. Am J Respir Crit Care Med 2000;159 (3 of part 2):639. (Abstract) Nayak, A et al. J Allergy Clin Immunol 1998;101 (1 of part 2): S233 (Abstract 965). Tomita, T et al. Arerugi 1999;48:459. Bateman, E et al. Allergy 1995;50 (suppl 26): 320. (Abstract P-0709). Laitinen, L et al. Allergy 1995; 50 (suppl 26): 320 (Abstract P-0710). Baba, K et al. Am Rev Resp Crit Care Med 1999;159:A626. Shingo, S et al. Theodore Reiss, personal communication, 2001.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Ducharme, F. 2002 Salary award of the Fonds de la Recherche en Santé du Québec. Ritz Kakuma was supported by the Canadian Cochrane Network.	RCTs only. Documented measures of efficacy other than compliance. For the SR/MA, the primary outcome measures were the number of exacerbations of asthma requiring rescue systemic glucocorticoids when the intervention was compared with the same or an increased dose of inhaled glucocorticoids and the change from the base-line dose of inhaled glucocorticoids required to main-tain control when the intervention was aimed to establish the steroid sparing effect. Secondary out-comes were changes in pulmonary function tests, symptoms, use of rescue ß2 agonists, quality of life, exacerbations requiring hospital admission, adverse effects, and withdrawals. data from 13 trials (one study in children and 12 in adults; six unpublished as of August 2001) were included in the review.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Ducharme, F. 2002 Salary award of the Fonds de la Recherche en Santé du Québec. Ritz Kakuma was supported by the Canadian Cochrane Network.	Anti-leukotrienes versus placebo as add--on therapy to inhaled glucocorticoids: Although four of the six identified trials contributed data to the primary outcome, only two tested anti-leukotrienes (montelukast; Singulair, Merck Frosst) at licensed doses. With the addition of licensed doses of anti-leukotrienes to glucocorticoids, a non-significant reduction in the risk of exacerbations requiring systemic steroids was observed (relative risk 0.61, 95% confidence interval 0.36 to 1.05). The only paediatric trial did not show any significant group dif-ference. When higher doses were examined, the addition of pranlukast (Ono, Japan), or zafirlukast (Accolate, Astra Zeneca) reduced the risk of exacerba-tions requiring systemic steroids by 66% (relative risk 0.34, 0.13 to 0.88) (fig 2). The number needed to treat was 20 (11 to 100). Within each stratum the results were homogeneous despite the different doses and anti-leukotrienes tested, age, baseline dose of inhaled glucocorticoids, and duration of anti-leukotriene use. No evidence was found of systematic bias identified by the measure of funnel plot asymmetry (intercept 0.17, –3.22 to 3.55). Pooling of the two trials of higher than licensed doses of pranlukast or zafirlukast for six weeks showed a s anti-leukotrienes to inhaled corticosteroids. This was shown in the magnitude of improvement from baseline Anti-leukotrienes as add-on therapy to inhaled glucocorticoids versus double dose inhaled glucocorticoids: The data from two unpublished trials, each testing two different doses of zafirlukast, were analysed. Pooling the licensed dose. No apparent group difference was found in the risk of an exacerbation requiring systemi 80 mg twice daily (relative risk 1.08, 0.47 to 2.50); the width of this confidence interval exceeded our definit trials prevented subgroup and sensitivity analyses. No group difference was found in secondary outcomes withdrawal due to poor asthma control, or hospital admission. Anti-leukotrienes versus placebo as add-on therapy to tapered doses of inhaled glucocorticoids: The data from four of the five identified trials testing licensed doses of anti-leukotrienes were provided in su the glucocorticoid sparing effect of anti-leukotrienes depends on showing adequate and comparable contro ingful group difference was observed either (–44.43 mcg/day, –147.87 to 59.02; random effect model). He analysis. The rate of complete glucocorticoid weaning was similar between groups (three trials, relative risk

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Ducharme, F. 2002 Salary award of the Fonds de la Recherche en Santé du Québec. Ritz Kakuma was supported by the Canadian Cochrane Network.	Anti-leukotrienes versus placebo as add-on therapy to inhaled glucocorticoids: No significant group difference was observed in the risk of overall with-drawals (relative risk 0.91, 0.54 to 1.53), withdrawals owing to adverse effects (0.65, 0.26 to 1.66), increased liver enzyme concentrations (1.02, 0.36 to 2.88), head-ache (1.16, 0.86 to 1.57), and nausea (0.45, 0.19 to 1.07). No death was reported. Pooling of the two trials of higher than licensed doses: No group difference in overall adverse events or nausea was observed; insufficient number of trials prevented pooling of data for other adverse effects. Anti-leukotrienes as add-on therapy to inhaled glucocorticoids versus double dose inhaled glucocorticoids: Zafirlukast (80 mg twice daily) was associated with an increased risk of increased liver enzyme concentrations (5.36, 1.40 to 20.44) and of withdrawal due to adverse events (2.77, 1.02 to 7.58)— that is, 1 in every 25 (95% confidence interval 14 to 100) patients and 1 in every 33 (16 to infinity) patients treated with high dose zafirlukast would have an increase in liver enz Anti-leukotrienes versus placebo as add-on therapy to tapered doses of inhal No group difference was found in the number of overall withdrawals, withdrav (0.90, 0.64 to 1.26), or nausea (1.14, 0.49 to 2.67). The similarity between gr	good

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
47	Ducharme, FM et al.□ 2006□ Cochrane Review□ Nederlands Astma Fonds NETHERLANDS, Francine M. Ducharme CANADA, NHS Research and Development UK	Systematic Review and Meta-analysis of randomised, parallel-group, trials	Fifteen randomised controlled trials - 6476 participants (80 children participants) - 6,030 patients included to meta-anaylsis	Compared the efficacy and safety profile of adding either daily LABA or LTRA in asthmatic patients who remained symptomatic□ on ICS.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Ducharme, FM et al. 2006 Cochrane Review Nederlands Astma Fonds NETHERLANDS, Francine M. Ducharme CANADA, NHS Research and Development UK	Nine full-text publications (Bjermer 2003; Ceylan 2004; Fish 2001; Grosclaude 2003; Ilowite 2004; Nelson 2000; Nelson 2001; Ringdal 2003; Storms 2004), two unpublished full-text reports (Hultquist 2000;McCarthy 2003) and four abstracts (Green (abs) 2002; Hendeles 2004; Nsouli 2001; Stelmach 2005). The abstracts did not provide data in sufficient detail to contribute to the meta-analyses. Therefore, the description hereafter pertained to eleven trials which contributed data from 6,030 patients to the meta-analysis.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Ducharme, FM et al. 2006 Cochrane Review Nederlands Astma Fonds NETHERLANDS, Francine M. Ducharme CANADA, NHS Research and Development UK	Only randomised controlled trials conducted in adults or children with recurrent asthma where a LABA (for example, salmeterol or formoterol) or LTRA (for example, montelukast, pranlukast, zafirlukast) was added to ICS for a minimum of 28 days were considered for inclusion. Inhaled short-acting ß2-agonists and short courses of oral steroids were permitted as rescue medications. Other daily asthma treatments were permitted, providing the dose remained constant during the intervention period. Twelve trials reported double-blinding while Ceylan 2004; Grosclaude 2003 and Nsouli 2001 were open-labelled. Nine double-blind trials reported the use of double-dummies to maintain allocation concealment; while three trial failed to clearly report means of blinding (Green (abs) 2002; Hendeles 2004; Stelmach 2005). Withdrawal rate was described in all but the two studies reported as abstracts (Green (abs) 2002; Nsouli 2001). Although total withdrawals were reported in Ceylan 2004, it was not clear how many participants from each group withdrew. Withdrawal rates varied from 8 to 17% in the LTRA group and 5 to

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Ducharme, FM et al. 2006 Cochrane Review Nederlands Astma Fonds NETHERLANDS, Francine M. Ducharme CANADA, NHS Research and Development UK	Symptoms: LABA + ICS > LTRA + ICS [% symptom free days: 6.75%; 95% CI 3.11 to 10.39, improvement in daytime symptom score: -0.18; 95% CI -0.25 to -0.12, decrease in nighttime awakenings: -0.12; 95% CI -0.19 to-0.06, increase in % awakening-free nights per week: 6.89%; 95% CI 2.87 to 10.91]. Exacerbations: LABA + ICS > LTRA + ICS [risk of exacerbation requiring systemic steroids: RR 0.83; 95% CI 0.71 to 0.97; regardless of LABA used, risk of exacerbation requiring hospital admission: RR 1.31; 95%CI: 0.58 to 2.98]. Rescue medicine use: LABA + ICS > LTRA + ICS [increase in % rescue free days: 8.96%; 95% CI 4.39 to 13.53, but there was significant heterogeneity in this pooled estimate with a significant difference between the two subgroups P < 0.05]. QOL: LABA + ICS > LTRA + ICS [increase (improvement) in Global Asthma Quality of Life score: 0.11; 95% CI 0.05 to 0.17]. Mortality: no difference (P = NR)

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Ducharme, FM et al. 2006 Cochrane Review Nederlands Astma Fonds NETHERLANDS, Francine M. Ducharme CANADA, NHS Research and Development UK	Withdrawals due to adverse effects: Ten studies with 6,225 patients reported withdrawals due to adverse effects (Bjermer 2003; Fish 2001; Grosclaude 2003; Hultquist 2000; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Ringdal 2003; Storms 2004). The overall estimate comparing LABA+ICS with LTRA+ICS did not show a significant difference between the groups (RR 1.02; 95%CI 0.80 to 1.32). There was also no significant difference in withdrawals due to adverse effects between subgroups when the studies were subgrouped according to type of LTRA. Withdrawals due to poor asthma control/exacerbations: Seven studies with 5,276 patients reported this outcome measure (Bjermer 2003; Fish 2001; Grosclaude 2003;Hultquist 2000; Ilowite 2004; Nelson 2000; Nelson 2001). There were no significant differences in the overall estimate (RR 0.87; 95%CI 0.49 to 1.56) or between the subgroups. There was heterogeneity present (I2= 46.6%). Patients with one or more exacerbations requiring hospital admission: Three studies with 3,747 patients reported this outcome (Bjermer 2003; Ilowite 2004; Ringdal 2003) comparing LABA+ICS to Montelukast+ICS Severe adverse events: Six studies with 5,592 patients reported this outcom Deaths: Only one study reported deaths (Bjermer 2003) with no significant di occurred). Headache: Ten studies with 6,187 patients reported headache as an adverse Hultquist 2000; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Rin Cardiovascular events: Five studies with 5,163 patients reported cardiovascu Oral moniliasis: Six studies with 5,203 patients reported number of patients v of oral moniliasis of 1% for LABA and 0.5% for LTRA. The risk difference for t Osteopenia/osteoporosis: Two studies reported this outcome (Bjermer 2003; Elevated liver enzymes: One study reported this outcome (Bjermer 2003) wit Overall adverse events: Eight studies (Bjermer 2003; Fish 2001; Ilowite 2004	good

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
2012	Gibson 2005 Cochrane	Systematic review and meta-analysis	4528	To determine the efficacy of adding LABA to maintenance ICS therapy in reducing the requirement for ICS while maintaining control of chronic asthma.
173	Greenstone 2005 Multinational Cochrane	Systematic review and meta-analysis	9509	To determine, in asthmatic patients, the effect of the combination of long-acting ß2 agonists and inhaled corticosteroids compared to a higher dose of inhaled corticosteroids on the incidence of asthma exacerbations, on pulmonary function and on other measures of asthma control and to look for characteristics associated with greater benefit for either treatment option.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Gibson 2005 Cochrane	19 citations (9 publications and 10 abstracts) describing 10 parallel designed RCTs - Baranuik 1999; Lalloo 2001; Bloom 2003; Dorinsky 2004; Kips 2000; Pauwels 1997; Busse 2003; Nielsen 1999; Self 1998; Lemanske 2001;)
Greenstone 2005 Multinational Cochrane	30 - three pediatric; 27 adult) (Fowler 2002, Pearlman 1999a, Heuck 2000, Baraniuk 1999, Bateman 2003, Bergmann 2004, Boulet 2003, Bouros 1999, Busse 2003, Johansson 2001, Lalloo 2003, Li 1999, Mitchell 2003, Ortega-Cisneros 1998, Van Noord 1999, Vermetten 1999, Wallin 2003, Condemi 1999, Greening 1994, Ind 2003, Jenkins 2000, Kalberg 1998, Kelsen 1999, Murray 1999, Woolcock 1996, Woolcock 1996, Kips 2000, O'Byrne 2001, Pauwels 1997, Verberne 1998a)

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Gibson 2005 Cochrane	Randomised controlled trials of parallel design only were considered. Double, single or unblinded studies were considered.
Greenstone 2005 Multinational Cochrane	RCTs - Trial duration was 24 weeks or less in all but four trials.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Gibson 2005 Cochrane	1) Abrupt fixed reduced ICS + LABA versus fixed moderate or high dose of the same ICS Exacerbations requiring OCS: RR 1.0 (95% CI 0.76 to 1.32), comparison 1.01. Withdrawal due to worsening asthma: RR 0.82 (95% CI 0.50 to 1.35), comparison 1.02. Rescue medication use (puffs/day) change from baseline: WMD -0.11 (95%CI -0.25 to 0.03), comparison 1.07. Percent rescue free days change from baseline: WMD 9.21 (95%CI 1.36 to 17.05). Chi2 = 5.11, P = 0.08, I2 = 60.9%, comparison 1.08. Night Waking change from baseline: WMD 0.02 (95%CI -0.09 to 0.12), comparison 1.11. Percent symptom free days: WMD 5.76 (95%CI 0.81 to 10.7), comparison 4.09. Night Waking change from baseline: WMD 0.02 (95%CI -0.09 to 0.12), comparison 3.11. Overall Withdrawals: RR 0.97 (95%CI 0.74 to 1.28), comparison 1.13. 2) Reduced or tapering ICS + LABA versus reduced or tapering dose of the same ICS according to asthma control [significantly greater proportion of participants in the LABA/ ICS group attained a > 50% reduction in ICS dose with no significant difference in FEV1(L), morning or evening PEF between treatment groups when compared to their baseline sensitivity period.]
Greenstone 2005 Multinational Cochrane	The combination of LABA and ICS resulted in greater improvement from baseline in symptom-free days [N=8 , WMD=11.90% (95% CI:7.37, 16.44), random effects model], and in the daytime use of rescue ß2 agonists than a higher dose of ICS [N=4,WMD= -0.99 puffs/day (95% CI: -1.41, -0.58), random effects Patients with exacerbation requiring hospitalisation [N=11, RR= 0.73 (95% CI: 0.36, 1.49), fixed effects model]. However, the Number of withdrawals due to poor asthma control [N=20, RR=0.69 (95%CI: 0.52, 0.93)]. Number of overall withdrawals (all reasons) [N=23, RR=0.92 (95%CI: 0.82, 1.03)]. Percentage of symptom-free days at endpoint [N=5,WMD= 5.22% (95% CI: -1.58, 12.02)], random effects model], Percentage of % symptom-free nights at endpoint [N=2,WMD= -2.10%(95%CI: -7.98, 3.79)], Change from baseline in nighttime awakenings [N=4, SMD= 0.01 (95% CI: -0.08, 0.10)].

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Gibson 2005 Cochrane	1) Abrupt fixed reduced ICS + LABA versus fixed moderate or high dose of the same ICS Adverse Events: RR 0.92 (95%CI 0.79 to 1.07), comparison 1.12 3) Reduced ICS + LABA versus ICS alone in participants who demonstrate deteriorating asthma control when ICS are reduced Adverse Events: RR 0.92 (95%CI 0.80 to 1.07), comparison 3.12.	Good
Greenstone 2005 Multinational Cochrane	There was no significant group difference in the rate of overall adverse events [N=15, RR=0.93 (95% CI: 0.84, 1.03), random effects model], or specific side effects, with the exception of a three-fold increase rate of tremor in the LABA group [N= 10, RR=2.96 (95%CI: 1.60, 5.45)]. The rate of withdrawals due to poor asthma control favoured the combination of LABA and ICS [N=20, RR= 0.69 (95%CI: 0.52, 0.93)].	Good

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
1608	Halpern, T et al 2003 United States GlaxoSmithKline	Meta-analysis	5278 (6 studies)	Compare the rate of hospitalization among patients with asthma treated with inhaled corticosteroids versus those treated with LTRA (for monotherapy) and to evaluate other resource use rates and costs for these patients.
183	Masoli 2005 New Zealand Funding NR; all authors report competing interests with prior grants from Astra Draco, GSK, and Novartis.	Meta-analysis	4576	To compare the clinical benefit of adding salmeterol to moderate doses of ICS (fluticasone propionate 200 mg/day or equivalent) with increasing the ICS dose by at least twofold in symptomatic adult patients with asthma not controlled on ICS.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Halpern, T et al 2003 United States GlaxoSmithKline	Oates, V and Gothard, L. PEER Study. 7/10/00. Available from GSK. Pathak, D et al. Pharmacotherapy 2002;22:166. Stanford, R et al. Chest 2001;120:225S. White, T et al. 11/27/00. Available from GSK. Stempel, D et al. J Allergy Clin Immunol 2001:107:94. Stempel, D et al. Respir Med 2001:95:227. 2 independent reviewers.
Masoli 2005 New Zealand Funding NR; all authors report competing interests with prior grants from Astra Draco, GSK, and Novartis.	van Noord 1999, Kalberg 1998, Greening 1994, Kelsen 1999, Murray 1999, Condemi 1999, Vermetten 1999, Bloom 2003, Busse 2003, Baraniuk 1999, Johansson 2001

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Halpern, T et al 2003 United States GlaxoSmithKline	studies from 1991 to 2000, prospective and retrospective comparative design, of patients receiving ICS or LTRA monotherapy (no other controller medicine) were included. Had to have defined inclusion and exclusion criteria, defined number of patients in each arm, defined treatment protocol, and separate results for each medication. Only studies presenting primary research were included. Duration had to be at least 6 months on all participants included. Only US studies. 5 were retrospective cohort studies; only 1 study was identified as a prospective trial comparing ICS and LTRA and icluding results on resource use or medical care costs. All 6 were supported by GSK.
Masoli 2005 New Zealand Funding NR; all authors report competing interests with prior grants from Astra Draco, GSK, and Novartis.	double blind, randomised trial; direct comparison between; studies of at least 12 weeks duration; and data on measures of clinical efficacy.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Halpern, T et al□ 2003□ United States□ GlaxoSmithKline	Hospitalizations: patients taking ICS had a signifcantly lower annual rate of hospitalization than did patients taking LTRA (2.23% vs 4.3%, respectively; p<0.05) The absolute risk reduction was 2.07% (NNT = 48 for 1 year). The difference in annual hospitalizaiton visit rates for each study in the primary analysis found that 2 studies had statistically significant differences in hospitalizaiton rates, whereas the differences int he other 2 studies were not statistically significant (p<0.05). Combining studies with the use of a random effects model or a fixed effects model produced similar effects. No significant heterogeneity (p=0.43). □ □ Annual visits to the ED due to asthma, ED costs, total drug costs, total asthma-related costs, and overall total costs:□ Mean annual rates of visits to the ED and total annual drug costs were significantly higher for patients taking LTRA than for those taking ICS (p<0.005 for each). The higher rate and lower cost of ED visits for those taking LTRA suggest that medical resources were used less at each visit as compared with those for patients taking ICS. □ □ Within-group analysis on before vs after treatment: Patients taking ICS had hospitalizaiton rates and ED vi
Masoli□ 2005□ New Zealand□ Funding NR; all authors report competing interests with prior grants from Astra Draco, GSK, and Novartis.	Salmeterol better for main outcomes: number of subjects withdrawn due to asthma (odds ratios 1.58; 95% CI 1.12 to 2.24) and with at least one moderate or severe exacerbation (OR 1.35, 95% CI 1.10 to 1.66) was higher in the high dose ICS group respectively.□ □ Among the secondary variables, for daytime b agonist use there was significantly greater benefit in the salmeterol group.□ □ Outcome measure is mean difference and represents the mean outcome measure for the group receiving added salmeterol minus the mean outcomes measure for the group receiving increased dose of ICS.□ □ Fixed effects Random effects Inconsistency measures□ Night awakenings (no/week) -0.03 (0.00 to -0.07) -0.03 (0.01 to -0.07) 20.5 (0.00 to 65.1)□ Day time b agonist use (puffs/day) -0.58 (-0.44 to -0.72) -0.60 (-0.35 to -0.84) 70.3 (30.5 to 87.3)□ Night time b agonist use (puffs/night) -0.08 (-0.02 to -0.13) -0.08 (-0.00 to -0.16) 58.0 (0.00 to 83.0)□ □

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Halpern, T et al 2003 United States GlaxoSmithKline	See above. Otherwise none reported.	fair
Masoli 2005 New Zealand Funding NR; all authors report competing interests with prior grants from Astra Draco, GSK, and Novartis.	None reported	Fair

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
228	Ni Chroinin 2004 Cochrane external support: Fonds de la Santé du Québec CANADA; Internal support: Canadian Cochrane Network - McGill University CANADA	Systematic review and meta-analysis	1061 (18 trials met the inclusion criteria; 9 (totaling 1061 adults) contributed sufficient data to be analysed)	To compare the efficacy of initiating anti-inflammatory therapy using the combination of inhaled corticosteroids and long-acting beta2- agonists (ICS+LABA) as compared to inhaled corticosteroids alone (ICS alone) in steroid-naive children and adults with persistent asthma.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Ni Chroinin□ 2004□ Cochrane□ external support: Fonds de la Santé du Québec CANADA; Internal support: Canadian Cochrane Network - McGill University CANADA	Creticos 1999, Nelson 2003; Di Franco 1999; Grutters 1997; O'Byrne 2001; Pearlman 1999; Weersink 1997; Chuchalin 2002

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Ni Chroinin□ 2004□ Cochrane□ external support: Fonds de la Santé du Québec CANADA; Internal support: Canadian Cochrane Network - McGill University CANADA	RCTs in which the combination of inhaled corticosteroids and long-acting beta2-agonists (ICS+LABA) was compared to the same dose of inhaled corticosteroid (ICS alone). Controlled studies with or without placebo were considered.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Ni Chroinin□ 2004□ Cochrane□ external support: Fonds de la Santé du Québec CANADA; Internal support: Canadian Cochrane Network - McGill University CANADA	Symptoms: LABA + ICS > ICS [reduction in symptom score: SMD (95% CI) -0.31 (-0.48 to -0.13); N= 4 trials; improvement in % of symptom-free days: WMD (95% CI) 10.74% (1.86 to 19.62); N=3 trials] Exacerbations: No difference [# of patients with ≥ 1 exacerbation requiring systemic oral corticosteroids: RR (95%CI)=1.19 (0.75, 1.88); data from 3 trials (N=514)] Rescue medicine use: No difference [use of rescue short-acting beta-agonist [N=5 trials; WMD (95%CI): -0.39 puffs/day (-0.88, 0.11) puff/d] Withdrawals: No difference [overall risk of withdrawals, RR (95%CI) 0.89 (0.64, 1.23); N=6 trials; withdrawals due to poor asthma control, RR (95%CI) 1.28 (0.48, 3.42); N=6 trials]

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Ni Chroinin□ 2004□ Cochrane□ external support: Fonds de la Santé du Québec CANADA; Internal support: Canadian Cochrane Network - McGill University CANADA	Any adverse effects (N=5 trials: RR 1.09; 95%CI 0.81 to 1.48),□ Withdrawals due to AEs(N=3 trials: RR 1.71; 95% CI 0.68 to 4.27), □ Oral candidiasis (N=2 trials: RR 0.43; 95% CI 0.07 to 2.84), □ Headache (N=2 trials: RR 1.92; 95% CI 0.54 to 6.85),□ Tremor (N=2 trials: RR=5.05; 95% CI 1.33 to 19.17). □	Good

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
172	Ni Chroinin, M et al.□ 2005□ Cochrane Review□ External sources of support: Francine Ducharme was supported by a National Scientist Award from the Fonds de la Santé du Québec CANADA□ Internal sources of support: Canadian Cochrane Network, McGill University CANADA	Systematic review and meta-analysis	26 trials involving 8147 asthmatic participants	To quantify in asthmatic patients the safety and efficacy of the addition of long-acting B¬2-agonists to inhaled corticosteroids on the□ incidence of asthma exacerbations, pulmonary function and other measures of asthma control.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Ni Chroinin, M et al. 2005 Cochrane Review External sources of support: Francine Ducharme was supported by a National Scientist Award from the Fonds de la Santé du Québec CANADA Internal sources of support: Canadian Cochrane Network, McGill University CANADA	Akpinarli ICS600 {published data only} Akpinarli A, Tuncer A, Saraclar Y, Sekerel BE, Kalayci O. [Effect of formoterol on clinical parameters and lung functions in patients with bronchial asthma: a randomised controlled trial]. Archives of Disease in Childhood 1999;81:45–8. Boyd ICS1675 {published data only} Boyd G. Salmeterol xinafoate in asthmatic patients under consideration for maintenance oral corticosteroid therapy. European Respiratory Journal 1995;8:1494–98. Buhl BUD400(bd) {published data only} Buhl R, Creemers JPHM, Vondra V, Martelli NA, Naya IP, Eksstrom T. Once daily budesonide /formoterol in a single inhaler in adults with moderate persistent asthma. Respiratory Medicine 2003; 97(4):323–30. Buhl BUD400(qd) {published data only} Buhl R, Creemers JPHM, Vondra V, Martelli NA. Improved and maintained asthma control with once-daily budesonide/formoterol single inhaler in mild-to-moderate persistent asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:21s. Buhl R,Creemers JPHM, Vondra V,MartelliNA. Once-daily budesonide/ formoterol via a single inhaler is effective in mild-to-moderate persistent asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:21s. Buhl R, Creemers JPHM, Vondra V,Martelli NA. Once daily symbic Ind PW, Dal Negro R, Colman N, Fletcher CP, Browning DC, James MH. Inhaled fluticasone propionate and salmeterol in moderate adult asthma II: exa and Critical Care Medicine 2002; Vol. 165, issue Suppl 8: A112. Edwards T, Gross G, Mitchell D, Chervinsky P, Woodring A, Baitinger L, et al. The salm Kavuru M, Melamed J, Gross G, Laforce C, House K, Prillaman B, et a¡¯. Salmeterol and fluticasone proprionate combined in a new powder inhalatio Immunology 2000;105(6):1108–16. Nathan RA, Dorinsky P, Rosenzweig JR, Shah T, Edin H, Prillaman B. Improved ability to perfrom strenous a the effect of salmeterol in older chidlren with chronic severe asthma. Respiratory Medicine 1995;89:435–40. Leblanc 1996 {published data only} Molimard M, Bourcereau J, Le Gros V, Bourdeix I, Leynadier F, Duroux P. Comparison between formoterol 12 ug bid and on-demand salbutamol inmoderate persistent asthma. RespiratoryMedicine 2001;95(1):64–70. Norhaya ICS890 {published data only} Norhaya MR, Yap T Barnes PJ, O¡¯Byrne PM, Rodriguez-Roisin R, RunnerstromE, Sandstrom T, Svensson K, Tattersfield A. Treatment of mild persistent asthma with low d of adding formoterol to budesonide in mild persistent asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:331s. O¡¯Byrne PM, Barnes ¢ç to budesonide Tubuhaler¢ç is safe and well tolerated in the long-term treatment ofmild asthma: results from the OPTIMA trial. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:330s. O¡¯Byrne BUD400 {published data only} O¡¯Byrne PM, Barnes PJ, Rodriguez-Roisi Pauwels RA, Lofdahl CG, Postma DA, Tattersfield AE, O¡¯Byrne P, Barnes PJ, Ullman A. [Effect of inhaled formoterol and budesonide on exacerbation propionate combination inhaler ismore cost effective than fluticasone propionate in patients with asthma. European Respiratory Society 1999 Annual Congress; Oct 9-13; Madrid, Spain. 1999. Russell ICS750 {published data only} Russell G,Williams DAJ,Weller P, Price JF. Salmeterol xin effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. PediatricsMay; 99(5):655–9. Vermeulen JH, Simon G, Tal A. Symbicort¢ç (Budesonide and formoterol in a single inhaler) improves lung function in asthmatic children aged 4-17 yea Malo JL, Chapman K, Grossman R, et al. Effects of the long acting beta agonist formoterol on asthma control in asthmatic patients using inhaled cortico Wallin FP800 {published data only} Sue-Chu M,Wallin A,Wilson S, Ward J, Sandstrom T, Djukanovic R, et al. Bronchial biopsy study in asthmatics treat Wallin A, Sue-Chu M, Bjermer L, Ward J, Sandstrom T, Lindberg A, et al. Effect of inhaled fluticasone with and without salmeterol on airway inflammatio Zetterstrom O, Buhl R, Mellem H. Efficacy and safety of symbicort ¢ç (budesonide and formoterol in a single inhaler) in adults with asthma.AnnualThora Ekstrom T. The new single inhaler product containing both budesonide/ formoterol improves asthma control in adults. European Respiratory Journal 2000; Vol. 16, issue Suppl 31:455s. Zetterström O, Buhl R, Mellem H, Perpiñá M, Hedman J, O¡¯Neill S, Ekström T. E Ekstrom T. Improved asthma control with budesonide /formoterol in a single inhaler, compared with budesonide alone. European Respiratory Journal 20 turbuhaler(R) when added to inhaled corticosteroid treatment in children with asthma. Pediatric Pulmonology 2004;37(2): 122–7.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Ni Chroinin, M et al. 2005 Cochrane Review External sources of support: Francine Ducharme was supported by a National Scientist Award from the Fonds de la Santé du Québec CANADA Internal sources of support: Canadian Cochrane Network, McGill University CANADA	Only randomised controlled trials conducted in adults or children, or both, in whom long-acting ©¬2-agonists were added to inhaled corticosteroids were included. Of 594 identified citations, 49 trials met the inclusion criteria: 27 full-text publications, one unpublished full-text report and 21 abstracts. Twenty-three citations (21 abstracts and two full-text publications) provided data in insufficient detail, 26 trials contributed to this systematic review. Twenty-four trials had a parallel group design studies and two were cross-over studies (Norhaya ICS890; Simons BUD150) which failed to provide results stratified by period. All but three trials (Akpinarli ICS600; Molimard ICSNR; Wallin FP800) were of high quality (Jadad score 4 or greater). All trials were randomised though the method of randomisation was not described in 12 trials. Twenty-seven trials were double blind with an appropriate means of blinding in all but two trials, in which it was not reported (D¡¯Urzo ICSNR; Wallin FP800). The remaining one trial was open label (Molimard ICSNR).

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Ni Chroinin, M et al. 2005 Cochrane Review External sources of support: Francine Ducharme was supported by a National Scientist Award from the Fonds de la Santé du Québec CANADA Internal sources of support: Canadian Cochrane Network, McGill University CANADA	ISymptoms: [daytime symptoms [N=5, SMD (95%CI) -0.34 (-0.44, -0.23)], night-time symptoms [N=2, SMD (95%CI) -0.18 (-0.31, -0.05)], and overall 24-hour symptoms [(N=2, SMD (95%CI) -0.28 (-0.45, -0.11) while increasing % symptom-free days during the observation period [(N=4, SMD (95%CI) 0.32 (0.02, 0.62)], the change from baseline in % symptom-free day [N=6, WMD (95%CI) 17.21 (12.06, 22.36)], in symptom-free nights [N=4, SMD (95%CI) 0.51 (0.28, 0.74)], and the change in % asthma-control days [N=2, WMD (95%CI) 15.61 (8.51, 22.70)] Nocturnal awakenings: [% nights with no awakening [N=2, WMD (95%CI) -1.37 (-2.75, 0.02)]; changes in % nights with no awakening [N=2, WMD (95%CI) 3.24 (-0.89, 7.38)]; night-time awakening [N=3, WMD (95%CI) -0.22 (-2.24, 1.81)] Exacerbations: [patients experiencing ≥1 exacerbation requiring OCS, RRR 19% with LABA [RR 95%CI) 0.81 (0.73, 0.90); Risk of exacerbation decreased from 27% to 22% with the addition of LABA, with ARR (95%CI)=5% (3%, 8%), and NNT (95%CI) with LABA to prevent 1 exacerbation over 1yr is 18 (13, 33); overall withdrawals [N=26 comparisons, RR (95%CI) 0.87 (0.77, 0.97), RD (95%CI) -0.02, (-0.04, 0.00); wit Rescue med use: [daytime use at endpoint [N=2, WMD (95%CI) -0.73 (-1.24, -0.22)puffs/d] night-time use Quality of life: [(N=2, WMD (95%CI) 0.33 (0.05, 0.6)].

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Ni Chroinin, M et al. 2005 Cochrane Review External sources of support: Francine Ducharme was supported by a National Scientist Award from the Fonds de la Santé du Québec CANADA Internal sources of support: Canadian Cochrane Network, McGill University CANADA	There was no apparent group difference in the risk of overall adverse effects (N = 11, RR 0.98, 95% CI 0.92 to 1.05), meeting our a priori definition of equivalence. There was also no group difference in the risk of serious adverse events (N = 4 comparisons, RR 1.16, 95% CI 0.30 to 4.42) or in any of the reported specific side effects including headache (N = 12, RR 1.13, 95%CI 0.92 to 1.41); hoarseness (N = 3 comparisons, RR 0.71, 95% CI 0.16 to 3.18, random-effects model); oral thrush (N = 4, RR 1.04, 95% CI 0.35 to 3.06); tachycardia or palpitations (N = 5, RR 2.13, 95% CI 0.77 to 5.88); cardiovascular adverse effects such as chest pain (N = 3, RR 0.90, 95%CI 0.32 to 2.54) or tremor (N = 7, RR 2.48, 95%CI 0.78 to 7.89, random-effectsmodel). However, the upper confidence interval for some adverse events was high (for example tachycardia, palpitations and tremor), ruling out total reassurance. The effect on growth, adrenal function and methacholine challenge could not be aggregated due to insufficient number of trials (fewer than 2) reporting these outcomes. Only one study reported dea	good

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
3052	Niebauer, K et al. 2006 US Funding: Genetech, Inc.	systematic review with meta-analysis	2056	To summarize asthma-related QOL outcomes associated with omalizumab therapy in moderate-to-severe allergic asthma.
5031	Rahimi et al. 2006 NR	Systematic review a	NR	To collect all studies about the effects of ICs on obstetrical outcomes and determine whether ICS use is harmful or safe during pregnancy

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Niebauer, K et al. 2006 US Funding: Genetech, Inc.	5 studies (multiple publcations, plus unpublished data from completed trials from Genetech): Busse 2001, Holgate 2004, Soler 2001, Vignola 2004, Finn 2003, Buhl 2002, Lemanske 2004, Milgrom 2001.
Rahimi et al. 2006 NR	4 studies: Bracken et al., 2003; Schatz et al., 2004; Martel et al., 2005; Otsuka et al., 2005

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Niebauer, K et al. 2006 US Funding: Genetech, Inc.	double-blind RCTs, all parallel group, phase 3 trials with 4-6 week run-in, 16-week steroid stabilization phase, 12-16 wk steroid-reduction phase, and either an open-label or double-blind extension phase.
Rahimi et al. 2006 NR	Studies that compared major malformation, preterm delivery

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Niebauer, K et al. 2006 US Funding: Genetech, Inc.	All results favored OM. For improvement of > 0.5 for the 3 respective phases: 1.35 (1.11-1.64; P = 0.003), 1.69 (1.40-2.05; P < 0.001), and 1.50 (1.15-1.95; P = 0.001). test of homogeneity was NS (P = 0.06 to 0.94) suggesting consistency across trials. For improvement of 1 or more for the 3 phases: 1.61 (1.29-2.00; p < 0.001), 2.03 (1.66-2.47; P < 0.001), and 1.25 (0.9-1.59; P = 0.08). Test of homogeneity NS for first two phases (P = 0.69 and 0.51), but evidence of heterogeneity for extension phase (P = 0.01). For improving AQLQ overall scores by 1.5 or more for the 3 phases: OR 1.80 (1.36-2.38; P < 0.001), 2.11 (1.68-2.65; P < 0.001), and 1.59 (1.21-2.08; P < 0.001). Tests of homogeneity NS for first two phases (P = 0.97 and 0.84), but evidence of heterogeneity in effects for extension phase (P = 0.04).
Rahimi et al. 2006 NR	The summary OR for major malformations in two studies was 0.96 with a 95% CI of 0.51 to 1.83 and a non-significant OR (P=0.9582). The summary OR for preterm delivery in three studies was 0.99 with a 95% CI of 0.8 to 1.22 and a non-significant OR (P=0.9687). The summary OR for low birth weight delivery in two studies was 0.89 with a 95% CI of 0.7 to 1.14 and a non-significant OR (P=0.4013). The summary OR for pregnancy-induced hypertension in three studies was 0.97 with a 95% CI of 0.84 to 1.2 and a non-significant OR (P=0.9932). The Breslow-Day tests for heterogeneity (P=0.9249, P=0.2521, P=0.6146 and P=0.0013 respectively) indicated that the studies for major malformation, preterm delivery and low birth weight were not significantly heterogeneous and could be combined. ICs do not increase the risk of major malformations, preterm delivery, low birth weight and pregnancy-induced hypertension; i.e., ICs did not increase the rates of any obstetrical outcomes.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Niebauer, K et al. 2006 US Funding: Genetech, Inc.	NR	Fair
Rahimi et al. 2006 NR	NR	Fair

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
1981	Salpeter 2006 salary support from Santa Clara Valley Medical Center for Drs. Salpeter and Ormiston.	Systematic review and meta-analysis	33826	To assess the risk for severe, life-threatening, or fatal asthma exacerbations associated with long-acting B-agonists.
4744	Sharek, PJ and DA Bergman 2000 US funding NR	systematic review with meta-analysis	855	To determine whether inhaled steroid therapy causes delayed linear growth in children with asthma.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Salpeter 2006 salary support from Santa Clara Valley Medical Center for Drs. Salpeter and Ormiston.	19 studies- Bensch et al., 2001; Bensch et al., 2002; Busse et al., 2004 D'Urzo et al., 2001; Foradil 040 trial, 2001; Foradil 041 trial, 2001 Foradil 2307 trial, 2005; Lazarus et al., 2001 Levy et al., 2005 Lockey et al., 1999; Price et al., 2002 Rosenthal et al., 1999; Salmeterol SLD-390 trial, 2001; SMART, 2006; Serevent 3014 trial, 2001; Steffensen et al., 1995; Taylor et al., 1998; Von Berg et al., Weinstein et al., 1998
Sharek, PJ and DA Bergman 2000 US funding NR	Doull et al 1995, Simons et al 1997, Tinkelman et al 1993, Verberne et al 1997, Allen et al 1998

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Salpeter 2006 salary support from Santa Clara Valley Medical Center for Drs. Salpeter and Ormiston.	Randomized, placebo-controlled trials that lasted at least 3 months and evaluated long-acting B-agonist use in patients with asthma.
Sharek, PJ and DA Bergman 2000 US funding NR	RCTs, subjects randomized to inhaled beclomethasone, budesonide, flunisolide, fluticasone, or triamcinolone versus a nonsteroidal inhaled control for a minimum of 3 months; and outcome convertible to linear growth velocity. English- and non–English-language trials were included.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Salpeter 2006 salary support from Santa Clara Valley Medical Center for Drs. Salpeter and Ormiston.	OR for hospitalization was 2.6 (CI, 1.6 to 4.3) for LABAs vs. placebo The risk difference for hospitalization attributed to LABAs was 0.7% (CI, 0.1% to 1.3%) over 6 months. risk for hospitalization was increased in children (OR, 3.9 [CI, 1.7 to 8.8]) and in adults (OR, 2.0 [CI, 1.0 to 3.9]). The risk for hospitalization was also increased with salmeterol (OR, 1.7 [CI, 1.1 to 2.7]) and with formoterol (OR, 3.2 [CI, 1.7 to 6.0]) OR for life-threatening asthma attacks attributed to LABAs was 1.8 (CI, 1.1 to 2.9, with a risk difference of 0.12% (CI, 0.01% to 0.3%) over 6 months. The risk for asthma-related deaths was increased (OR, 3.5 [CI, 1.3 to 9.3]), with a pooled risk difference of 0.07% (CI, 0.01% to 0.1%)
Sharek, PJ and DA Bergman 2000 US funding NR	Results divided by ICS. Of the 5 studies included, 4 studies of BDP (450 subjects) showed a decrease in linear growth velocity of 1.51 cm/year (95% confidence interval: 1.15, 1.87). One study of FP (183 subjects) showed a decrease in linear growth velocity of 0.43 cm/year (95% confidence interval: .01,.85). Sensitivity analysis in the beclomethasone subgroup, which evaluated study quality, mode of medication delivery, control medication, and tatistical model, showed similar results.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Salpeter 2006 salary support from Santa Clara Valley Medical Center for Drs. Salpeter and Ormiston.	NR	Good
Sharek, PJ and DA Bergman 2000 US funding NR	as above	Good

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
3768	Sharek, PJ et al 1999 Cochrane Database of Systematic Reviews Internal support from NHS Research and Development UK	systematic review with meta-analysis	273 (3 studies)	To determine whether inhaled beclomethasone causes significant delay in the linear growth of children with asthma.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Sharek, PJ et al 1999 Cochrane Database of Systematic Reviews Internal support from NHS Research and Development UK	3 studies: Doull 1995, Verberne 1997, and Simons 1997.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Sharek, PJ et al 1999 Cochrane Database of Systematic Reviews Internal support from NHS Research and Development UK	Inclusion criteria: Single or double-blind RCTs comparing beclomethasone delivered by nebulizer, MDI, diskhaler or rotahaler for a minimum of 3 months to placebo or nonsteroidal medication. Results: all were RCTs. Each was double blind (subject and provider) to treatment assignment. Quality ratings: Jadad scores (Jadad 1996), resulted in a grade of 5 for one study [Doull 1995], grade 4 for one study [Verberne 1997] and grade of 3 for the third [Simons 1997].

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Sharek, PJ et al 1999 Cochrane Database of Systematic Reviews Internal support from NHS Research and Development UK	All three of the included studies were consistent in their conclusions that beclomethasone decreased linear growth of children with asthma. Doull: treatment (4.12 cm/year with S.D. 1.41 cm/year) versus placebo group (5.94 cm/year with S.D. 1.15 cm/year). Verberne treatment (4.70 cm/year with S.D. 1.87 cm/year) versus control group (6.10 cm/year with S.D. 2.04 cm/year). Simons (3.96 cm/year with S.D. 2.04 cm/year) versus control group (5.04 cm/year with S.D. 2.04 cm/year). The average decrease, calculated through meta-analysis, was -1.54 cm per year (95% CI -1.15, -1.94). [meta-analysis shows a statistically significant decrease in linear growth velocity of children with mild to moderate asthma treated with moderate doses of beclomethasone.] There was no heterogeneity between studies; chi square was 2.71 with 2 degrees of freedom >.99. Authors' conclusions In children with mild-moderate asthma, beclomethasone 200 mcg twice daily caused a decrease in linear growth of -1.54 cm per year. These studies lasted a maximum of 54 weeks, so it remains unclear whether the decrease in growth is sustained or whether it reverses with 'catch up' after therapy is discontinued.We a

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Sharek, PJ et al 1999 Cochrane Database of Systematic Reviews Internal support from NHS Research and Development UK	See above.	Good

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
4745	Sharma et al. 2003 India NR	meta-analysis	635	To determine the effect of ICSs on bone loss in patients with bronchial asthma
1417	Uboweja et al. 2006 India funding NR	meta-analysis	63,738 (approximately 20,000 cases and 50,000 controls)	The objective of this study was to quantify the risk of cataract among users of inhaled corticosteroids (ICS).

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Sharma et al. 2003 India NR	Wong et al. 2000, Boulet et al. 1994, Israel et al. 2001, Wisniewski et al. 1997, Luengo et al. 1997, Packe et al. 1996
Uboweja et al. 2006 India funding NR	4 studies: Jick et al 2001, Cumming et al 1997, Garbe et al 1998, Smeeth et al 2003

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Sharma et al. 2003 India NR	Case control or prospective: published in peer reviewed journals; examined the effect of inhaled steroids on adult populations; median duration of at least 3 years; estimated lumbar spine BMD; lumbar spine BMD with actual numerical values reported; compared treatment group with controls
Uboweja et al. 2006 India funding NR	Evaluated the association between ICS and cataract in adult population. All were retrospective studies published in peer reviewed journals, data about dose and duration of therapy were not available for all of them.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Sharma et al. 2003 India NR	Mean BMD of ICS-exposed group was decreased by 4.2% when compared to the non-exposed group (NS). Mean difference in BMD favoring controls 0.049 (CI 0.028 to 0.070 g/cm2 (P = 0.8))
Uboweja et al. 2006 India funding NR	The pooled OR (95% CI) by the fixed effects Mantel–Haenszel method was 1.48 (1.39–1.57) and by the random effects DerSimonian–Laird method was 1.48 (1.30–1.68). The test for heterogeneity was not significant (data NR). A total number of nine negative studies would be required to make the results of our metaanalysis non-significant. Number needed to harm is 16 with 95% CI of 13–19. Visual inspection of the funnel plot (figure 2) does not rule out publication bias.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Sharma et al. 2003 India NR	see main results	Fair
Uboweja et al. 2006 India funding NR	see main results	Fair, no critical appraisal of studies.

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
3006	Walker 2006 UK, Cochrane Database of Systematic Reviews No external support; Internal sources of support: NHS Research and Development UK, The Thriplow Charitable Trust UK, and Nederlands Asthma Fonds NETHERLANDS	systematic review with meta-analysis	3143 (14 trials)	To determine the efficacy of anti-IgE (Omalizumab) compared with placebo in patients with allergic asthma; to compare the clinical outcomes in studies that have compared anti-IgE monoclonal antibodies with placebo or other conventional therapy in the treatment of chronic asthma

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Walker 2006 UK, Cochrane Database of Systematic Reviews No external support; Internal sources of support: NHS Research and Development UK, The Thriplow Charitable Trust UK, and Nederlands Asthma Fonds NETHERLANDS	14 trials (more than 14 articles): Boulet 1997; Bruno 2005; Busse 2001 [Bousquet 2004; Busse 2001; Finn 2003; Kaiser J. 2003; Lanier 2001; Massanari 2005]; Djukanovic 2004 [Djukanovic 2003 and 2004]; Fahy 1997; Fahy 1999; Hanf 2005 [Hanf 2005; Noga 2005]; Holgate 2004 [Chung 2002; Holgate 2001; Holgate 2004]; Holgate 2004 [Chung 2002; Holgate 2001; Holgate 2004]; Humbert 2005 [Bleecker 2005; Humbert 2005; Korenblat 2005; Korenblat 2005; Korenblat 2004; Matz 2005; Novartis. Study number 2306.]; Milgrom 1999 [Metzger 1998; Milgrom 1999]; Milgrom 2001 [Berger 2003; Buhl 2001; Kaiser fda.gov 2003; Lemanske 2002; Milgrom 2001; Milgrom 2005; Nayak 2000]; Solèr 2001 [Bousquet 2004; Buhl 2002; Buhl 2002; Kaiser fda.gov 2003; Massanari 2005; Soler 2001; Solèr 2001; Solèr 2005]; van Rensen 2005; Vignola 2004 [Boulet 2003; Dahl 2004; Harnest 2004; Vignola 2004; Vignola 2003]

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Walker 2006 UK, Cochrane Database of Systematic Reviews No external support; Internal sources of support: NHS Research and Development UK, The Thriplow Charitable Trust UK, and Nederlands Asthma Fonds NETHERLANDS	All trials were double-blind RCTs of parallel group design; examining anti-IgE administered in any manner for any duration. Trials with co-interventions were included as long as they were the same in each arm

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Walker 2006 UK, Cochrane Database of Systematic Reviews No external support; Internal sources of support: NHS Research and Development UK, The Thriplow Charitable Trust UK, and Nederlands Asthma Fonds NETHERLANDS	Symptoms: End of treatment: Moderate/severe and severe participants receiving SQ OM had significantly lower asthma symptom scores during stable steroid phases (MD -0.46 (95% CI: -0.75, -0.29). There were no significant changes in asthma symptoms in the pediatric study (median nocturnal asthma scores were 0 in both groups throughout the study). Change from baseline in symptom scores: significant reductions in symptom scores from baseline in favor of SQ OM in two trials (Vignola 2004 (-1.8, P =0.023); Humbert 2005 (P = 0.039, no mean scores presented). Exacerbations: Stable steroid phase: Significant reduction in the odds of a patient having an asthma exacerbation in favor of SQ OM (OR 0.55, 95% CI: 0.45, 0.69). Assuming a baseline risk of 25%, the NNT to prevent one exacerbation was 10 (95% CI: 8, 14) Exacerbations per participant: When exacerbation rates were expressed as means, fewer asthma exacerbations per patient in favor of OM (-0.18 exacerbations (95% CI: -0.1, -0.25; seven studies, 2570 participants); moderate level of heterogeneity ; random effects modeling did not change the point estimate (95%CI: -0.08, -0.27) Tapering phase: OM patients less likely to experience an exacerbation (OR 0.46 (95% CI: 0.36, 0.59); four Rescue med use: Stable phase: Moderate to severe adolescent and adult participants required significantly less rescue beta Tapering phase: Change from baseline in rescue medication use: OM treatment enabled participants to us QOL: Stable phase: Change from baseline in quality of life scores: significantly greater improvement in overall AC

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Walker 2006 UK, Cochrane Database of Systematic Reviews No external support; Internal sources of support: NHS Research and Development UK, The Thriplow Charitable Trust UK, and Nederlands Asthma Fonds NETHERLANDS	POOLED data from all the available [Omalizumab + steroid vs. placebo + steroid] studies regardless of whether they had conducted a steroid tapering phase. All between 28 and 32 weeks in duration. No difference in headache, urticaria, number of participants with any adverse events, and withdrawals due to adverse events. Omalizumab led to significantly greater injection site reactions compared with placebo [OR: 2 (95% CI 1.37 to 2.92), CER: 5.5%]; NNT(h)=21.	Good

Evidence Table 2. Systematic reviews of controller medications of asthma

	Author Year Country Funding	Study design:	Number of patients:	Aims of review:
25	Walters, EH et al. 2007 Cochrane Review Commonwealth Department of Health and Aging AUSTRALIA	All randomised studies, both open and blinded, of at least four weeks duration, comparing a LABA given twice daily with a placebo, in chronic asthma. Selection criteria to this updated review have been altered to accommodate recently published Cochrane reviews on combination and addition of LABA to ICS therapy. Studies in which all individuals were uniformly taking ICS were excluded from this review.	Sixty-seven studies (representing 68 experimental comparisons) randomising 42,333 participants	Compare the effects of regular inhaled LABA versus placebo in chronic asthma. The specific purpose of the review was to assess whether there are any beneficial or harmful effects from the regular use of inhaled LABA compared with placebo on the primary outcome of asthma control.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Studies included in analysis or review:
Walters, EH et al. 2007 Cochrane Review Commonwealth Department of Health and Aging AUSTRALIA	Fifty-four studies were of parallel group design and 13 of cross over design. Adinoff 1998 {published data only} Adinoff A, et al. Salmeterol compared with current therapies in chronic asthma. Journal of Family Practice 1998;47(4):278–84. ; Bensch 2001 {published data only} Bensch G, et al. A randomized, 12-week, double-blind, placebo-controlled study comparing formoterol dry powder inhaler with albuterol metereddose inhaler. Annals of Allergy Asthma & Immunology 2001;86(1): 19–27. ; Della Cioppa G, et al. QID Albuterol worsens peak flow variability in asthma whereas BID Formoterol does not [abstract]. Annals of Allergy 1998;80:88. ; FORNDA 20831_40. A twelve week, double-blind, parallel group trial comparing the safety, tolerability and efficacy of formoterol dry powder capsules for inhalation delivered by a single-dose inhaler versus albuterol metered dose inhaler device versus placebo in patients with mild to moderate asthma. www.fda.gov 2001. ; Mann M, et al. Serious asthma exacerbations in asthmatics treated with highdose formoterol. Chest 2003;124(1):70–4. ; Bensch 2002 {published data only} Bensch G, et al. One-year efficacy and safety of inhaled formoterol dry powder in children with persistent asthma. Annals of A the long acting beta2 agonist salmeterol in mild to moderate asthmatic patients. Thorax 1993;48(11):1121–4. ; Boulet 1997 {published data only} Boulet Boulet L, et al. Tolerance to the protective effects of salmeterol on methacholine-induced bronchoconstriction- influence of inhaled corticosteroids. Europ between short-acting and long-acting beta2-agonists. 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Reduced protection against exercise induced bronchoconstrction after chronic dosing with salmeterol. Respiratory Medicine 1994;88(5):363–8. Roberts 1999 {published data only}Roberts B, Bradding P, Holgate S. Effects of a six week cou Effect of long-term salmeterol therapy compared with as-needed albuterol use on airway hyperresponsiveness. Chest 1999;116(3):595– 602. SAS30003 {unpublished data only} SAS30003. A stratified, randomized, double-blind, placebo-controlled, parallel-group, 12-week trial evaluating Rooklin A, Elkayam D, Weiler J, Windom H, Schoaf L, Scott C, et al. The fluticasone propionate/salmeterol HFA MDI is significantly more efficacious in treating asthma than placebo HFA MDI, fluticasone propionate CFC MDI or salmeterol CFC MDI. Journal of Allergy and Clinicial Immunology 2001;107(2):100s. SAS30004. A randomized, double-blind, placebo-controlled, parallel- group 12-week trial evaluati

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Characteristics of included studies:
Walters, EH et al. 2007 Cochrane Review Commonwealth Department of Health and Aging AUSTRALIA	Participants in one treatment arm used a LABA, either salmeterol or formoterol (also known as eformoterol), administered twice daily via any inhalation device. The second treatment arm consisted of regular doses of placebo, administered in the same way. The minimum period of treatment four weeks in this update.

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Main results:
Walters, EH et al. 2007 Cochrane Review Commonwealth Department of Health and Aging AUSTRALIA	SYMPTOM SCORES: There were significantly fewer symptoms in the LABA group across the board on a variety of measures at the end of treatment. Scales used to measure asthma symptoms varied from 3 to 6 points and scores were generally derived as a composite based on a number of symptoms, e.g. cough, wheezing, shortness of breath and chest tightness assessed during the day and/or overnight and whether sleep was broken by asthma symptoms. All measures showed significant advantages in the LABA compared with placebo. Daytime symptoms were significantly better in LABA treated participants (-0.34 95% CI -0.44 to -0.25; 14 studies, 1836 participants). Nocturnal symptoms were also better in LABA treated participants: SMD-0.54 (95%CI -0.64 to -0.45 in eight studies with 1758 participants). There was no significant difference between the subgroups analysed on the basis of including background ICS use. Subgroup analysis of symptom score data indicated that the effect of LABAs was consistent across the groups of trials based on the classifications of severity in the review. Symptoms fell from baseline by a greater amount during treatment RESCUE BRONCHODILATOR USE: LABA treated participants used significantly less short-acting beta-2 in SABA usage for 24 hours: -0.9 puffs/d, 95%CI -1 to -0.7; eight studies, 1885 participants; mean change hours: -1.2 puffs/d, 95% CI -1.4 to -1; 12 studies, 2197 participants; SABA use (day): -1 puffs/d, (95% CI -1 studies, 691 participants; change in SABA use (night): -0.54, 95% CI -0.7 to -0.4; two studies, 633 participa in asthma severity and treatment may have been the different short acting beta-2 agonist agents used, the varying inhalational devices. Heterogeneity persisted in the subgroup analyses. Results of a similar magnit EXACERBATIONS OF ASTHMA: MAJOR EXACERBATIONS: Twenty-three studies (5995 participants) re MINOR EXACERBATIONS OF ASTHMA: Taylor 1998 applied a somewhat onerous definition for a minor SECONDARY OUTCOMES: QUALITY OF LIFE: The asthma specific measures most often used in the st for analyses. For the global score, there was a clinically and statistically significant advantage to the LABA One crossover study (Juniper 1995) used the same instrument to assess quality of life in 140 participants c to 0.61).

Evidence Table 2. Systematic reviews of controller medications of asthma

Author Year Country Funding	Adverse Events:	Quality rating:
Walters, EH et al. 2007 Cochrane Review Commonwealth Department of Health and Aging AUSTRALIA	Asthma-related Death: Findings from SMART indicated that in participants using mixed co-interventions (including ICS) at baseline there was a significant increase in the odds of asthma-related death occurring in the LABA treated group (13 versus 3; RR 4.4, 1.25 to 15.3; N = 26355). This represents an absolute increase of one extra death over six months for every 1250 patients treated with LABA, but the confidence interval is wide (95% CI 700 to 10,000). The size of this difference was consistent across all the mortality and life threatening experience outcomes measured in this study, and was statistically significant for asthma related death, respiratory related death and the combined outcome of asthma-related death and life threatening experiences, but not for all cause mortality (with or without life-threatening experiences or the combined endpoint of respiratory-related death or life-threatening experiences). In those not using ICS at baseline, the number of participants suffering asthma-related death was higher in LABA than placebo treated groups (9 versus 0, N = 14090). The published trial report did not provide an estimate of the risk r Serious adverse events: There was a significant increase in the odds of asthr Total and drug-related adverse events: There was no significant difference be 95% CI 1.10 to 2.56; eight studies, N = 1170). There was no significant differe myalgia/fatigue, insomnia, upper respiratory tract infection, of asthma, muscu Withdrawals: All-cause study withdrawal was less likely on LABA than on pla = 30599). There was no significant difference in the likelihood of withdrawal d 1.11, 95% CI 0.93 to 1.32; 21 studies, N = 30943). Withdrawals due to lack o than on placebo (OR 0.60, 95% CI 0.53 to 0.68; 14 studies, N = 29466). Ther exacerbations of asthma (OR 0.82, 95% CI 0.46 to 1.46; seven studies, N = 1	Good