Drug Class Review

Controller Medications for Asthma

Final Update 1 Evidence Tables

April 2011

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 safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

Information in this document is new for Update 1.

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Abbreviations used in evidence tables

Abbreviation	Term
ACT	Active-control trial
AD	adjustable dosing
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AQLQ	Asthma Quality of Life Questionnaire
ARF	Arformoterol
BDP	beclomethasone dipropionate
bid	Twice daily
BIS	Budesonide inhalation suspension
BMI	Body mass index
BUD	Budesonide
BUD/FM	budesonide and formoterol in one inhaler
BUD+FM	budesonide and formoterol in separate inhalers
CCT	Controlled clinical trial
CI	Confidence interval
CIC	Ciclesonide
CNS	Central nervous system
CR	Controlled release
CV	Cardiovascular
CVS	Cardiovascular system
d	Day
DB	Double-blind
DD	double dummy
dL	Deciliter
DPI	dry powder inhaler
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Ejection fraction
eFM	Eformoterol
ER	Extended release
FD	fixed dose
FDA	US Food and Drug Administration
FLUN	Flunisolide
FM	Formoterol
FP	Fluticasone Propionate
FP/SM	fluticasone and salmeterol in one inhaler
FP+SM	fluticasone and salmeterol in separate inhalers
FrACQ	French version of the Juniper Asthma Control Questionnaire
FU	Follow-up

Abbreviation	Term
G	Gram
GI	Gastrointestinal
GP	General practitioner
GPRD	general practice research database
H	Hour
HDL-C	High density lipoprotein cholesterol
HFA	hydrofluoroalkane propellant
HMO	Health maintenance organization
HR	Hazard ratio
HRQOL	Health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
ICS	Inhaled Corticosteroids
IOP	intraocular pressure
IR	Immediate release
ITT	Intention-to-treat
L	Liter
LA	Long acting
LABAs	Long-Acting Beta-2 Agonists
LDL-C	Low-density lipoprotein cholesterol
LM	Leukotriene Modifiers
LOCF	Last Observation Carried Forward
LS means	Least squares means
LTRAs	Leukotriene receptor antagonists
MA	meta-analysis
MANCOVA	Multivariate analysis of covariance
mcg	Microgram
MDI	metered dose inhaler
Mg	Milligram
min	Minute
ML	Montelukast
mL	Milliliter
mo	Month
MOM	Mometasone
N	Sample size (entire sample)
N	Subgroup sample size
NA	Not applicable
NNT	number needed to treat
NNT(h)	number needed to treat/harm
NR	Not reported
NS	Not significant
NSD	No significant difference

Abbreviation	Term
OCS	oral corticosteroids
OM	Omalizumab
OR	Odds ratio
P	*P* value
P	Placebo
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PAR	persistent allergic rhinitis
PCT	Placebo-controlled trial
pMDI	pressurized metered dose inhaler
PPY	Per person year
PSC	posterior subcapsular cataracts
qd	Once daily
QOL	Quality of life
RAMQ	regi de l'assurance maladie du Quebec database
RCT	randomized controlled trial
RCT	Randomized controlled trial
RQLQ	Rhinitis Quality of Life Questionnaire
RR	Relative risk
SABA	Short-Acting Beta-Agonist
SB	Single-blind
SD	Standard deviation
SE	Standard error
SM	Salmeterol
SMD	standard mean difference
SPT	skin prick test
SR	systematic review
TAA	Triamcinolone Acetonide
tid	Three times daily
VAS	Visual analog scale
vs.	Compared with (versus)
WD	Withdrawal
XR	Extended release
y	Year
ZAF	Zafirlukast

Evidence Table 1. Trials key questions 1 and 2

Author Year Country Trial name Quality rating	Population	Interventions: Medication, total daily dose Steroid dose range	Allowed other medications/ interventions	Age Race / ethnicity Sex	Other population characteristics	N	Efficacy and effectiveness outcomes	Adverse events reported	Withdrawals because of adverse events	Funding
Aalbers et al. 2010 Companion with Aalbers et al. 2004 Country and setting: Six countries: Denmark, Finland, Germany, Norway, Sweden and The Netherlands Multicenter: 93 centres Fair	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. Aalbers, 2010 analyzed data with only those ≥16 years of age	G1: BUD/FM DPI adjustable dose G2: BUD/FM DPI fixed dose G3: SM/ FP DPI Total daily dose: G1: 320 - 640mcg / 9 - 18mcg (average use 544mcg/15mcg per day) G2: 640 mcg / 18 mcg G3: 100mcg / 500 mcg Steroid dosing range (Low, medium or high): G 1: low - medium G 2: medium G3: medium	short-acting beta 2 agonist for rescue	Mean age (years): G1: 47 G2: 46 G3: 46 Sex (% female): G1: 57 G2: 55 G3: 51 Aalbers et al, 2010 Mean age (years): G1: 48 G2: 46 G3: 46 Sex (% female): G1: 57 G2: 55 G3: 51	Smoking NR	G1: 219 G2: 215 G3: 224 Aalbers et al, 2010 G1: 213 G2: 213 G3: 222	Rescue med use during 24 hour period: mean difference between groups in number of occasions/day during open extension = G1-endpoint: G2-endpoint: G3- endpoint: 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: G1 end: 34 G2 end: 50 G3 end: 58 P: p = 0.019 for BUD/FM AD versus SM/FP; CI -4.8 to 55.9 for BUD/FM AD versus BUD/FM FD Exacerbations requiring hospitalizations or ER visits G1 end: 2 G2 end: 3 G3 end: 8 P=0.018 for G2 v G3 and 0.093 for G1 v G3 Exacerbations requiring oral steroid dose G1 end: 32 G2 end: 47 G3 end: 50	Incidence ot AE was similar in all groups. G1: 56% G2: 58% G3: 65% Most common AE (range) Respiratory infection (16-23%) Rhinitis (1-6%) Viral infection (2-5%) Dysphonia G1: 1% G2: 1% G3: 7% P=0.00056 for G1 and G2 v G3 29 serious AE recorded in G1: 8 G2: 11 G3: 4	G1: 5 G2: 10 G3: 9	AstraZeneca
Aalbers et al. 2010 Companion with Aalbers et al. 2004 cont'd							Nocturnal awakenings: no significant differences were observed between the fixed doses of BUD/FM and SM/FP for nighttime awakenings Other: Adherence Avg number of maintenance inhalations per day G1: 3.43 G2: 3.94 G3: 2.00			

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Adachi 2007 Japan N/A poor	Patients aged between 16 and 75 years with moderate to severe asthma	G1: CIC, 400 mcg (320mcg ex-actuator) High dose (or med if using ex-actuator dose) G2: CIC, 800 mcg (640mcg ex-actuator) High dose G3: BDP, 800 mcg (CFC-BDP) (ex-valve) Medium dose	NR	G1: mean age 52.2; 47% female G2: mean age 52.4; 54% female G3: mean age 51.6; 40.6% female	Smoking: NR	319	Rescue medication use: Mean change from baseline (times used per day): G1: -0.01 G2: -0.44 G3: 0.07 G1 vs. G2: p = 0.029 G2 vs. G3: p = 0.007 G1 vs. G3: NR	"No large differences between the groups in the number and types of adverse events" Oral Candidiasis: G1: 0% G2: 0% Hoarseness; "Fewer than 2 participants per group" Deaths: G1: 0% G2: 0%	NR	Teijin Pharma
Adachi 2007 Cont'd							Symptom Score: Asthmatic score decreased over time in G1 and G2 (data in figure only). Decrease in asthmatic score was greater in G2 than in G3. G2 asthmatic score had decreased significantly more than G3 at week 6 (p=0.034) and week 8 (p=0.008) Scale: uses the rating standard of the Japanese Society of Allergology, calculated as the sum of the symptom score based on the asthmatic symptoms and of the therapy score based on the use of asthma medication.			

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Bailey 2008 United States Fair	African American by self-report, 12–65 years of age with persistent asthma for at least 6 months, had a forced expiratory volume in one second (FEV1) 60–90% of predicted, FEV1 reversibility of 12% following 2–4 puffs of albuterol, and symptomatic while being treated with ICS at a low and consistent dose (FP 200 mcg daily or equivalent) for at least 1 month	2-week screening period on low dose ICS; a 4-week open-label FP 250 mcg twice daily (BID) run-in; a 52-week double-blind period (FP/SM 100/50 mcg [n¼239] or FP 100 mcg [n¼236] BID), and a 4-week FP 250 mcg BID run-out period	Rescue med-albuterol	Age: G1 = 31.5 G2 = 32.2 Black: 100% self identified as African-American % female: G1 = 60% G2 = 64%		G1: 239 G2: 236	24-hour symptom score Baseline G1: 1.54 (0.076) G2: 1.67 (0.076) Change from baseline G1: –0.26 (0.065) G2: –0.23 (0.061) (–0.26, 0.06), P = 0.216 % symptom-free days Baseline G1: 26.7 (2.48) G2: 23.2 (2.36) Change from baseline G1: 10.8 (2.46) G2: 8.9 (2.21) (–2.9, 9.6), P = 0.296 24-hour albuterol use, puffs/24 hours Baseline G1: 1.62 (0.107) G2: 1.55 (0.113) Change from baseline G1: –0.35 (0.096) G2: –0.15 (0.103) (–0.41, 0.05), P = 0.122 % albuterol-free days Baseline G1: 37.9 (2.72) G2: 42.1 (2.72) Change from baseline G1: 10.8 (2.50) G2: 5.6 (2.54) (–1.8, 10.9), P = 0.159 Nighttime awakenings, per night Baseline G1: 0.41 (0.047) G2: 0.40 (0.044) Change from baseline G1: –0.14 (0.035) G2: –0.06 (0.035) (–0.15, 0.00), *P* = 0.050	FP/SM 100/50 mcg vs. FP 100 mcg Number of subjects with any adverse event, n (%) G1: 146 (61) G2: 161 (68) Infection and infestations n (%) Upper respiratory tract infection G1: 32 (13) G2: 32 (14) Nasopharyngitis G1: 18 (8) G2: 41 (17) Sinusitis G1: 17 (7) G2: 27 (11) Bronchitis G1: 6 (3) G2: 13 (6) Gastroenteritis viral G1: 6 (3) G2: 9 (4) Influenza G1: 9 (4) G2: 5 (2) Rhinitis G1: 7 (3) G2: 2 (51) Urinary tract infection G1: 6 (3) G2: 3 (1)	G1: 5 (2%) G2: 6 (3%)	GlaxoSmithKline

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Bailey 2008 cont'd							Exacerbations G1: 0.449 per year G2: 0.529 per year in FP P = 0.169). During doubleblind treatment, G1: 69 exacerbations in 47 out of 239 subjects (20%) G2: 85 exacerbations in 54 out of 236 subjects (23%)	Respiratory, thoracic and mediastinal disorders, n (%) Pharyngolaryngeal pain G1: 20 (8) G2: 17 (7) Cough G1: 15 (6) G2: 17 (7) Sinus congestion G1: 7 (3) G2: 9 (4) Nasal congestion G1: 9 (4) G2: 6 (3) Rhinitis allergic G1: 10 (4) G2: 2 (51) Nervous system disorders, n (%) Headache G1: 34 (14) G2: 41 (17) Sinus headache G1: 5 (2) G2: 8 (3) Musculoskeletal and connective tissue disorders, n (%) Back pain G1: 11 (5) G2: 21 (9)		

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Bailey 2008 cont'd								Arthralgia G1: 10 (4) G2: 6 (3) Myalgia G1: 9 (4) G2: 3 (1) Pain in extremity G1: 6 (3) G2: 6 (3) Neck pain G1: 3 (1) G2: 8 (3) Gastrointestinal disorders, n (%) Toothache G1: 13 (5) G2: 8 (3) Abdominal pain upper G1: 12 (5) G2: 7 (3) Nausea G1: 9 (4) G2: 7 (3) General disorders, n (%) Pain G1: 4 (2) G2: 9 (4) Pyrexia G1: 6 (3) G2: 7 (3)		
Bateman 2008 Multinational N/A Fair	Outpatients aged 12–75 years with a >6-month history of moderate to severe asthma	G1: CIC, 640 mcg (two puffs of 160 mcgex-actuator [200 mcgex-valve] BID) High dose G2: FP, 660 mcg (three puffs of 110 mcgex-actuator [125 ex-valve] BID) High dose	Patients using LABAs, oral beta-2 agonists, theophylline, LTRAs or lipoxygenase inhibitors could continue treatment provided the dosage was kept constant throughout the trial. Salbutamol 100 mcg/puff as rescue medication	G1: median age 43; 62% female; ethnicity NR G2: median age 44; 60% female; ethnicity NR	Ex-/current smokers G1: 32% G2: 34%	528	Rescue medication use: Puffs/day, change from baseline: G1: -0.07 (p=0.0005) G2: -0.14 (p<.0001) difference not statistically significant between groups Rescue medication-free days: G1: 89% G2: 84% difference not statistically significant between groups	Overall Adverse Events: G1: 373 G2: 401 Oral Candidiasis: G1: 2.0% G2: 4.8% (numbers from safety set) Dysphonia; G1: 3.1% G2: 9.2% (numbers from safety set) Pharyngolaryngeal pain (numbers from safety set): G1: 4.3% G2: 4.4%	NR	ALTANA Pharma AG, Konstanz, Germany

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Bateman 2008 cont'd							Asthma symptom sum scores, change from baseline: G1: -0.14 (p<.0001) G2: -0.14 (p<.0001) difference not statistically significant between groups Asthma symptom free days: G1: 82% G2: 81% difference not statistically significant betweem groups. Scale: 5 points (0= no symptoms, 4= asthma very bad)	Headache: G1: 2.4% G2: 4.4% (numbers from safety set) Upper Respiratory Tract Infection: G1: 8.2% G2: 7.3% (numbers from safety set) Nasopharyngitis (numbers from safety set) G1: 11.8% G2: 8.8% Rhinitis: G1: 3.1% G2: 2.9% (numbers from safety set)		
Bateman 2008 cont'd							Exacerbations (requiring use of a systemic steroid): G1: 6 patients (2.4%) G2: 7 patients (2.6%) 95% CI: -0.031, 0.028; below the stipulated non-inferiority acceptance limit of 5% Oral Steroids: G1: 6 patients (2.4%) G2: 7 patients (2.6%) AQLQ Change from baseline: G1: 0.18 +/- 0.05 (p=0.0004) G2: 0.15 +/- 0.05 (p = 0.0026) LS mean +/- SEM for the treatment difference = 0.03 +/- 0.07 (95% CI:-0.10, 0.16)	(Numbers from safety set) Bronchitis G1: 3.5% G2: 4.0% Sinusitis G1: 3.5% G2: 3.3% Influenza G1: 3.1% G2: 4.4% Back pain G1: 3.1% G2: 1.1%		

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Berger 2010 USA N/A Fair	Ages 6-11 with a documented diagnosis of mild to moderate asthma >=6 months; receipt of daily ICS treatment for >=4 weeks before screening	G1: BUD/FM pMDI, 640/18mcg (medium dose BUD); G2: BUD DPI, 800mcg (medium dose)	If subjects experience uncontrolled ashtma after 2 wks, other agents could be added-on (incl. leukotriene receptor antagonists, inhaled nonsteroidals, methylxanthines, and SABAs) but not addt'l LABA or ICS	G1: Age= 9 White= 88.6% Black= 8.9% Asian= 0.8% Other race= 1.6% Female= 35.8% G2: Age= 9 White= 92.1% Black= 4.8% Asian= 1.6% Other race= 1.6% Female= 36.5%	Smoking: NR	Randomized N = 187	Symptoms: 5-point Likert scales: MD REPORT OF SYMPTOMS: A great deal better: G1 = 47.1% G2 = 24.6% Somewhat better: G1 = 33.6% G2 = 52.5% Unchanged: G1 = 16% G2 = 18% Somewhat worse: G1 = 3.4% G2 = 1.6% A great deal worse: G1 = 0.0% G2 = 3.3%	Overall Adverse Events: G1: N=104 (84.6%) G2: N=54 (85.7%) Treatment-related Adverse Events: G1:N=6 (4.9%) G2: N=4 (6.3%) Growth: G1: 2.51cm G2: 2.10cm NS Oral Candidiasis: G1: 1.6% G2: 0% Cough: G1: 0.8% G2: 1.6% G1: 12.2% G2: 7.9%	G1: N=3 (2.4%) G2: N=2 (3.2%)	Pharmaceutical: AstraZaneca
Berger 2010 cont'd							CAREGIVER REPORT OF SYMPTOMS: A great deal better: G1 = 41.1% G2 = 22.2% Somewhat better: G1 = 28.0% G2 = 29.6% Unchanged: G1 = 26.2% G2 = 40.7% Somewhat worse: G1 = 3.7% G2 = 3.7% Much worse: G1 = 0.9% G2 = 3.7%	Deaths: G1: N=0 G2: N=0 Asthma reported as AE: G1: 13.0% G2: 9.5%		

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Berger 2010 cont'd							(PAQLQ(S)) mean (SD) change from baseline: G1 = 0.53 (0.83) G2 = 0.36 (0.97) Mean difference = 0.35 95% CI [0.14, 0.57], p<0.001 "did not reach the minimally important difference" Pediatric Asthma Caregiver AQLQ mean change from b/l: G1 = 0.39 G2 = 0.17 Mean difference = 0.26, 95% CI [0.08, 0.45], p<0.01 "did not reach the minimally important difference" Caregiver absent from work due to child's asthma or breathing problems: G1 = 0.503 days/subject-treatment year; 13.8% ≥1 day; G2 = 1.011 days/subject-treatment year; 19.0% >=1 day			
Berger 2010 cont'd							Child unable to participate in daily activities: G1 = 1.752 days/subject-treatment year; 29.3% >/=1 day; G2 = 3.662 days/subject-treament year; 44.4% >/=1 day diff in % with 1 or more days: p<0.05 Hospitalizations: G1 = 2; G2 = 1 Urgent care: G1 N=4 (3.3%); G2 N=7 (11.1%) p<0.05 Unscheduled provider visits: G1 N=32 (26.0%); G2 = 14 (22.2%) Phone calls to provider: G1 N=36 (29.3%); G2 N=17 (27.0%)			

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Bleecker 2010	Male and female subjects with persistent asthma for at least 3 months, aged 12 years and older, treated with only SABAs on an as-needed or scheduled basis for at least 4 weeks	G1-G3 (FP/SM): 200 (low)/100 mcg G4-G6 (SM): 100mcg	NR	Age G1: 33.8 G2: 33.3 G3: 31.0 G4: 30.0 G5: 35.2 G6: 32.8 Race/Ethnicity (White/black/other) % G1: 49/33/18 G2: 65/20/15 G3: 62/18/20 G4: 50/36/14 G5: 62/21/17 G6: 60/17/23 % female G1: 70 G2: 60 G3: 64 G4: 63 G5: 55 G6: 64	Smokers: None	Overall: FP/SM: 272 SM: 272 By genotype, ITT population: G1 (FP/SM Arg/Arg):89 G2 (FP/SM Gly/Gly): 91 G3 (FP/SM Arg/Gly): 92 G4 (SM Arg/Arg): 90 G5 (SM Gly/Gly): 92 G6 (SM Arg/Gly): 90	Mean change in as-needed IB use, puffs per day (SE) G1: -0.5 (0.1) G2: -0.6 (0.1) G3: -0.6 (.01) G4: -0.4 (.01) G5: -0.4 (.01) G6: -0.5 (.01) % change in Symptom free days (SE) G1: 9.9 (2.8) G2: 18.2 (2.9) G3: 14.6 (3.2) G4: 9.6 (3.2) G5: 8.2 (2.7) G6: 9.1 (2.7)	Sore throat: G1-G3: 2-6; G4-G6: 1-3% Headache: G1-G3: 9-21; G4-G6: 7-13 Upper Respiratory Tract infection: G1-G3: 1-4; G4-G6: 2-8 Cough: G1-G3: 1-7; G4-G6: 0-3%		
Bleecker 2010 cont'd							Exacerbations: G1:0 (1 occurred the day after the end of RCT) G2: 1 G3: 0 G4: 3 G5: 4 G6: 3 G1-3 (FP/SM) > G4-6 (SM); P = 0.006 By race White or other/Black/Hispanic or Latino G1: 0/0/0 G2: 1/0/0 G3: 0/0/0 G4: 1/2/0 G5: 1/1/2 G6: 1/0/2			

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Boonsawat 2008 Multiple (9 countries) NA Good	Ages 12-79 with documented history of mild asthma for >=6 months	G1: SM/FP combination 50ug/100ug (low dose FP) G2: FP 100ug q.d.: (low dose FP) G3 (PBO)	None	Age: G1 = 34.7 G2 = 34.0 G3 = 33.4 Race NR Female: G1 = 54% G2 = 56% G3 = 46%	Smoking: NR	Randomized N = 464	Rescue Medication Use: % of rescue medication-free days (OR [95% CI]): G1 vs G3 = 0.19 [0.12, 0.32], p<0.001 ; G1 vs G2 = 0.56 [0.34, 0.90] p=0.018; Mean 24-hour rescue salbutamol use (OR [95% CI]): G1 vs G3 = -0.17 [-0.23, -0.11] Symptoms: % of symptom-free days (median): G1 = 93% G2 = 87% G3 = 79% % of symptom-free days (OR [CI]): G1 vs G3 = 0.24 [0.15, 0.38] - p<0.001 G1 vs G2 = 0.55 [0.34, 0.87] - p=0.011 G2 vs G3 = 0.44 [0.28, 0.68] - p<0.001; Achievement of "well-controlled asthma" (%): G1 = 52% G2 = 42% (p=NS, G1 vs G2) G3 = 26% (p=0.004, G1 vs G2)	Overall Adverse Events: G1: N=49 (33%) G2: N=57 (37%) G3: N=74 (48%) Cough: G1: 1.3% G2: 0.7% Sore Throat: G1: 0.7% Hoarseness: G1: 0.7% G2: 0.7% Deaths: NR Severe asthma exacerbation (considered an AE here): G3: 0.7% Nasopharyngitis: across all groups: 7-13%	G1: N=2 (1.3%) G2: N=1 (0.7%) G3: N=2 (1.3%)	Pharmaceutical: GlaxoSmithKline
Boonsawat 2008 cont'd							Exacerbations: G1 N=3 (3 patients) G2 N=9 (8 patients) G3 N=15 (12 patients) Oral Steroid Courses: G1 N=3 (3 patients) G2 N=9 (8 patients) G3 N=15 (12 patients)			

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Boulet 2006 Multinational - Canada and Europe NA Fair	12 - 75 years of age; persistent mild to moderate asthma for at least 6 months as defined by the American Thoracic Society criteria	G1: 320ug (equivalent to 400ug ex-valve) Medium dose G2: 320ug (equivalent to 400ug Turbohaler) Low dose	Salbutamol 100ug/puff served as rescue medication	G1: Median age, 39 years; Female, 56% G2: Median age, 42 years; Female, 62% Overall: Race/Ethnicity, 96% Caucasian	Smoking: G1: Smokers and Ex-Smokers: 25% G2: Smokers and Ex-Smokers: 32%	359 patients were randomized	Rescue Medication Use: G1: experienced a significant reduction in the median rescue medication use over the course of treatment (P = 0.009). Data shown in figure only. G2: experienced no change in the median rescue medication use over the course of treatment (P = 0.626). Data shown in figure only. Median rescue medication use for G1 vs G2, P = 0.026 Median percentage of rescue medication-free days was similar in both groups, G1: 57.5% vs G2 53.6%	Overall Adverse Events: NR Sore Throat: G1: 2% G2: 1% Upper Respiratory Tract Infection: G1: 12% G2: 19% Respiratory Infection (Bronchitis): G1: 3% G2: 3% Rhinitis: G1: 2% G2: 3% Asthma G1: 9% G2: 12% Pharyngitis G1: 3% G2: 3%	NR	ALTANA Pharma AG, Konstanz, Germany
Boulet 2006 cont'd							Symptoms: No significant differences between the two groups in median asthma symptom score sums, night scores, and daytime scores. Data not shown. [Daytime asthma scores based on a five point scale: 0 (no symptoms) to 4 (asthma very bad, unable to carry out daily activities as usual). Night time asthma score ranged from 0 (no symptoms, slept through the night) to 4 (bad night, awake most of the night because of asthma)]. Exacerbations: G1: 1 patient had exacerbation G2: none reported	Sinusitis G1: 2% G2: 2% Voice Alteration: G1: 2% G2: 1%		

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Boulet 2007 Multiple (Austria, Canada, Germany, Hungary, South Africa, Spain) NA Fair	12-75 years with moderate asthma for >=6 months	G1: CIC 320ug (ex-mouthpiece) (medium dose) G2: FP 400ug (ex-valve) (medium dose)	Salbutamol as rescue med	Age: G1 = 38 G2 = 40 Race NR Female: G1: 62% G2: 61%	Smoker/Ex: G1 = 29% G2 = 31%	Randomized N = 474	Rescue Medication Use: % rescue medication-free days: G1: 89% G2: 88% Symptoms: % symptom-free days: G1: 88% G2: 88% Asthma symptom- and rescue medication-free days: G1: 85% G2: 84% Change in daytime symptom scores: G1: -0.25 G2: -0.29 Change in total symptom scores: G1: -0.29 G2: -0.29	Overall Adverse Events: Total: 178 patients (37.7%) G1: 36.1% G2: 39.3% Oral Candidiasis: G1: 0% G2: 3.8% p=0.002 (1-sided) Dysphonia: G1: N=5 G2: N=6 Sore Throat: (Reported as "pharyngolaryngeal":) G1: 3.4% G2: 1.7% Deaths: G1: 0% G2: 0% Nasopharyngitis: G1: 6.4% G2: 6.3%	G1: 4 (1.7%) G2: 10 (4.2%)	Pharmaceutical: ALTANA

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Buhl 2006 cont'd							Symptoms: G1: Total Asthma Symptom Score Baseline 1.48 (median) Change -0.75 P-value vs baseline <0.0001 G2:Total Asthma Symptom Score Baseline 1.57 (median) Change -0.86 P-value vs baseline <0.0001 Change vs FP 0.07 (point estimate), 95% CI -0.11, 0.29), P-value 0.387 G1: Daytime Symptom Score Baseline 0.86 (median) Change -0.43 P-value vs baseline <0.0001 G2: Daytime Symptom Score Baseline 1.00 (median) Change -0.50 P-value vs baseline <0.0001	Respiratory Infection: Bronchitis- G1: 4% G2: 3% Pharyngitis- G1: 4% G2: 3% Rhinitis: G1: 3% G2: 3% Deaths: G1: 0% G2: 0% Asthma: G1: 3% G2: 1% Oral candidiasis or voice alteration occurred in 3 patients treated with FP but neither occurred in patients treated with CIC.		
Boulet 2007 cont'd							Asthma worsening: G1: 1.7% G2: 4.2% Exacerbations: G1: 1.3% G2: 2.1% AQLQ: Mean change from baseline: G1: 0.29 G2: 0.11 Difference = 0.18, p=0.005 (one-sided for superiority) Other validated HRQOL measure: HRQoL net benefit (from AQLQ): G1: 21.2% G2: 6.8% *Net benefit = the proportion of patients w/ improvement of 0.5 in AQLQ(S) score minus proportion with worse score.	% events "likely or definitely related to the treatment": G1: 9 (3.9%) G2: 21 (8.8%)		

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Buhl 2006 Germany, Austria, The Netherlands, Spainn, Hungary, Poland, South Africa NA Fair	12 - 75 years of age; diagnosis of all severities of asthma > 6 months (American Thoracic Society Guidelines)	G1: 160ug (Low) G2: 176ug (Low)	Salbutamol as rescue med	G1: Median age, 41 years; Female, 61%; Race/Ethnicity, NR G2: Median age, 38 years; Female, 54%; Race/Ethnicity, NR	Smoking: NR	529 randomized 484 completed the study, 451 comprised the PP analysis population	Rescue Medication Use: CIC and FP both significantly reduced rescue medication use from baseline, P<0.0001 for both groups. G1 change vs G2 change (point estimate) = 0.14, 95% CI -0.00, 0.43; P-value = 0.130. G1: Median baseline puffs/day = 1.43; change from baseline -1.00 G2: Median baseline puffs/day = 1.71; change from baseline -1.21.	Overall Adverse Events: 270 events experienced by 186 participants G1: 97 (36%) patients G2: 89 (34%) patients Headache: G1: 3% G2: 4% Upper Respiratory Tract Infection: G1: 8% G2: 8%	G1: 6 (2.26%) G2: 3 (1.14%)	ALTANA Pharma AG, Konstanz, Germany
Buhl 2006 cont'd							Change vs FP 0.00 (point estimate), 95% CI -0.00, 0.0.14), P-value 0.317 G1: Nighttime Symptom Score Baseline 0.50 (median) Change -0.29 P-value vs baseline <0.0001 G2: Nighttime Symptom Score Baseline 0.50 (median) Change -0.33 P-value vs baseline <0.0001 Change vs FP 0.00 (point estimate), 95% CI 0.00, 0.10), P-value 0.530 daytime and nighttime scores based on 5 point scale (0-4), 0 = no asthma, 4 = highest discomfort related to asthma symptoms.			

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Chervinsky, 2008 Companion to Noonan, 2006	Patients 12 years or older (eligible)(but data collected from those 18 and older), documented diagnosis of moderate to severe persistent asthma (defined by the American Thoracic Society) for 6 months or more were eligible. Patients required to have a prebronchodilator (FEV1) of 45% to 85% of predicted normal, to have an FEV1 reversibility of 12% or higher and 0.20 L or higher of baseline value within 15 to 30 minutes after a standard albuterol dose, and to have used medium to high doses of ICS alone or in combination with other asthma maintenance medications for 4 weeks or more before screening.	G1: BUD/FM 640ug/18ug (medium) G2:BUD 640ug pMDI (medium) G3: FM DPI 18ug G4:BUD/FM DPI (medium) 640ug/18ug G5:PBO	NR	G1:43.4y, 82.1%white, 12.8% black, 5.1% other, 67.5% female G2:42.5y, 76.5%white, 16.7% black,6.9 % other, 66.7% female G3: 43.4y,72.5 %white, 18.3% black, 9.2% other, 67.9% female G4: 41.4y, 77.3%white, 17.3% black, 5.5% other, 56.4% female G5: 44.3y, 82.6% white, 13.9% black, 3.5% other, 60.0% female	NR	G1: N=117 G2: N=102 G3: N=109 G4:N=110 G5: N=115	Rescue med use, inhalations per day: Change from baseline: G1:= -1.04 G2= -0.57 G3= -0.68 G4= -1.41 G5= 0.73 G1 vs G2:- 0.68 (-1.14 to -0.22); p < 0.01 G1 vs G3: -0.68 (-1.13 to -0.22), p <0.01 G1 vs G4: 0.30 (- 0.15 to 0.75), p = NS G1 vs G5: -2.02 (-2.46 to -1.58), p≤0.001 Daily asthma symptom scores: Change from baseline: G1= -0.29 G2= -0.15 G3= -0.12 G4= -0.30 G5= +0.07 G1 vs G2: -0.17 (-0.27 to -0.07); p≤0.001 G1 vs G3: -0.20 (-0.30 to -0.10); p≤0.001 G1 vs G4: 0.02 (-0.08 to 0.12); p≤0.001 G1 vs G5: -0.40 (-0.50 to -0.30)p≤0.001			AstraZeneca
Chervinsky, 2008 cont'd							AQLQ Change from baseline: G1= 0.41 G2= 0.23 G3= - 0.10 G4= 0.56 G5= -0.22 Adjusted mean differences between groups, (95%CI): G1 vs G2: 0.29 (0.058 to 0.527);p<0.05 G1 vs G3: 0.60 (0.362 to 0.833); p≤0.0014 G1 vs G4: -0.10 (-0.334 to 0.131);p=NS G1 vs G5: 0.70 (0.468 to 0.929); p ≤0.001			

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Chervinsky, 2008 cont'd							% Symptom free days, Change from baseline: G1: 20.15 G2: 8.63 G3: 4.80 G4:19.68 G5: 0.99 % Symptom free days, Adjusted mean difference between groups (95% CI) G1 vs G3: 13.15 (6.31 to 19.99), G1 vs G4: 16.70 (9.92 to 23.48), G1 vs G2: 1.14 (-5.67 to 7.95) G1 vs G5: 20.69 (14.04 to 27.34) %Rescue medication-free days, Change from baseline: G1: 30.44 G2: 10.99 G3: 18.19 G4:35.64 G5; -2.19 % Rescue medication-free days, (95% CI): G1 vs G3: 21.37 (13.83 to 28.90) G1 vs G4: 16.01 (8.54 to 23.49), G1 vs G2: -4.51 (-12.00 to 2.99), G1 vs G5: 35.29 (28.00 to 42.59)			
Chervinsky, 2008 cont'd							Asthma control days, % (95% CI): G1 vs G3: 12.87 (6.77 to 18.97), G1 vs G4: 14.47 (8.43 to 20.52), G1 vs G2: 0.49 (-5.58 to 6.56), G1 vs G5: 18.16 (12.23 to 24.09) Awakening free nights, % (5% CI): G1 vs G3:-2.57 (-6.60 to 1.45), G1 vs G4: 2.16 (-1.84 to 6.16), G1 vs G2: -2.25 (-6.26 to 1.75), G1 vs G5: 7.21 (3.31 to 11.11)			

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Chuchalin 2008 Multiple NA Fair	Ages 12-79 with documented history of mild asthma	G1: (PBO) G2: 100ug FP - low dose G3: 50ug SM + 100ug FP (low dose)	None	G1: Age = 35.0 White = 70% Black = <1% Asian = 23% Other = 8% Female = 61% G2: Age = 33.8 White = 69% Black = 1% Asian = 22% Other = 7% Female = 58% G3: Age = 33.8 White = 68% Black = 2% Asian = 22% Other = 8% Female = 56%	Smoking: G1: never smoked = 78% current smoker = 7% former smoker = 14% G2: never smoked = 78% current smoker = 8% former smoker = 15% G3: never smoked = 77% current smoker = 9% former smoker = 15%	Randomized (ITT): N=2258	Rescue Medication Use: Mean 24-hour use (median over weeks 1-52): G1: 0.29 G2: 0.11 G3: 0.13 Symptoms: Mean 24-hour asthma symptom score: G1: 0.54 G2: 0.28 G3: 0.32 Mean %age of symptom-free 24-hour periods: G1: 64.8 G2: 79.8 G3: 77.0 Median asthma control questionnaire score: G1: 0.71 G2: 0.43 G3: 0.43	Overall Adverse Events: Total # patients with AE G1: 205 (65%) G2: 608 (63%) G3: 579 (60%) Percent of patients with SAE G1: 6% G2: 3% G3: 3% Oral Candidiasis: G1: 0% G2: 17 (2%) G3: 2 (<1%) Cough: G1: 5% G2: 4% G3: 4% Sore Throat (Pharyngolaryngeal pain): G1: 3% G2: 5% G3: 5%	G1: 4 (1.3%) G2: 15 (1.5%) G3: 15 (1.5%)	Pharmaceutical: GlaxoSmithKline

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Chucalin 2008 cont'd							Achievement of "well-controlled" asthma over final 8 weeks of treatment: G1: 54% G2: 75% G3: 73% OR for achieving "well-controlled" vs PBO (G1): G2: 2.8 G3: 2.4 OR for achieving "well-controlled" versus G2: G3: 0.9 (NS) Achievement of "totally-controlled" asthma over final 8 weeks of treatment: G1: 20% G2: 34% G3: 28% OR for achieving "well-controlled" versus G2: G3: 0.8	Headache: G1: 16% G2: 16% G3: 16% Upper Respiratory Tract Infection: G1: 11% G2: 12% G3: 11% Respiratory Infection: G1: 5% G2: 4% G3: 4% Rhinitis: G1: 5% G2: 5% G3: 3% Deaths: G1: 1 G2: NR G3: NR		
Chuchalin 2008 cont'd							Exacerbations: Adjusted mean exacerbation (all severities) rates per patient per year: G1: 2.88 G2: 1.87 G3: 1.41 Moderate/severe exacerbation rate (adjusted mean rate per year): G1: 0.33 G2: 0.10 G3: 0.13 Reduction in overall exacerbation rates vs PBO (G1): G2: 51% G3: 35%	Nasopharyngitis: G1: 17% G2: 16% G3: 16% Pharyngitis: G1: 3% G2: 5% G3: 4% Serious Adverse Events (SAE): G1: 6% G2: 3% G3: 3%		

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Chuchalin 2008 cont'd							Hospitalizations: G1: NR G2: N=5 (<1%) G3: N=3 (<1%) Urgent Care: Any healthcare contacts: G1: N=7 (2%) G2: N=5 (<1%) G3: N=3 (<1%) ER visits: G1: NR G2: N=14 (1.4%) G3: N=14 (1.4%)			
Chylack 2008	Male and female patients ≥18 years of age with a history of moderate-to-severe persistent asthma for ≥2 months and a forced expiratory volume in 1 second (FEV1) of ≥40% and ≤85% of predicted; documented ICS use ≥1 month before screening, the ability to demonstrate acceptable oral inhaler technique, and to have been a non-smoker for ≥1 year, with a <10 pack/year smoking history	G1 (CIC): 640mcg/d (ex-mouthpiece) (high) G2 (BEC): 640mcg/d (high) (ex-mouthpiece)	NR	Age (mean): G1 = 42.9 G2 = 43.3 White: G1 = 83% G2 = 84% Black: G1 = 9.2% G2 = 8.5% Other race: G1 = 7.8% G2 = 7.5% % female: G1 = 60.0% G2 = 60.2%	NR	Randomized: 1,568 Treated: 1,552 modified ITT: 1485	NR	Overall AEs: G1: 648 (83.5%) G2: 664 (85.6%) Oral Candidiasis: G1: 1.4% G2: 6.3% Dysphonia: G1: 1.5% G2: 1.3% Retinal hemorrhage (N): G1: 1 G2: 0 Pharyngitis (%): G1: 8% G2: 8.4% Hypertension, increased transaminases, cortical cataract (N): G1: 0 G2: 3 (presume 1 each of the above) Deaths: G1: 0.01% G2: 0.01%	G1: 29 (3.7%) G2: 22 (2.8%)	Sanofi-aventis US and Nycomed

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Connolly 1995 UK Fair	Age 18-70 with mild asthma, receiving no ICS or doses up to 200mcg daily of BDP or BUD, clinical requirement for ICS at study doses, asthma symptom score of 1 or more on at least 2 of the previous 10 days, FEV1 at least 50% of predicted normal after 4 hours of no beta-agonist, either at least 15% reversibility in FEV1 15 minutes after inhalation of 200mcg salbutamol or diurnal variation in PEF of at least 15% on 2 or more days of week prior to run-in	G1: BUD 400mcg day (low) G2: FP 200mcg day (low) G1: RPD G2: Diskhaler	NR	G1 (BUD): Age = 39.1 % female = 57 Race NR G2 (FP): Age = 40.2 % female = 57 Race NR	Smoking NR	G1: N = 91 G2: N = 98	Data reported as medians % rescue-free days: G1 = NR (shown in graph) G2 = 17% increase P = 0.01 favoring G2 % rescue-free nights: G1 = 2% increase G2 = 14% increase P = 0.02 Likert scale of asthma control (excellent; good; moderate; poor) % physicians rating "excellent" asthma control: G1 = 24% G2 = 38% P= 0.04 % patients rating "excellent" asthma control: G1 = 30% G2 = 41% P = 0.1 Data reported as medians % symptom-free days: G1 = no change G2 = 24% increase P = 0.05 % symptom-free nights: G1 = 17% increase G2 = 29% increase P = 0.05	Number of events G1: N=170 G2: N=186 Patients reporting adverse events G1: 59 (65%) G2: 69 (70%) Suspected: G1 = 1 (1%); G2 = 3 (3%) Confirmed: G1 = 0; G2 = 0 Sore Throat G1 = 16 events G2 = 14 events Headache G1 = 30 events G2 = 28 events Upper Respiratory Infection G1 = 7 events G2 = 5 events Acute nasopharyngitis: G1 = 5 events G2 = 16 events	G1: 1 (1.0%) G2: 1 (1.0%)	NR
Covar 2008 USA PACT for original study Fair	children 6 to 14 years of age with documented mild-moderate persistent asthma	G1: FP 200ug (low) G2: FP 100ug (low) and SM 100ug G3: ML 5mg	NR	NR	Smoking: NR	285	Exacerbations: G1: 0 exacerbations:n= 59 (61%) 1 exacerbation: n=22 (23%) 2 exacerbations: n=10 (10%) 3 exacerbations n=5 (5%) G2: 0 exacerbations: 46 (49%) 1 exacerbations: n=27 (29%) 2 exacerbations: n=13 (14%) 3 exacerbations: n=8 (9%) G3: 0 exacerbations: 42 (44%) 1 exacerbations: n=25 (26%) 2 exacerbations: n=12 (13%) 3 exacerbations: n=16 (17%) G1 vs. G3 p = 0.009 G1 vs. G2 p = 0.09 G2 vs. G3, p = 0.2			grants from: 1)National Heart, Lung, and Blood Institute, 2)General Clinical Research Centers at Wash U SOM, and 3)National Jewish Medical and Research Center

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Covar 2008 cont'd							ORs for exacerbations: G3 vs G1, Unadjusted OR (95%CI) 1.91 (1.24, 2.95) (p=0.003) G2 vs G1, Unadjusted OR (95%CI) 1.51 (0.97, 2.34), p = 0.066 Urgent Care: Over twice as many ED/urgent care visits for exacerbations were reported in the ML groups (n=26) and the PACT combination (n=28) compared with the FP monotherapy (n=10; P=.7 PACT combination vs ML; P < .001 PACT combination vs FP monotherapy; P=.003 ML vs FP monotherapy).			
Covar 2008 cont'd							Other: Rates of exacerbations per patient year: 1.0 for ML, 0.8 for PACT combination, and 0.6 for FP monotherapy (p=.01). More than half of the participants in either the ML (56%) or PACT combination (51%) groups but only 39% in the FP monotherapy group developed at least 1 exacerbation during the trial (P=.004 ML vs FP monotherapy; P=.09 FP monotherapy vs PACT combination;P =.2 ML vs PACT combination). One or 2 exacerbations occurred equally in the 3 treatment groups. However, 55% of children with 3 exacerbations were from the ML group, 27% from the PACT combination, and only 17% from the FP monotherapy (P=.21 PACT combination vs ML; P=.6 PACT combination vs FP monotherapy; P=.04ML vs FP monotherapy)			

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Dahl 2010 Multinational NA Fair	Female and male patients aged 12-75 years with a history of persistent mild to moderate bronchial asthma for at least 6 months, but otherwise in good health	G1: CIC 80 ug - low (ex-mouthpiece) G2: FP 200 ug daily - low (ex-valve)	Salbutamol as rescue med	Given for ITT popn: Mean Age: G1 = 42 G2 = 41 % female: G1 = 58 G2 = 63 Race NR	Smoking: Ex- / current smoker (%): G1 = 22 G2 = 31	480 randomized & ITT; PP = 423	Symptoms: % of days with asthma control (no asthma symptoms and no rescue med use): G1: 30 to 75; difference = 45%; G2: 23 to 79; difference = 56%; Between-group difference = NSD (p=0.1475) G1 base 30% end 75% vs G2 base 23% end 79% HL point estimate: 4.25; P = 0.1475 Exacerbations: G1: 5 (2.1%) G2: 9 (3.8%) [5 (2.1) exacerbations requiriing oral steroids] AQLQ: Change from baseline (SE): G1: 0.40 (0.05) G2: 0.45 (0.05) NSD between groups (P >=0.3830) Least squares mean diff between groups = -0.05 (0.07) (95% CI: -0.19, 0.09; P = 0.5049 Adherence: 99%	Overall Adverse Events: G1: 106 (44%); G2: 103 (43%) SAEs: G1: 2 G2: 2 Oral Candidiasis: G1: 5 (2.1%) G2: 12 (5.0%) Upper Respiratory Tract Infection: G1: 16 (6.7%) G2: 12 (5.0%) Deaths: NR Other: Nasopharyngitis G1: 26 (10.8%) G2: 25 (10.4%) Sinusitis G1: 6 (2.5%) G2: 11 (4.6%)	G1: 4 (1.7%) G2: 8 (3.3%)	NycomedGmbh
de Blic 2009 12 European countries NA Fair	Children, aged 4–11 yrs, with a clinical history of asthma for at least 6 months	SFC 100/200 mcg (Low) FP 400 mcg (Med)	Currently receiving ICS (beclometh DP 400 mcg bid or equivalent) Run-in: FP 100 mcg bid x4wks	Age: 8.1 8.0 Race: NR Female: 45% 46%	Smoking: NR	321 *after exclusion of one study site N=303	Rescue Medication Use: Median % rescue-free days: G1: 95.1 G2: 94.0 p=0.025 % rescue-free days: 0-25% (G1: 0.03, G2: 0.05) 25-50% (G1: 0.03, G2: 0.05) 50-75% (G1: 0.07, G2: 0.13) 75-100% (G1: 0.59, G2: 0.58) 100% (G1: 0.29, G2: 0.19)	Overall Adverse Events: NR *reported only proportion of subjects with AE G1: 87 (58%) G2: 86 (56%) Respiratory Infection (Laryngotracheitis): G1: n=1 G2: n=0	G1: 0% G2: 1% (n=2)	GlaxoSmithKline

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de Blic 2009 cont'd							Symptoms: "Well controlled" (WC) at 12wks: G1= 65 (43%), G2= 61 (40%), p=0.535 "Totally controlled" (TC) at 12 wks: G1=28, 19%, G2= 23, 15% p=0.389 % Symptom free days (proportions): 0-25% (G1: 0.21, G2: 0.20) 25-50% (G1: 0.11, G2: 0.16) 50-75% (G1: 0.18, G2: 0.17) 75-100% (G1: 0.41, G2: 0.39) 100% (G1: 0.09, G2: 0.08) Mean night-time awakenings (baseline (sd), Wk12 (se)): G1: 0.6 (1.18), 0.3 (0.08) G2: 0.4 (0.58), 0.3 (0.08) Difference: 0 [-0.2, 0.3] p=0.721	Serious Adverse Events: 3 subjects (2%) in each group reported a serious adverse event, G1: laryngotracheitis, asthma exacerbation and concussion G2:wound infection, asthma exacerbation and gastritis		
de Blic 2009 cont'd							Exacerbations: G1: 2 (1%) G2: 2 (1% Oral Steroid Courses: G1: 2 (1%) G2: 1 (NR) Adherence: Subjects taking >75% of Rx'd meds: G1: 138 (92%) G2: 144 (94%) Other: Median time to first wk of WC: G1: 2 weeks G2: 2 weeks Time to 75% having at least one WC wk: G1=4wks, G2=6wks (p=NS)			

Evidence Table 1. Trials key questions 1 and 2

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Edin 2009 USA NA Fair	patients were at least 12y, medical history of moderate asthma (as defined by the American Thoracic Society), required asthma pharmacotherapy for the 6 months before screening	Study 1: GI:(FP/SM):176mcg/84ug (low) G2: (SM) 84mcg G3 (FP) 176mcg (low) Study 2: G1 (FP/SM): 440ug/84mcg (med) G2 (SM) 84mcg G3 (FP) 440mcg (med)	None	Study 1: Overall: Age 34 yrs., 80% White, 52% Female, G1 : age 32.8, female 57%, white 73% G2: age 34.4, female 46%, white 80% G3: age 34.7, female 52%, white 83% G4: age 33.2, female 53%, white 84% Study 2: Overall: Age 39 yrs; 83.8% White; 60.5% Female, G1 : age 38.8, female 61%, white 78% G2: age 37.5, female 62%, white 88% G3:age 39.1,female 63%, white 82% G4: age 41.1, female 56, white 87%	Smoking: NR	Study 1: n=360 Study 2: n=365 A total of 720 of 725 patients were included in analyses	AQLQ: Study 1 p-value from baseline to endpoint: G1 FP/SM, change 1.34, p ≤ 0.05 G2 SM, change 0.45, p ≤ 0.05 G3 FP, change 0.81, p ≤ 0.05 G4 PBO, change 0.20, p = NS Study 2: GI FP/SM, change 0.89, p ≤ 0.05 G2 SM, change 0.34, p ≤ 0.05 G3 FP, change 0.43, p ≤ 0.05 G4 PBO, change -0.22, p ≤ 0.05 Mean Differences among Treatment Groups in AQLQ domain scores: Study 1: G1 vs. G2: 0.89, p ≤ 0.05 G1 vs. G3: 0.53, p ≥ 0.5 G1 vs. G4: 1.14, p ≤ 0.05 Study 2: G1 vs. G2: 0.55, p ≤ 0.05 G1 vs. G3: 0.46, p ≤ 0.05 G1 vs. G4: 1.11, p ≤ 0.05			GlaxoSmithKline
Edin 2009 cont'd										

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Eid 2010 USA NCT00316321 Fair	6 to 15 years; with a documented mild to moderate asthma diagnosis for 6 months	G1: 160/9 ug - low G2: 160/18 ug - low G3: 160 ug - low	Albuterol as rescue med	Mean age: G1: 10.5 G2: 10.2 G3: 10.1 Race/Etnicity (White/Black/Other): G1: 76.1/15.2/8.7 G2: 71.4/17.3/11.3 G3: 75.7/13.6/10.7 % female: G1: 29.3 G2: 34.5 G3: 36.7	Smoking: NR	Randomized: 522	Rescue Medication Use: % Change from baseline Symptom free days/ awakening free nights G1: -0.9 (24.3) / -1.8 (9.0) G2: -0.2 (24.6) / -2.4 (8.9) G3: -3.7 (27.3) / -2.7 (9.0) Daytime /night time rescue medication use G1: 0.00 (0.33) / -0.01 (0.26) G2: 0.08 (0.43) / 0.02 (0.30) G3: 0.10 ((0.31) / 0.07 (0.29) Daytime G1 vs. G3 and G1 vs. G2 P < 0.05 Night time G1 vs G3 P < 0.01 Rescue medication free days G1: 1.6 (18.6) G2: -2.2 (16.7) G3: -5.4 (91.9) G1 vs G3 P < 0.05 Asthma control days G1: -3.5 (23.7) G2: -3.9 (23.8) G3: -8.0 (27.6)	Overall Adverse Events: NR Oral Candidiasis: overall 1.3% Sore Throat (Pharyngolaryngeal pain): G1: 10.9% G2: 8.3% G3: 4.7% Headache: G1: 11.4% G2: 7.7% G3: 10.1% Upper Respiratory Tract Infection: G1: 6.0% G2 7.7% G3: 9.5% Viral Upper Respiratory Tract Infection: G1: 7.6% G2: 5.4% G3: 4.1%	G1: 2 (1.2%) G2: 5 (3.0%) G3: 1 (0.6%)	AstraZeneca
Eid 2010 cont'd							Symptoms: % Change from baseline (SD) Daytime Symptom Score G1: 0.03 (0.21) G2: 0.03 (0.26) G3: 0.06 (0.28) Night time Symptom Score G1: 0.02 (0.18) G2: 0.03 (0.24) G3: 0.5 (0.26) Exacerbations: G1: 15 (8.2) G2: 33 (19.6) G3: 26 (15.5) PAQLQ change from baseline (SD): G1: -0.09 (0.90) G2: -0.08 (0.78) G3: -0.03 (0.64)	Bacterial Respitory Tract Infection: G1: 1.1% G2: 3.0% G3: 0.6% Deaths: None Other: Nasopharyngitis G1: 8.2 G2: 8.9 G3: 5.9 Sinusitis G1: 2.2 G2: 6.0 G3: 5.9		

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Gappa 2009 Germany VIAPAED Fair	Age 4-16; symptomatic persistent mild to moderate seasonal or perennial asthma	G1: SFC 100/200 mcg (low) G2: FP 400mcg (med)	None	Age: 9.6 9.4 Race: NR Female: 33% 31%	Smoking: NR	281 (Efficacy) 282 (Adverse Events)	Rescue Medication Use: % days without salbutamol: G1: 39.9 G2: 32.4 Diff [95% CI]= 8.0 [0.6, 15.3] Symptoms: **All 5-point scales (0-4) Change from baseline score, night: G1: -0.5 G2: -0.5 Diff [95% CI]= 0.01 [-0.11, 0.13] Change from baseline score, day: G1: -0.8 G2: -0.8 Diff [95% CI]= 0.02 [-0.14, 0.18] % days without symptoms: G1: 41.5 G2: 33.3 Diff [95% CI]= 8.7 [1.2, 16.3]	Overall Adverse Events: 160 adverse events overall noted in 87 patients, G1: 78 events in 43 patients vs G2 82 events in 44 patients p=NR Cough: G1: n=1, 0.7% G2: n=2, 1.4% Headache: G1: n=2, 1.5% G2: n=4, 2.8% Upper Respiratory Tract Infection (Laryngitis (mild)): G1: 0 (n=0) G2: <1 (n=1) Respiratory Infection: G1: n=4, 2.9% G2: n=3, 2.1%	G1: 0 G2: 0	GlaxoSmithKline
Gappa 2009 cont'd							Other: # weeks "controlled": 3.4 2.7 p=0.02 % Good control at wk 2: 43 32 p=NR	Rhinitis: G1: n=2, 1.5% G2: n=4, 2.8% Deaths: G1: 0 G2: 0		

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Hansel 2006 Europe (including UK, France, Germany, & Holland) NA Fair	Male and female patients aged 12 to 75 years with primarily mild to moderate asthma for >6 months, as defined by American Thoracic Society criteria	G1: CIC 80 mcg (low) G2: CIC 320 mcg (med) G3: BUD 400 mcg (low)	salbutamol or terbutaline as rescue medication	Mean Age: G1: 38 G2: 41 G3: 45 Race: NR Female: G1: 49% G2: 43% G3: 45%	Smokers: G1: 13% G2: 8% G3: 7%	554	Rescue Medication Use: Decrease from baseline at day 1 (mean puffs/d): G1: -0.34 G2: -0.61 G3: -0.66 all p<0.001 Decrease from baseline at wk 12 (mean puffs/d): G1: -0.68 G2: -1.00 G3: -1.04 all p<0.001	Overall Adverse Events: G1: 67 (36.8%); G2: 80 (40.8%); G3: 60 (33.9%) Headache: n= 6, 3.3% n=7, 3.6% n=0, 0% p=NR Upper Respiratory Tract Infection: n= 21, 11.5% n= 10, 5.1% n=14, 7.9% p=NR Respiratory Infection (Bronchitis): n=7, 3.8% n=12, 6.1% n=7, 4.0% p=NR Rhinitis: n=5, 2.7% n=7, 3.6% n=8, 4.5% p=NR	G1: 8, 4.4% G2: 4, 2.1% G3: 3, 1.7%	ALTANA Pharma AG

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Hansel 2006 cont'd							Symptoms: **All- 5-point Likert scales (0-4)** Daily Asthma Symptom Score (change): G1: -0.43 G2: -0.62 G3: -0.57 all p<0.001 Daytime Symptom Score (change): G1: -0.29 G2: -0.33 G3: -0.29 all p<0.001 Nighttime Symptom Score (change): G1: -0.14 G2: -0.17 G3: 0.0 all p<0.001 Comparisons between treatments for daily, daytime, and nighttime asthma symptom scores did not yield any significant differences throughout the study.	Deaths: NR Other: Cortisol decrease form baseline (nmol/mmol creatinine): G1: -0.54, not significant G2: +0.16 not significant G3: -1.42, p<0.05 p<0.05 (G1 vs G3) serious Aes (thought unrelated to study): G1: pulmonary embolus and chest pain, G2: surgery, abdominal pain, G3: eteritis and neoplasm		
Harnest 2008 Multinational NA Fair	>12 mo of moderate to severe asthma	G1: MF 800 mcg (high) G2: FP 1000 mcg (high)	"most patients (84%) did not receive concomitant LABA treatment"	Age: G1: 48 G2: 49 White: G1: 100% G2: 100% Female: G1: 58% G2: 50%	Smoking: NR	203 (202 after withdrawal)	Rescue Medication Use: Salbutamol use (puffs/d, change from baseline): -1.1 -1.5 p=0.890 (95% CI -0.46, 0.53) Symptoms: AM Asthma symptom scores (change from baseline to wk 12): -0.5 -0.6 p=0.251 (95%CI -0.06, 0.24) PM Asthma symptom scores (change from baseline to wk 12): -0.6 -0.7 p=0.618 (95%CI -0.13, 0.21) AM Asthma symptom scores (change from baseline to wk 6): -0.43 -0.60 p=0.028			Integrated Therapeutics Group, GROUP, INC, a wholly owned subsidiary of Schering-Plough.

Evidence Table 1. Trials key questions 1 and 2

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Harnest 2008 cont'd							AM Asthma symptom scores (change from baseline to wk 7): -0.45 -0.63 p=0.022 AM Asthma symptom scores (change from baseline to wk 9): -0.44 -0.65 p=0.014 PM Asthma symptom scores (change from baseline to wk 7): -0.49 =0.76 p=0.021 Symptom scoring: 4 point scale for day and nocturnal scores, day 0-no asthma symptoms 3-marked/disturbing symptoms that prevented some activities; night: 0-slept through the night 3-awake most or all of night by coughing and/or asthma			
Harnest 2008 cont'd							Exacerbations: MF: n=2, 2%, FP: n=4, 4%; P = NS Oral Steroid Courses: MF: n=2, 2%, FP: n=4, 4%; P = NS Adherence: G1: 98 (92%) G2: 86 (90%) Response rate (rated as "improved or much improved" by investigators): G1: 65% G2: 62%			

Evidence Table 1. Trials key questions 1 and 2

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Huchon 2009 Russia, France, Poland, Romania, Hungary, Belgium NA Good	men and non-pregnant women (18-70 years), moderate to severe persistent asthma according to GINA 2005	BDP/FM 400/24 mcg (med) BDP 1000 mcg + FM 24 mcg (high) BDP 1000 mcg (high)	NR	Mean: Age: G1: 47 G2: 47 G3: 47 Race: NR Female: G1: 65% G2: 65% G3: 63%	Smokers: G1: 5.7% G2: 5.9% G3: 3.8%	645	Rescue Medication Use: Did not compare group differences. Salbutamol use fell significantly from baseline to end of treatment in G1 (-0.29 puffs/day, 95%CI -0.44, -0.14) and G2 (-0.36 puffs/day, 95%CI -0.52, -0.19). No change in baseline in G3 Symptoms: Did not report scores; "values at the end of the study were signifcantly higher" in G1 than in G2 (p<0.05) or G3 (p<0.01) (not clear which values it is referring to)	Overall Adverse Events: NR Total Treatment-related AE: G1: 84 G2: 98 G3: 126 Deaths: NR Other: Did not statistically compare cortisol levels or changes between groups. Only commented on change from baseline: G1: significant increase in cortisol vs baseline (p<0.05) but remained within normal range (Change 101.65); G2 and G3 "no inhibition of adrenal function after 24 weeks" (respective changes -27.90, and 27.08)	From WebTable3 5 (2%) 6 (3%) 4 (2%)	Chiesl Farmacetuici SpA (Italy)
Huchon 2009 cont'd							Exacerbations: G1: 281 G2: 351 G3: 428 p=NR Severe: G1: 96 G2: 145 G3: 160 p=NR Other: G3 vs G1: G3 had more overall exacerbations per patient than G1 (2.0 vs 1.3, p=0.001), more mild-moderate exacerbations (1.2 vs 0.9, p=0.022), and more severe exacerbations (0.8 vs 0.5, p=0.030). G1 vs G2: No difference in the exacerbations per patient.			

Evidence Table 1. Trials key questions 1 and 2

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Kerwin 2008	Patients ≤12 years of age, medical history of asthma (as defined by the American Thoracic Society) requiring physician prescribed asthma therapy for at least 3 months duration, and were using short-acting beta2-agonists alone for at least 1 month prior to screening. At screening, required to have a forced expiratory volume in 1 s (FEV1) between 50% and 85% predicted value before administration of a bronchodilator and demonstrate a greater-or-equal, slanted12% increase in FEV1 within 30 min following two puffs (180 mcg) of inhaled albuterol.	G1: FP/SM 250/50 mcg G2: FP 250 mcg G3; FP/SM 100/50 mcg BID G4: PBO	NR	Overall: Mean age 32.9 Caucasian 77% African-American 12% Asian 2% Hispanic 8 Other 1% 58% female	NR	G1: N = 210 G2: N = 212 G3; N = 210 G4: N= 212 1946 assessed, 844 randomized	Rescue medication use: 24 hr use Adjusted mean change (SE) G1: -1.9 (0.18) G2: -1.5 (0.19) G3; -1.8 (0.17) G4: -0.4 (0.15) Treatment difference P value G1 vs. G2: -P = 0.041 G2 vs.. G4: P < 0.001 G1 vs.. G3: P = 0.061 Symptoms: Range 0-9 Adjusted mean change (SE) G1: -1.3 (0.10) G2: -1.1 (0.10) G3; -1.4 (0.10) G4: -0.7 (0.10) Treatment difference (SE) and 95% CI G1 vs. G2: -0.2 (0.13) (-0.5 to 0) G2 vs.. G4: -0.4 (0.13) (-0.7 to -0.2) G1 vs.. G3: 0.1 ((0.13) -0.2 to 0.3)	NR	NR	GlaxoSmithKline

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Knox 2007 United Kingdom, Belgium NA Fair	17-75 yo; asthma >6 mo with an FEV1 ≥ 90% of predicted and to have had maintained asthma control over the previous 3 months using FP 250 µg twice daily, or equivalent, with short-acting bronchodilator use as rescue medication only.	G1: CIC 160 mcg (low) (e-mouthpiece) G2: FP 500 (med) (ex-valve)	Salbutamol rescue	G1: Age 43 Asian 3.4% Black 0% White 94.8% Other 1.7% Female 48.3% G2: Age 46 Asian 3.8% Black 1.9% White 92.5% Other 1.9% Female 56.6%	Smokers: G1: 3.4% G2: 1.9%	111	Rescue Medication Use: Median use: G1: 0 at baseline, no change G2: 0 at baseline, no change Median % days free from rescue medication use: G1: 100 G2: 100 Symptoms: Median asthma symptom scores (day, night, and sum): G1: 0 at baseline, no change G2: 0 at baseline, no change Median % days with asthma control: G1: 97 G2: 98 (p=NS) Median % symptom-free days: G1: 98 G2: 98 Median % days free of nocutrnal awakenings: G1: 100 G2: 100	Overall Adverse Events: *Treatment-emergent AE (TEAE) G1: 42 G2: 49 Oral Candidiasis: Pt w/ frequent reported AE (n) G1: 0 G2: 1 Dysphonia: Pt w/ frequent reported AE (n) G1: 1 G2: 0 Sore Throat: Pt w/ frequent reported pharyngolaryngeal pain (%) G1: 3.4 G2: 3.8 Upper Respiratory Tract Infection: Pt w/ frequent reported AE G1: 3.4% G2: 9.4%	G1: 1 G2: 0 Withdrawal due to asthma exacerbation: G1: 1 G2: 0	ALTANA
Knox 2007 cont'd							Exacerbations: G1: 2 G2: 1 p=NS	Respiratory Infection : Pt w/ frequent reported AE Acute Bronchitis G1: 3.4% G2: 1.9% Lower RTI G1: 3.4% G2: 0% Nasopharyngitis: G1: 3.4% G2: 5.7% Rhinitis: Pt w/ frequent reported AE: G1: 0% G2: 3.8%		

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Knox 2007 cont'd								Deaths: NR Other: Three A.E.s - pleurisy viral, meningitis mumps and orchitis mumps - in 2 pts in G1 classified as SAE. Pt w/ frequent reported AE Sinusitis: G1: 1.7% G2: 3.8% Vomiting: G1: 0% G2: 3.8% Asthma: G1: 6.9% G2: 5.7%		
Koenig 2008 United Staes NA Fair	>15 yo; diagnosis of all severities of asthma	G1: FP/SM 200/100 mcg (low) G2: FP 200 mcg (low) G3: SM 100 mcg (NA) G4: ML 10 mg (NA)	Albuterol	G1: Age 40.4, Caucasian 88% Af. Am. 5% Hispanic 5% Asian 3% Other 0% Female 61% G2: Age 42.0 Cauc. 87% AfAm. 6% Hisp 3% Asian 3% Other 1% Female 57%	Smoking: NR	647	Rescue Medication Use: % Rescue-free days (change from baseline): G1: 5.7 [SE 3.1] (p<0.05 vs all) G2: -9.6 [SE 3.1](p<0.05 vs G4) G3: -15.5 [SE 3.2] G4: -20.7 [SE 3.1] Albuterol use (puffs/d, change form baseline): G1: -0.0 [SE 0.2] (p<0.05 vs all) G2: 0.9 [SE 0.2] (p<0.05 vs G4) G3: 1.6 [SE 0.2] G4: 1.7 [SE 0.2]	Overall Adverse Events: NR % subjects with adverse events: G1: 58 G2: 48 G3: 50 G4: 44 Oral Candidiasis: G1: 2% G2: <1% G3: 0% G4: 0% Headache: G1: 6% G2: 3% G3: 4% G4: 4%	NR	GlaxoSmithKline

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Koenig 2008 cont'd				G3: Age 41.7 Cauc. 83% AfAm 9% Hisp 3% Asian 5% Other 1% Female 61% G4: Age 40.1 Cauc. 87% AfAm. 7% Hisp 4% Asian 1% Other 1% Female 55%			Symptoms: Asthma symptom score (change from baseline, Likert 0 [no symptoms] to 5 [severe symptoms]): G1: -0.1 [SE 0.1](p<0.05 vs G3 and G4, p=NS vs G2) G2: 0.1 [SE 0.1] (p=NS vs G4) G3: 0.4 [SE 0.1] G4: 0.4 [SE 0.1] % Symptom-free days (change at endpoint): G1: 5.7 [SE 2.7] (p<0.05 vs G3 and G4) G2: -0.5 [SE 2.7] (p=NS vs G4) G3: -5.1 [SE 2.8] G4: -10.0 [SE 2.7] Nighttime awakenings (change at endpoint): G1: 0.00 [SE 0.03](p<0.05 vs G3 and G4, p=NS vs G2) G2: 0.09 [SE 0.03] (p=NS vs G4) G3: 0.19 [SE 0.03] G4: 0.19 [SE 0.03]	Upper Respiratory Tract Infection: G1: 5% G2: 8% G3: 6% G4: 5% Deaths: NR		
Koenig 2008 cont'd							Exacerbation: G1: 2% G2: 8% G3: 23% G4: 11% p=NR Adherence: % Remaining in study at wk 16: G1: 92 (p<0.001 vs all) G2: 74 G3: 54 G4: 53			
Kulus 2010 Subanalysis of to Lanier, 2009 Not abstracted Poor quality										
Kuna 2010 Companion to Kuna, 2007 No new data to abstract										

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Langdon 1994 UK Fair	Adult asthmatics (18-70 yrs) receiving either no ICS or up to 600mcg daily of BDP or BUD and considered by their physician to require ICS therapy at the study doses	G1: BUD 800mcg day (medium) G2: FP 400mcg day (medium) G1: RPD G2: Diskhaler	NR	G1 (BUD): Age = 41 % female = 43 Race NR G2 (FP): Age = 39 % female = 51 Race NR	Smoking NR	G1: N = 136 G2:N = 139	Data reported in graph only. P values for the difference between groups at 8 weeks. Nighttime (# puffs) 8 weeks - estimated from graph: G1 = 0.6; G2 = 0.3; P = 0.086 Daytime (# puffs) 8 weeks - estimated from graph: G1 = 1.25; G2 = 1.0; P = 0.41 Likert scale of asthma control (excellent; good; moderate; poor) % physicians rating "excellent" asthma control: G1 = 19%; G2 = 39%; P < 0.001 % patients rating "excellent" asthma control: G1 = 24%; G2 = 42%; P < 0.001 Hospitalizations: G1 = 1 (hospitalization for drainage of sebaceous cyst) G2 = 1 (hospitalization due to worsening phlebitis) "Compliance" (recorded use of study meds): G1 = 88%; G2 = 81% % symptom-free days and nights reported in graph only. (see p. 93)	Non-serious AEs: Total = 194 patients G1 = 84 (62%) G2 = 110 (79%) Oral Candidiasis: Suspected: G1 = 5 (4%) G2 = 14 (10%) Confirmed: G1 = 1 (0.7%) G2 =9 (6.5%) Cough G1 = 6 events G2 = 10 events Sore Throat: G1 = 17 events G2 = 19 events Headache: G1 = 33 events G2 = 37 events Upper Respiratory Infection G1 = 16 events G2 = 22 events Rhinitis G1 = 1 event G2 = 11 events Acute nasopharyngitis: G1 = 12 G2 = 18 "Asthma-related events" G1 = 9 G2 = 7	G1: 6 (4.4%) G2: 4 (2.9%)	NR

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Lanier 2009 Related to Kulus, 2010	Age 6 to 12 years with moderate-to-severe allergic (IgE-mediated) asthma; inadequately controlled asthma despite at least medium doses of ICS; dayt or night symptoms, an increase of 12% in FEV1 after 4 puffs (100 mg) or up to 5 mg nebulized albuterol, had exacerbations (2 within 1 year, 3 within 2 years, or 1 severe exacerbation requiring hospitalization within 1 year); weigh 20 to 150 kg, positive skin prick test result to at least 1 perennial allergen and/or a positive radioallergosorbent test, and a total serum IgE level of 30 to 1300 IU/mL.	2:1 to receive OM (75-375 mg sc, q2 or q4 wk) or PBO over a period of 52 weeks (24-week fixed-steroid phase followed by a 28-week adjustable-steroid phase).	Yes - steroids	Age: G1 = 8.7 G2 = 8.4 White: G1 = 59.1% G2 = 61.8% Black: G1 = 16.4% G2 = 14.5% Asian G1 = 0% G2 = 1.0% Other race: G1 = 24.5% G2 = 22.7% % female: G1 = 631.8% G2 = 33.3%		G1: 421 G2: 207	24 week rate of exacerbations G1: 0.45 G2: 0.64; P = 0 .007). RR (OM:PBO; 95% CI) 0.69 (0.53-0.90), which equates to a 31% reduction with OM 52 week rate of exacerbations G1: 0.78 G2: 1.36 P = < 0.001 43% reduction (RR [95% CI], 0.57 [0.45-0.73]	OM vs. PBO n (%) Nasopharyngitis G1: 117 (27.8) G2: 56 (27.1) Sinusitis G1: 70 (16.6) G2: 39 (18.8) URTI G1: 69 (16.4) G2: 46 (22.2) Pyrexia G1: 59 (14.0) G2: 20 (9.7) Headache G1: 58 (13.8) G2: 33 (15.9) Influenza G1: 51 (12.1) G2: 28 (13.5) Cough G1: 44 (10.5) G2: 25 (12.1) Bronchitis G1: 37 (8.8) G2: 29 (14.0) Viral URTI G1: 34 (8.1) G2: 26 (12.6) Vomiting G1: 34 (8.1) G2: 24 (11.6)	G1:2 (0.5%) G2: 1 (0.5%)	Novartis Pharma AG
Lemanske 2010 United States Best Add-on Therapy Giving Effective Responses (BADGER) Fair	Mild-to-moderate asthma, ability to perform reproducible spirometry	G1: 500mcg FP (High) G2: 200mcg/100mcg FP/SM (Low) G3: 200mcg FP + ML 5-10mg (Low)	None	A: 6-11 yr pts (N=126) B: 12-17 yr pts (N=56) Mean age (yrs, A/B): 9.1 / 14.7 Race/Ethnicity (% A/B): Hisptanic/Latino: 30/39 White: 43/36 Black: 29/21 Hispanic White: 22/27 Other: 6/16 Female (%, A/B): 34/36	Smoking: NR	Randomized: 182 (126 age 6-11yr, 56 age 12-17yr) 165 completed 2 periods, 157 completed all 3 periods G1: 61 G2: 61 G3: 60	Exacerbations: 4 total 1 during run-in period 3 during treatment period; 1 each in G1, G2 and G3 Oral Steroid Courses: G1: 47 G2: 30 G3: 43 Hospitalization: 1 required during each treatment period Adherence: 84% for study tablets 87% for study inhalers			Government: Grants from the National Heart, Lung and Blood Institute, National Institute of Allergy and Infectious Diseases, National Center for Research Resource

Evidence Table 1. Trials key questions 1 and 2

Author Year Country Trial name Quality rating	Population	Interventions: Medication, total daily dose Steroid dose range	Allowed other medications/ interventions	Age Race / ethnicity Sex	Other population characteristics	N	Efficacy and effectiveness outcomes	Adverse events reported	Withdrawals because of adverse events	Funding
Li 2010 Related to Malone et al, 2004 International SFA106484 Fair	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	Intervention: G1: FP/SM G2: FP Total daily dose: G1: 200mcg/100mcg G2: 200mcg Steroid dosing range: G1: low G2: low Delivery device: G1: Diskus G2: Diskus	Albuterol pMDI as rescue medication	Age (mean) G1: 7.7 G2: 7.6 Race/ethnicity Hispanic or Latino(%) G1:40 G2:41 Not Hispanic or Latino (%) G1: 60 G2: 59 White(%) G1: 67 G2: 64 Black(%) G1: 4 G2: 5 Other(%) G1: 29 G2: 31		G1: 173 G2: 177	N/A	N (%) Subjects with any AE Infections and infestations G1: 107 (62); G2: 110 (62) Nasopharyngitis G1: 16 (9); G2: 21 (12) Upper Respiratory Infection G1: 11 (6); G2: 13 (7) Pharyngitis G1: 4 (2); G2: 12 (7) Rhinitis G1: 8 (5); G2: 6 (3) Sinusitis G1:5 (3); G2: 4 (2) Headache G1: 26 (15); G2: 26 (15) Cough G1: 9 (5); G2: 7 (4) Pharyngolaryngeal pain G1: 6 (3); G2: 2 (1) Pyrexia G1: 8 (5); G2: 16 (9) Vomiting G1: 3 (2); G2: 5 (3)	NR	GlaxoSmithKline
Li 2010 Related to Malone et al, 2004 cont'd								N (%) Cardiovascular Events Subjects with Any Event G1: 107 (62); G2: 110 (62) ECG Change G1: 3 (2); G2: 2 (1) ECG abnormal G1: 1 (<1); G2: 1 (<1) ECG QTcB Interval Prolonged G1: 16 (9); G2: 8 (5) Intraventricular conduction defect G1: 7 (4); G2: 11(6) Cardiac arrhythmia G1: 1 (<1); G2: 0 Premature atrial contraction G1: 1 (<1); G2: 0 Sinus tachycardia G1: 1 (<1); G2: 0 Supraventricular ectopics G1: 0; G2: 1 (<1)		

Evidence Table 1. Trials key questions 1 and 2

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Lipworth, 2005	>18 yo; mild-to-moderate persistent asthma for ≥ 6 months with acceptable inhaler technique; who used β2-agonists on demand at least 2 times per week for 6 months before screening; FEV1 of 70% of predicted or greater at screening	G1: PBO G2: CIC 320 mcg (med) G3: CIC 640 mcg (high) G4: FP 880 mcg (high) All doses are ex-mouthpiece	None allowed	G1: Age (mean) 36.3, White 85.4, Black 12.2, Asian 0, Other 2.4, Female 61.0 G2: Age (mean) 36.9, White 87.5, Black 7.5, Asian 0, Other 5.0, Female 42.5 G3: Age (mean) 38.2, White 88.1, Black 9.5, Asian 2.4, Other 0, Female52.4 G4: Age (mean) 36.4, White 80.5, Black 9.8, Asian 2.4, Other 7.3, Female 51.2	NR	G1: 41 G2: 40 G3: 42 G4: 41	Patient compliance reported: Compliance (canister weight of 90% or greater) G1: 29/41 (70.7%) G2: 29/40 (72.5%) G3: 30/42 (71.4%) G4: 23/41 (56.1%)	Number having at least 1 treatment-emergent AE G1: 35 G2/G3: 53 G4: 32 oral candiadiasis (confirmed): G1: 0 G2/G3: 2 (2.4%) G4: 9 (22) hoarseness G1: 0 G2/G3: 2 (2.4%) G4: 3 (7.3%)	Overall: 3.7% G1: 7 G2/G3: 1.2 G4: 2.4	Sanofi-Aventis; ALTANA
Lu 2009 USA NA Fair	Adult patients 15 to 65 yrs old with a ≥1-year clinical history of asthma symptoms	G1: 10mg G2: 400mcg (low) G3: 10mg + 10mg G4: 10mg	NR	Mean age 34 yrs 4.9% Black 86.2% Caucasian 5.2% Hispanic 3.7% Other 52.0% Female	Smoking: NR	406	Rescue Medication Use: Daily Beta agonist use: LS Mean (95% CI) G1 vs. G2 -5.04 (-14.37 to 4.29) Symptoms: Daytime asthma symptom score (range 0 to 6): LS mean (95% CI) G1 vs. G2 -0.05 (-0.22 to 0.11)	Overall Adverse Events: Clinical AEs % (n) G1: 49.6% (128) G2: 50.8% (65) Deaths: NR	15 (3.7%)	Merck and Co
Magnussen 2007 Germany, Poland, Czech Republic, France, Italy, The Netherlands, Slovakia, Spain NA Fair	>12 yo; persistent asthma of all severities for at least 6 mo	G1: CIC 80 (low) G2: CIC 160 (low) G3: FP 176 (low)	Rescue medication allowed	G1: Age 29 Race NR Female 47% G2: Age 32 Race NR Female 50% G3: Age 33 Race NR Female 53%	Smokers: G1: 23% G2: 21% G3: 24%	Randomized: 808 ITT: 807 Per Protocol (PP): 697	Rescue Medication Use: Change from baseline (puffs/d): G1: -0.58 (p=0.364 vs G3; 95%CI -0.14, 0.14) G2: -0.57 (p=0.422 vs G3; 95%CI -0.14, 0.14) G3: -0.57 Baseline vs. Endpoint all groups, p < 0.0001			ALTANA

Evidence Table 1. Trials key questions 1 and 2

Author Year Country Trial name Quality rating	Population	Interventions: Medication, total daily dose Steroid dose range	Allowed other medications/ interventions	Age Race / ethnicity Sex	Other population characteristics	N	Efficacy and effectiveness outcomes	Adverse events reported	Withdrawals because of adverse events	Funding
Magnussen 2007 cont'd							Symptoms: 5-point scale: 0 (very well, no symptoms) to 4 (asthma very bad, unable to carry out daily activities as usual) Change from baseline (score sum): G1: -0.68 (p=0.649 vs G3; 95%CI -0.14, 0.18) G2: -0.64 (p=0.833 vs G3; 95%CI -0.10, 0.26) G3: -0.71 Baseline vs. Endpoint for all groups, p <0.0001 Daytime Symptom Score Change from baseline: G1: -0.43 (p=0.611 vs G3; 95%CI -0.12, 0.14) G2: -0.36 (p=0.87 vs G3; 95% CI -0.00, 0.14) G3: -0.43 Baseline vs. Endpoint for all groups, p <0.0001			
Magnussen 2007 cont'd							Nighttime symptom Score Change from baseline: G1: -0.25 (p=0.443 vs G3; 95%CI -0.07, 0.05) G2: -0.25 (p=0.559 vs G3; 95% CI -0.05, 0.10) G3: -0.25 Baseline vs. Endpoint for all groups, p <0.0001 Oral Steroid Courses: G1: 2 G2: 2 G3: 1			

Evidence Table 1. Trials key questions 1 and 2

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Maspero 2008 Multinational - Latin America and Turkey PEACE Fair	6 to 14 years of age; diagnosis of asthma >6 months (American Thoracic Society definition)	G1: 100 ug SM / 200 ug FP G2: 5 mg ML	NR	G1: Mean age 9.3 years Female 44% American hispanic 83% White 10% G2: Mean age 9.3 years Female 33% American hispanic 84% White 10%	Smoking: NR	Randomized: 548	Rescue Medication Use: Greater improvement in rescue-free 24 hour periods in G1 than G2 (p < 0.001) OR FP/SM:ML 3.24 95%CI 2.09-5.02 Symptoms: Greater improvement in % symptom-free 24 hour periods in G1 than G2 (p=0.025); FP/SM:ML OR 1.74 95%CI 1.07-2.82 G1: median % asthma-controlled weeks 83.3%; G2: median % ashtma controlled weeks 66.7% (difference 16.7%, p<.001) Daytime symptom scores range: 0 (no symptoms) to 5 (symptoms that caused discomfort and prevented normal daily activities) Nighttime symptom scores range: 0 (no symptoms) to 3 (symptoms that caused the caregiver or child to be awake most of the night)	Overall Adverse Events: G1: 155/281 (55%) G2: 153/267 (57%) Headache: G1: 66/281 (23%) G2: 72/267 (27%) Deaths: NR	G1: 2/281 (.7%) G2: 3/267 (1.1%)	GlaxoSmithKline
Maspero 2008 cont'd							Exacerbations: G1: mean rate over 12 weeks = 0.12 G2: mean rate over 12 weeks = 0.30 G1:G2 ratio = 0.40 95%CI 0.29-0.57 (p < 0.001) PAQLQ: G1: mean change from baseline = 0.9 G2: mean change from baseline = 0.8 Difference = 0.09, 95%CI -0.12, 0.30 p=ns PACQLQ: G1: mean change from baseline = 1.5 G2: mean change from baseline = 1.0 Difference = 0.54, 95% CI 0.06, 1.02 p = 0.028			

Evidence Table 1. Trials key questions 1 and 2

Author Year Country Trial name Quality rating	Population	Interventions: Medication, total daily dose Steroid dose range	Allowed other medications/ interventions	Age Race / ethnicity Sex	Other population characteristics	N	Efficacy and effectiveness outcomes	Adverse events reported	Withdrawals because of adverse events	Funding
Maspero 2008 cont'd							Hospitalization: G1: none G2: 3 (all due to asthma exacerbations) Adherence: % of patients that took > 80% of their prescribed medications: G1: 87% G2: 84% Other: percent nights with no awakenings OR FP/SM: ML 2.33 95% CI 0.73-7.47			
Massanari et al. 2009 US Fair (Pooled analysis of 5 RCT's, only adolescent patients (12-17 years old) analyzed)	Patients aged 12 to 75 years with a diagnosis of moderate to severe persistent, allergic asthma (for > 1 year),inadequately controlled despite at least medium-dose ICS therapy.	G1: OM 0.016 mg/kg per IgE IU/mL Q2-4 weeks G2: PBO	At least medium dose ICS therapy	G1: Mean age, 14.2 years; Female 38.2%; Race NR G2: Mean age, 14.2 years; Female 37.1%; Race NR	Smoking NR	G1: N = 76 G2: N = 70	Oral Steroid Courses G1: mean number of bursts of systemtic corticosteroids = 0.3 G2: mean number of bursts = 0.9 RR = 0.47 (0.22-0.99, p = 0.047) Symprom Score G1: symptom scores significantly improved (LSM, -0.72; 95% CI, -1.23 to -0.22) G2: NR Missed School/Work G1: mean number of school days missed = 0.7 G2: mean number of school days missed = 1.7 RR = 0.41 (95% CI, 0.17-0.96) Hospitalzations (# events) G1: 1 G2: 2 Vistis related to asthma G1: 0 unscheduled office visits for worsening asthma G2: 8 unscheduled office visits for worsening asthma G1: 2 patients had ER visits G2: No ER visits	AEs were similar between groups, most common: injection site reaction, viral infection, upper respiratory infection, sinusitis, headache, and pharygitis. AEs related to study drug occurred in about 4.0% of the adolescent patients (3.8% with OM, and 4.2% with PBO) Serious AEs occurred in 4 patients in the omalizumab group (infectious mononucleosis, forearm fracture, bipolar disorder, and asthma exacerbation). Serious AEs in the PBO group occurred in 1 patient (asthma exacerbation)	G1: 0 G2: 1	Novartis Genetech

Evidence Table 1. Trials key questions 1 and 2

Author Year Country Trial name Quality rating	Population	Interventions: Medication, total daily dose Steroid dose range	Allowed other medications/ interventions	Age Race / ethnicity Sex	Other population characteristics	N	Efficacy and effectiveness outcomes	Adverse events reported	Withdrawals because of adverse events	Funding
Murphy 2008 A substudy of patients ≥18 years from Corren et al, 2007 United States Fair	Age ≥18 years with a documented diagnosis of mild to moderate asthma of >6 months' duration, low to medium doses of ICSs, either alone or in combination with other asthma maintenance medications, consistently for >4 weeks	G1: Bud/FM G2: Bud G3: FM G4: PBO Total daily dose (mcg): G1: 320/18 G2: 320 G3: 18 G4: NA Steroid dosing range (Low, medium or high): G1: low G2: low G3: NA Delivery device: G1: pMDI G2: pMDI G3: DPI G4: NA	Albuterol pMDI as rescue medication	Age (mean) G1: 41.1 G2: 41.8 G3: 40.0 G4: 39.1 Race/Ethnicity (%) G1: White 86.7; Black 7.6; Other 5.7 G2: White 85; Black 10; Other 5.0 G3 White 88.2; Black 8.6; Other 3.2 G4: White 91.6; Black 5.6; Other 2.8 Sex % female G1: 62.9 G2: 67 G3: 68.8 G4: 65.4	Smoking NR	G1: 105 G2: 100 G3: 93 G4: 107	AQLQ overall (mean change from baseline) G1: 0.79 G2: 0.73 G3: 0.44 G4: 0.05 Adjusted mean differences between groups BUD/FM-BUD: 0.16 (-0.10, 0.41) P=0.234 BUD/FM-FM: 0.49 (0.22, 0.75) P<0.001 BUD/FM-PBO: 0.84 (0.58, 1.09) P<0.001 Asthma daily symptom score (mean change) G1: -0.45 G2: -0.43 G3: -0.28 G4: -0.08 Adjusted mean differences between groups BUD/FM-BUD: -0.02 (p=0.793) BUD/FM-FM: -0.17 (p=0.008) BUD/FM=PBO: -0.38 (p<0.001) % symptom Free Days (mean change) G1: 24.71 G2: 24.64 G3: 15.99 G4: 6.01 Adjusted mean differences between groups BUD/FM-BUD: 0.37 (p=0.930) BUD/FM-FM: 10.14 (p=0.020) BUD/FM-PBO: 19.52 (p<0.001)	NR	NR	AstraZeneca

Evidence Table 1. Trials key questions 1 and 2

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Murphy 2008 A substudy of patients ≥18 years from Corren et al, 2007 cont'd							Rescue medication use (mean change): G1: -1.91 G2: -1.52 G3: -1.55 G4: 0.15 Adjusted mean difference between groups: BUD/FM-BUD: -0.52 (p=0.044) BUD/FM-FM: -0.47 (p=0.079) BUD/FM=PBO: -1.94 (p<0.001) % Rescue medicine free days (mean change) G1: 40.86 G2: 30.64 G3: 32.04 G4: 6.75 Adjusted mean difference between groups: BUD/FM-BUD: 14.14 (p<0.001) BUD/FM-FM: 10.85 (p=0.012) BUD/FM=PBO: 34.43 (p<0.001) % Awakening-free nights (mean change) G1: 21.41 G2: 21.19 G3: 19.56 G4: 13.19 Adjusted mean difference between groups: BUD/FM-BUD: 1.27 (p=0.538) BUD/FM-FM: 2.96 (p-0.165) BUD/FM=PBO: 9.45 (p<0.001)			
O'Byrne 2008 Multinational FACET for original trial Fair	Reported in Pauwels, 1997	G1: (BUD 200ug/d+ PBO) Low dose G2: (BUD 800ug/d) Low to med G3: (BUD 200ug/d+ 24ugFM) Low dose G4: (BUD 800ug/d+24ugFM) Low to med	Terbutaline 250ug allowed as prn medication	G1: age 42, female (105/213=49.3%) G2: age 44, female (112/214=52.3%) G3: age 41, female (106/210=50.5%) G4: age 42, female (112/215=52.1%) Race not reported	Smoking: NR	Randomized: n=852 Completed study: n=694	Rescue Medication Use: The proportion of patients in each treatment group with as-needed rescue medication of four or more inhalations per wk at baseline was between 40 and 43% Oral Steroid Courses: G1: 0.72, 32% G2: 0.36, 22% G3: 0.48, 24% G4: 0.19, 14% Adherence: 81% completed the 12 month study			AstraZeneca

Evidence Table 1. Trials key questions 1 and 2

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O'Byrne 2008 cont'd							Other: Mean weeks spent in each of the asthma groups G1:well: 23.9, intermed 11.2, poor 8.6 G2: well 25.6, intermed 13.7, poor 6.5 G3: well 29.1, intermed 10.8, poor 5.0 G4: well 33.1, intermed 9.6, poor 3.3 For WELL controlled weeks: G2: Increased time of well controlled asthma from 56%to 57%, 2 % improvement (95% CI -9 to 12%, p = 0.76) G3: increased time of well controlled asthma from 56% to 66%, a 19% improvement (95% CI 3-35% p=0.017) G4:increased time of well controlled asthma from 57 to 74% of weeks, a 29% improvement (95%CI 13-47%, p<0.001)			
O'Byrne 2008 cont'd							Adding FM to therapy was significantly more effective than increasing the budesonid dose fourfold in increaseing the time with well-controlled asthma (increase, 16%; 95% CI 1-33%, p = 0.035) For POORLY controlled weeks: G2: decreased the number of weeks with poorly controlled asthma from 21 - 15%, a reduction of 29% (95% CI 7-44%, p = 0.01) G3: time poorly controlled decreased from 21 to 12% of weeks when FM added, reduction of 43% (95% CI 25-57%, p<0.001) G4: decreased time with poor control from 15 to 8% of weeks, rate reduction of 50% (95%CI 30-64% p<0.001)			

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Ohbayashi 2008 Japan NA Fair	Patients with mild to moderate persistent asthma (classified according to the Global Initiative on Asthma (GINA) guidelines) stably controlled with the FP Diskus®, with good compliance and adherence to treatment for more than 6 months	G1: FP diskus dose NR G2: BDP group dose "set to be equivalent to that of the FP previously used"	LABAs, LTRAs and or theophylline, used before the study were allowed as concurrent drugs during the study; doses kept constant throughout the study periods	G1: FP group age 61.0 years Race/Ethnicity NR 52% Female G2: BDP group age 67.9 years Race/Ethnicity NR 29% Female	Smoking: G1: 0% smokers, 28% ex-smokers G2: 4% smokers, 42% ex-smokers	Randomized: 50 patients	AQLQ: Overall score not reported. Stage 1: G2: HFA-BDP Group: Increase in symptoms score, p = 0.033 Increase in Activity Limitation score, p = 0.036 From second stage: In the HFA-BDP group, the scores in both symptom (p=0.015) and activity limitation domains (0.044) significantly increased after the switch (second cross-over) from FP to HFA-BDP. Adherence: 1 participant in the BDP group was dropped after randomization			NR
Ohta 2009 Japan NA Fair	Moderate-to-severe asthma according to the Japanese Guidelines on the Prevention and Management of Asthma	G1: at least 0.016 mg/kg per IU/mL of IgE	BDP at > 800 mg/day (or equivalent), and one or more contoller medications (LABA, theophylline, LTRA, OCS) and rescue medication	G1: Mean age 48.8 years Female 51% Ethnicity NR (Japanese) G2: Mean age 49.2 years Female 57.3% Ethnicity NR (Japanese)	Smoking: G1: Smokers and Ex-smokers: 57% G2: Smokers and ex-smokers: 48.2%	327 were randomized (G1 = 158, G2 = 169) 315 received allocated treatment and were analyzed	Rescue Medication Use: G1: Experienced a reduction in the mean medication use G2: Experienced a reduction in mean rescue medication use, Symptoms: G1: experienced a reduction in mean asthma symptom score, data shown in figure only (significance not reported) G2: experienced a reduction in mean asthma symptom score, data shown in figure only (significance not reported) Range of scale not reported.	Overall Adverse Events: G1: 136 (90.1%) G2: 142 (86.6%) Sore Throat (Pharyngolaryngeal pain): G1: 5.3%, n=8 G2: 6.7%, n=11 Headache: G1: 11.3%, n=17 G2: 13.4%, n=22 Upper Respiratory Tract Inflammation: G1: 8.6%, n=13 G2: 7.9%, n=13 Nasopharyngitis: G1: 48.3%, n=73 G2: 42.7%, n=70 Deaths: NR	G1: 6 (1.9%) G2: 7 (2.2%)	Novartis Pharma K.K., Tokyo, Japan

Evidence Table 1. Trials key questions 1 and 2

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Ohta 2009 cont'd							Exacerbations: G1: 6 patients (4.0%) G2: 18 patients (11.0%) OR G1:G2= 0.32 (p=0.0192) Oral Steroid Courses: G1: 6 patients (4.0%) G2: 18 patients (11.0%) Ability to participate in sports, physical activity: Both groups improved in daily activity score Adherence: G1: 13 (4.1%) discontinued treatment G2: 28 (8.9%) discontinued treatment			
Pearlman 2004 USA Protocol SAS30003 Fair	Age 12 and older, history of asthma, requiring asthma pharmacotherapy for at least 6 months prior, FEV1 between 40% and 85% of predicted, at least 15% increase in FEV1 within 30 minutes of 180mcg albuterol. Stratified into 2 groups based on asthma therapy at baseline: ICS for at least 3 months at specific doses or SABA as-needed or SM only	G1: FP/SM 176mcg/88mcg day (low) G2: FP 176mcg/day (low) G3: SM 84mcg/day G4: PBO Delivery devices:	NR	G1 (FP/SM): Age = 32.8 White = 73%, Black = 18%, Other = 9% Female = 62% G2 (FP): Age = 34.7 White = 83%, Black = 10%, Other = 7% Female = 58% G3 (SM): Age = 34.4 White = 80%, Black = 12%, Other = 8% Female = 50% G4 (PBO): Age = 33.2 White = 84%, Black = 8%, Other = 8% Female = 53%	Smoking NR	G1: N = 92 G2: N = 89 G3: N = 92 G4: N = 87	Change in puffs/day: G1 = -2.1 G2 = -0.4 G3 = -0.8 G4 = NR P<0.002, G1 vs. G2, G3 Change in rescue-free days (%; SE): G1 = 42.1; 4.7 G2 = 13.5; 4.0 G3 = 21.1; 4.0 G4 = 3.2; 4.0 p <0.006, G1 vs. G2, G3, and G4 AQLQ: Mean change from baseline: G1: 1.34 G2: 0.81 G3: 0.45 G4: 0.20 Adherence: range 97%-98% Change in symptom-free days (%; SE): G1 = 39.7; 4.4 G2 = 9.5; 4.0 G3 = 15.8; 3.8 G4 = 5.2; 3.5 p<0.001 for G1 vs. G2, G3, and G4 Change in nights with no awakenings (%; SE): G1 = 9.0; 1.6 G2 = 5.3; 1.7 G3 = 1.8; 1.7 G4 = -4.3; 2.7 p <0.006, G1 vs. G2, G3, and G4	Potentially drug-related AEs: G1 = 7% G2 = 6% G3 = 11% G4 = 6%	Withdrawn due to worsening asthma: G1 = 2 G2 = 8 G3 = 25 G4 = 28 G1 v G4 p<0.001 G1 v G3 p<0.001 G1 v G2 p=0.076 Total Withdrawals, n (%): G1 = 7 (8%) G2 = 14 (16%) G3 = 29 (32%) G4 = 31 (36%)	GlaxoSmithKline

Evidence Table 1. Trials key questions 1 and 2

Author Year Country Trial name Quality rating	Population	Interventions: Medication, total daily dose Steroid dose range	Allowed other medications/ interventions	Age Race / ethnicity Sex	Other population characteristics	N	Efficacy and effectiveness outcomes	Adverse events reported	Withdrawals because of adverse events	Funding
Pedersen 2006 Multinational (8 countries) NA Fair	Patients were between the ages of 6-15 years with persistent asthma of all severities (as defined by the American Thoracic Society) for at least 6 months	G1: CIC 160 mcg BID (equivalent to 100 mcgBID ex-valve) (low dose) G2: FP 176 mcg BID (equivalent to 100 mcgBID ex-valve) (low dose)	Beta-2 agonist as needed	G1: Median age, 10 years 33% Female G2: Median age, 10 years 37% Female Overall Ethnicity: 70% Caucasian of European descent 7% Caucasian of nonEuropean descent 4% Black 19% Other	0% Smokers	Randomized: 556	Rescue Medication Use: G1: median change from baseline = -1.14 (p< 0.0001) by PP analysis G2: median change from baseline = -1.07 (p<.0001) by PP analysis Symptoms: G1 and G2: median change in total asthma symptom score = -1.43 (p<0.0001) by PP analysis (confirmed by ITT) Median change from baseline in daytime asthma symptom score: G1: -0.64 (p<.0001) G2: -0.58 (p<.0001) Median change from baseline in nighttime asthma symptom score: G1: -0.50 (p<.0001) G2: -0.44 (p<.0001)	Headache: G1: 3.6%, n=10 G2: 2.5%, n=7 Upper Respiratory Tract Infection: G1: 6.9%, n=19 G2: 6.5%, n=18 Respiratory Infection (Bronchitis): G1: 1.8%, n=5 G2: 2.5%, n=7 Rhinitis: G1: 7.9%, n=22 G2: 8.2%, n=23 Deaths: NR	G1: 0 G2: <1%	ALTANA Pharma AG, Konstanz, Germany
Pedersen 2006 cont'd							Symptom scale: daytime and nighttime, each scored from 0 (no symptoms) to 4 (awake most of the night because of asthma or being unable to carry out daytime activities because of asthma) Exacerbations: G1: 1.8% (N = 5) G2: 1.4% (N=4)	Other: Pharyngitis G1: 4.3%, n=12 G2: 3.9%, n=11 Asthma G1: 3.6%, n=10 G2: 2.9%, n=8 Infection G1: 2.5%, n=7 G2: 2.5%, n=7 Sinusitis G1: 1.8%, n=5 G2: 3.2%, n=9		

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Pedersen 2009 Multinational - Brazil, Germany, Hungary, Poland, Portugal, South Africa NA Fair	Male and female out patients aged 6-11 years with a history of persistent bronchial asthma, as defined by the American Thoracic Society, for ≥ 6 months	G1: CIC 80 mcg daily (ex-actuator; equivalent to 100 and 200 mcgex-valve) (low dose) G2: CIC 160 mcg daily (ex-actuator; equivalent to 100 and 200 mcgex-valve) (low dose) G3: FP 88 mcg twice daily (ex-actuator; equivalent to 100 twice daily ex-valve) (low dose)	Salbutamol 100ug/puff served as rescue medication Patients allowed to continue nasal corticosteroids at a constant dose.	G1: Median age, 9 years 34.9% Female Ethnicity NR G2: Median age, 9 years 34.7% Female Ethnicity NR G3: Median age, 9 years 34.4% Female Ethnicity NR	Smoking: NR	Randomized: 744	Rescue Medication Use: G1: Median Change from baseline -1.2 (p < .0001) G2: Median Change from baseline -1.13 (p < .0001) G3: Median Change from baseline -1.29 (p < .0001)	Overall Adverse Events: G1: 46.4% G2: 41.7% G3: 47.6% Oral Candidiasis: G1: 0% G2: 0.43% G3: 0.41% Deaths: NR	Withdrawals because of exacerbations: G1: 13 (5.2%) G2: 5 (2.1%) G3: 2 (0.8%)	Nycomed GmbH
Pedersen 2009 cont'd							Symptoms: Range of symptom scale: 9 points (daytime 0-4, nighttime 0-4) G1: Experienced a significant reduction in the median asthma symptom score sum over the course of treatment of -0.86 (p < .0001) G2: Experienced a significant reduction in the median asthma symptom score sum over the course of treatment of -0.86 (p < .0001) G3: Experienced a significant reduction in the median asthma symptom score sum over the course of treatment of -0.93 (p < .0001)			
Pedersen 2009 cont'd							Exacerbations: G1: 7.1% (n=18) G2: 2.9% (n=7) G3: 2.0% (n=5) PAQLQ: Improved from baseline for overall scores in all treatment groups (p<.0001 for all) - data not shown Between-treatment analyses confirmed non-inferiority of G1 and G2 to G3 (p<.0001, one-sided, for all)			

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Author Year Country Trial name Quality rating	Population	Interventions: Medication, total daily dose Steroid dose range	Allowed other medications/ interventions	Age Race / ethnicity Sex	Other population characteristics	N	Efficacy and effectiveness outcomes	Adverse events reported	Withdrawals because of adverse events	Funding
Pedersen 2009 cont'd							PACQLQ: Improved from baseline for overall scores in all treatment groups (p<.0001 for all) - data not shown Between-treatment analyses confirmed non-inferiority of G1 and G2 to G3 (p<.0001, one-sided, for all)			
Peters 2008 USA NA Fair	> 12 years with a documented clinical diagnosis of moderate to severe asthma, as defined by the American Thoracic Society	G1: BUD/FM 640/18 mcgBID (160/4.5 x 4 inhalations) (high daily dose) G2: BUD/FM 320/9 mcgBID (160/4.5 x 2 inhalations) (medium daily dose) G3: BUD 640 mcg(160 x 4 inhalations) (high daily dose)	Albuterol pMDI 90 mcg/inhalation as rescue medication After randomization, LTRA's, inhaled nonsteroidal anti-inflammatory agents, and methylxanthines were allowed as add-on therapy for adjunctive treatment of an asthma exacerbation or for additional asthma controller therapy to prevent withdrawal from the study. Nasal ICSs and nasal cromolyn sodium were permitted as well as non asthma meds	G1: mean age 41.0 years 63% Female 86.5% White 8.1% Black 1.6% Asian 3.8% Other G2: mean age 38.6 years 59.1% Female 88.6% White 7.6% Black 1.5% Asian 2.3% Other G3: mean age 39.8 years 68.4% Female 87.2% White 10.5% Black 0% Asian 2.3% Other	Smoking: NR (current smokers excluded, although those with <20pack year history allowed)	Randomized: 708 patients G1: 443 G2: 132 G3: 133	Rescue medication-free days % (mean change from baseline): G1: 22.78 , SD 30.86 G2: 22.16, SD 32.08 G3: 7.56, SD 26.47 Differences between groups: G1 - G2: 2.35 (95% CI: -2.42, 7.11) G1 - G3: 18.40 (95% CI: 13.63, 23.17) (p<.001) G2 - G3: 16.06 (95% CI: 10.14, 21.97) (p<.001) Rescue medication use, inhalations/day (mean change from baseline): G1: -0.80, SD 1.42 G2: -0.74, SD 1.79 G3: -0.15 SD 1.33 Differences between groups: G1-G2: -0.16 (95% CI: -0.37, 0.06) G1-G3: -0.87 (95% CI: -1.08, -0.66) (p<.001) G2-G3: -0.72 (95% CI: -0.98, -0.45) (p<.001)	Overall Adverse Events: Number of patients with any AE: G1: 394 (88.9%) G2: 111 (84.1%) G3: 118 (88.7%) Oral Candidiasis: G1: n=53, 12.0% G2: n=13, 9.8% G3: n=12, 9.0% Cough: G1: n=34, 7.7% G2: n=7, 5.3% G3: n=9, 6.8% Sore Throat (Pharyngolaryngeal pain): G1: n= 57, 12.9% G2: n=11, 8.3% G3: n=17, 12.8% Headache: G1:n=28, 6.3% G2: n= 11, 8.3% G3: n= 10, 7.5%	G1: 35 (7.9%) G2: 8 (6.1%) G3: 7 (5.3%)	AstraZeneca, Wilmington, Delaware

Evidence Table 1. Trials key questions 1 and 2

Author Year Country Trial name Quality rating	Population	Interventions: Medication, total daily dose Steroid dose range	Allowed other medications/ interventions	Age Race / ethnicity Sex	Other population characteristics	N	Efficacy and effectiveness outcomes	Adverse events reported	Withdrawals because of adverse events	Funding
Peters 2008 cont'd							Symptom-free days, % (mean change from baseline): G1: 19.00, SD 30.08 (significance not shown) G2: 23.46, SD 33.47 (significance not shown) G3: 5.93, SD 24.07 (significance not shown) Differences between groups: G1-G2: -2.32 (95% CI: -7.35, 2.72) G1-G3: 14.15 (95% CI: 9.15, 19.15) (p<.001) G2-G3: 16.46 (95% CI: 10.24, 22.69) (p<.001) Exacerbations: % of patients with at least one exacerbation: G1: 12.2% G2: 14.4% G3: 21.8% Differences between groups: G1-G2: no significant difference G2-G3: p=0.117 G1-G3: p=0.006	Upper Respiratory Tract Infection: G1: n=80, 18.1% G2: n= 29, 22.0% G3: n= 21, 15.8% Respiratory Infection: Bronchitis G1: n= 24, 5.4% G2: n=9, 6.8% G3: n=13, 9.8% Viral URI G1: n=33, 7.4% G2: n=9, 6.8% G3: n=14, 10.5% Rhinitis (Nasal congestion): G1:n= 20, 4.5% G2: n=7, 5.3% G3: n=5, 3.8% Deaths: 0		
Peters 2008 cont'd							Number of asthma exacerbations per patient-treatment year: G1: 0.174 G2: 0.185 G3: 0.315 Differences between groups: G1-G2: no significant differences G1-G3: p=0.004 G2-G3: p=0.049 G1 showed a statistically significant increase in the time to first exacerbation compared with G3 (p=0.005) No significant differences between G2 and G3 (p=0.105), or between G1 and G2 (p=0.537). Hospitalizations: % of patients with at least one hospitalization due to asthma: G1: 0.5% (n=2) G2: 1.5% (n=2) G3: 0% (n=0)	Other: Sinusitis G1: n=53, 12.0% G2: n= 14, 10.6% G3: n=20, 15.0% Naspharyngitis G1: n=95, 21.4% G2: n=28, 21.2% G3: n=32, 24.1%		

Evidence Table 1. Trials key questions 1 and 2

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Peters 2008 cont'd							Urgent Care: Patients with at least one visit to ED or urgent care, N: G1: 11 / 443 G2: 4 / 132 G3: 1 / 133			
Renzi 2010 Canada NA Fair	Male and females; ≥ 12 y; documented history of mild asthma treated with SAVA onlyu with FEV1≥ 80% predicted	G1: FP/SM, 200/100 mcg Low G2: FP, 100mcg Low	Rescue salbutamol suphate HFA aerosol	G1: Mean Age 34.8 Caucasian 89% Black 2% Asian 9% Other <1% Female 64% G2: Mean Age 34.3 Caucasian 90% Black 2% Asian 7% Other 2% Female 64%	Smokers: Current: G1: 9% G2: 15% Former: G1: 32% G2: 21%	526	Rescue Medication Use: Mean Change Daily Rescue Use G1: -1.2 SD 0.04 G2: -1.0 SD 0.04 G1 vs. G2, p = 0.028 G1 higher mean percentage of rescue-free days than G2: 8.4 (95%CI 3.1, 13.5), p = 0.001 Symptoms: G1 higher mean percentage of symptom-free days than G2: 7.7 (95%CI 1.9, 13.5), p = 0.009 Exacerbations: G1: 3 (6%) G2: 3 (6%) Mortality: G1: 0 G2: 1 death due to cardiac arrest	In text: "no single drug-related event occurred in more than 2% of patients in either group" Serious Adverse Events: G1: 3 (1%) G2: 4(1%)	In Figure: G1: 6 (2%) G2: 11 (4%) In Text reports: G1: 5 (2%) G2: 9 (3%)	GlaxoSmithKline, Inc
Renzi 2010 cont'd							Urgent Care: G1: 3 G2: 3 Other: Any Unscheduled contact G1: 17 G2: 24 Phone Call G1: 3 G2: 7 Office/practice visit G1: 14 G2: 19 Outpatient Clinic G1: 1 G2: 6 Adherence: Average compliance to study drug according to patient daily diary card was approximately 90% for both treatment groups.			

Evidence Table 1. Trials key questions 1 and 2

Author Year Country Trial name Quality rating	Population	Interventions: Medication, total daily dose Steroid dose range	Allowed other medications/ interventions	Age Race / ethnicity Sex	Other population characteristics	N	Efficacy and effectiveness outcomes	Adverse events reported	Withdrawals because of adverse events	Funding
Sears 2008 Canada NA Fair	Age > 12 years; asthma diagnosis for > 3 months (using the American Thoracic Society definition	G1: BUD/FM 160/4.5 mcgBID plus additional doses as needed (up to 12 inhalations daily) G2: conventional best practice	G1: BUD/FM as rescue medication G2: Any therapy including either ICS/LABA combination product but not use of BUD/FM as both maintenance and reliever therapy	G1: mean age 42.1 57.8% Female 94.3% Caucasian 2.3% Black 2.2% Oriental G2: mean age 43.1 62.5% Female 94.8% Caucasian 3.3% Black 1.7% Oriental	Smoking: G1: mean history pack-years 4.8 G2: mean history pack-years 4.8	Randomized: 1,538 patients	Rescue Medication Use: As-needed inhalations during treatment period, mean inhalations per day: G1: 0.94 G2: 1.09 Mean treatmnet difference: -0.158 (95% CI: -0.265, -0.052, p = 0.0036) As-needed free days during treatment period, %: G1: 60.1% G2: 61.1% Mean treatmnet difference: 0.024 (95% CI: -3.162, -3.210, p=0.9881)	Overall Adverse Events: G1: 474 patients (61.4%) G2: 491 patients (64.1%) Deaths: G1: (1/772) 13% G2: (2/766) 26%	G1: 27 (3.5%) G2: 7 (0.9%)	Affiliated/Supported by with AstraZeneca, Wilmington, Delaware
Sears 2008 cont'd							Patients with >2 inhalations/day on >1 day: G1: 294 G2: 369 OR: 0.679 (95% CI 0.553-0.833, p = 0.0002) Patients with >8 inhalations/day on >1 day: G1: 15 G2: 30 OR: 0.495 (95% CI: 0.264-0.928, p=0.0283) Symptoms: ACQ-5, mean decrease from baseline: G1: -0.19 G2: -0.15 Representing an improvement in asthma control in both groups. No significant difference between groups (p=0.46) Scale: seven point, from 0 (good control) to 6 (poor control)			

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Sears 2008 cont'd							Exacerbations: Severe asthma exacerbations, events per patient per year: G1: 0.19 (0.15-0.24) G2: 0.21 (0.17-0.26 Treatment comparison: 0.92 (0.67-1.28, p=0.63) Oral Steroid Courses: Oral glucocorticosteorid, events per patinet per year: G1: 0.18 (0.14-0.23) G2: 0.17 (0.14-0.22) Treatment comparison: 1.03 (0.73-1.45, p=0.86)			
Sears 2008 cont'd							Mortality: G1: 1 death (due to injury) G2: 2 deaths (due to MI and myopericarditis) Hospitalizations: G1: 0 G2: 1 Urgent Care: ER treatment, at least one event: G1: 16 (2.1%) G2: 23 (3.0%) ER treatment, total events G1: 16 G2: 28 Other: Hospitalization and/or ER treatment, events per patient per year: G1: 0.04 (0.03-0.07) G2: 0.08 (0.05-0.11) Treatment comparison: 0.59 (0.32-1.09, p=0.09)			

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Ukena 2007 cont'd							Daytime symptom score, change from baseline: G1: -0.39 (p < .0001) G2: -0.33 (p < .0001) G1 vs G2: PE 0.00 (-0.14, 0.17) p = 0.586 Nighttime symptom score, change from baseline: G1: -0.21 (p < .0001) G2: -0.20 (p < .0001) G1 vs. G2: PE 0.00 (-0.13, 0.10) p = 0.797 Scale: 5 points Daytime: 0 (very well, no symptoms) to 4 (asthma very bad, unable to carry out daily activities as usual) Nighttime: 0 (no symptoms, slept through the night) to 4 (bad night, awake most of the night because of asthma)			
Ukena 2007 Germany, Netherlands, Switzerland NA Fair	Patients (aged 12–75 years), with at least 6 months' history of asthma of all severities as defined by American Thoracic Society criteria	G1: CIC 320 mcg medium dose G2: BUD 400 mcg Low dose	Short-acting beta-agonists as rescue medication	G1: Median age, 44 57% Female Ethnicity NR G2: Median age, 46 51% Female Ethnicity NR	Smoking: G1: patients w/ history of smoking, 36% G2: patients w/ history of smoking, 33%	Randomized: 399	Rescue Medication Use: Puffs per day, change from baseline G1: -0.42 (p < .0001) G2: -0.57 (P < .0001) G1 vs G2: PE 0.00 (-0.14, 0.29) p = 0.687 Exacerbations: G1: N = 2 G2: N = 1 Symptoms: Asthma symptom score sum, change from baseline: G1: -0.62 (p < .0001) G2: -0.74 (p < .0001) G1 vs G2: PE 0.00 (-0.21, 0.29) p = 0.863	Overall Adverse Events: G1: 73 events (28% of patients) G2: 71 events (27% of patients) Oral Candidiasis: GI: n=1 G2: n=0 Dysphonia: G1: n=1 G2: n=0 Cough: G1: n=1 G2: n=0 Headache: G1: n=1 G2: n=0 Deaths: NR	G1: 5 (2 due to asthma exacerbation and 3 due to other adverse events) G2: 3 (1 due to asthma exacerbation and 2 due to other adverse events)	ALTANA Pharma AG, Konstanz, Germany

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Vermeulen 2007 Multinational - Hungary, Poland, Serbia/Montenegro, South Africa, Spain NA Fair	Patients aged 12–17 years with a history of severe asthma, according to the Global Initiative for Asthma (GINA) 2003 classification	G1: CIC 320 mcg(two puffs of 160 mcg ex-actuator corresponding to two puffs of 200 mcg ex-valve) Medium dose G2: BUD 800 mcg (ex-valve equivalent to 640mcg ex-mouthpiece) (four inhalations of 200 mcg from the turbuhaler device) Medium dose	Salbutamol 100ug/puff served as rescue medication	G1: median age, 14.0 29.4% Female Ethnicity NR G2: median age, 14.0 38.9% Female Ethnicity NR	Smokers: G1: 0% G2: 0%	Randomized: 403	Rescue Medication Use: Puffs per day, change from baseline G1: -0.07 (p<.0001) G2: -0.07 (p = 0.0003) Symptoms: Symptom sum score, change from baseline G1: -0.07 (p = 0.0005) G2: -0.14 (p = 0.0001) No statistically significant difference (p not shown). 5-point scales (nighttime: 0 = no asthma symptoms, slept through the night to 4 = bad night, awake most of the night because of asthma; daytime: 0 = very well, no asthma symptoms to 4 = asthma very bad, unable to carry out daily activities as usual) Exacerbations: G1: n=7, 2.6% G2: n=2, 1.5% PAQLQ (change from baseline): G1: 0.19 + 0.05 (p=0.0001) G2: 0.18 + 0.06 (p=0.0056)	Overall Adverse Events: G1: 26.5% of patients experienced an event (72 patients) G2: 18.3% of patients experienced an event (24 patients) Oral Candidiasis: G1: 0% G2: 0% Upper Respiratory Tract Infection: G1: 2.2% G2: 2.3% Deaths: G1: 0% G2: 0% Other: Nasopharyngitis G1: 2.6% G2: 0.8% Pharyngitis G1: 5.9% G2: 3.8%	NR	ALTANA Pharma AG, Konstanz, Germany

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von Berg 2007 Multinational8 countries - Australia, Germany, Hungary, Poland, Portugal, Serbia and Montenegro, South Africa and Spain NA Fair	Patients aged 6–11 yr with a documented diagnosis of persistent moderate to severe asthma for at least 6 months	G1: CIC 160 mcg (ex-actuator; equivalent to 200 mcgex-valve) Low dose G2: BUD 400 mcg (ex-valve) Low dose	Salbutamol for rescue medication	G1: Median age 9 37% Female Ethnicity NR G2: Median age 9 35% Female Ethnicity NR	Smoking: NR	Randomized: 621	Rescue Medication Use: Puffs per day, mean change from baseline: G1: -1.58 (p<.0001) G2: -1.64 (p<.0001) Difference between groups not significant (95% CI: -0.26, -0.29, p = 0.8593) Exacerbations: G1: 2.6% G2: 1%	Overall Adverse Events: 38% of patients (n=158 in G1, n=78 in G2) experienced an AE Growth: Mean body height increase, in centimeters: G1: 1.18 (p<.0001) G2: 0.70 (p<.0001) Increase in body height significantly greater in G1 than G2 (difference b/t groups = 0.481 cm, p = .0025, two-sided) Oral Candidiasis and Dysphonia, combined: G1: 0.2% G2: 1.5%	G1: 12 (2.9%) G2: 2 (1%)	ALTANA Pharma AG, Konstanz, Germany
von Berg 2007 cont'd							Symptoms: Asthma symptom score sum, change from baseline: G1: -1.18 (p<.0001) G2: -1.19 (p<.0001) % Days without asthma symptoms and without need for rescue medication: G1: 73% G2: 70% Percentage of nocturnal awakening-free days: G1: 98.5% G2: 98.5% Scale: daytime and nighttime symptom scores, each on a 5-point scale (0=no asthma-related symptoms, 4=the highest discomfort from asthma-related symptoms (i.e. unable to carry out daytime activities b/c of asthma or awake most of the night b/c of asthma))	Upper Respiratory Tract Infection: G1: 3.6% G2: 6.3% Deaths: NR Other: Pharyngitis G1: 6.0% G2: 6.8% Nasopharyngitis G1: 4.1% G2: 5.4%		

Evidence Table 1. Trials key questions 1 and 2

Author Year Country Trial name Quality rating	Population	Interventions: Medication, total daily dose Steroid dose range	Allowed other medications/ interventions	Age Race / ethnicity Sex	Other population characteristics	N	Efficacy and effectiveness outcomes	Adverse events reported	Withdrawals because of adverse events	Funding
von Berg 2007 cont'd							PAQLQ(S) (change from baseline): G1: 0.69 (p<.0001) G2: 0.70 (p<.0001) Non inferiority of CIC vs BUD was demonstrated in the PAQLQ(S) (95% CI: -0.12, 0.10, p=0.5738 one sided superiority) PACQLQ (change from baseline): G1: 0.88 (p<.0001) G2: 0.96 (p<.0001) non-inferiority of CIC vs BUD was demonstrated in the PAQLQ (95% CI: -0.27, 0.13, p=0.7657, one sided superiority) Adherence: G1: 94% compliance with treatment G2: 94% compliance with treatment			

Evidence Table 2. Internal validity: Trials key question 1

Author	Year	Trial Name	Efficacy and Effectiveness Outcomes Quality Rating Good, Fair, Poor	Randomization adequate? Yes, No, CND	Allocation concealment adequate? Yes, No, CND	Groups similar at baseline? Yes, No, CND	Outcome assessors masked? Yes, No, CND	Care provider masked? Yes, No, CND	Patient masked? Yes, No, CND
Aalbers	2010	NA	Fair	Yes	Yes	Yes	NR	Yes	Yes
Adachi	2007	NA	Poor	CND	No	Yes	No	No	No
Bailey	2008	NA	Fair	CND	CND	Yes	CND	CND	Yes
Bateman	2008	NA	Fair	Yes	No	No	No	No	CND
Berger	2010	NA	Fair	Yes	No	Yes	No	No	No
Boonsawat	2008	NA	Fair	CND	CND	Yes	Yes	Yes	Yes
Boulet	2007	NA	Fair	Yes	CND	Yes	No	No	No
Boulet	2006	NA	Fair	Yes	CND	Yes	CND	Yes	Yes
Buhl	2006	NA	Fair	CND	CND	Yes	CND	Yes	Yes
Chervinsky	2008	NA	Fair	CND	CND	Yes	CND	Yes	Yes
Chucalin	2008	NA	Fair	CND	CND	Yes	CND	Yes	Yes
Connolly	1995	NA	Fair	CND	No	Yes	No	No	No
Covar	2008	NA (PACT for original trial)	Fair	CND	CND	CND	CND	CND	CND
Dahl	2010	NR	Fair	Yes	CND	Yes	CND	Yes	Yes
de Blic	2009	NA	Fair	CND	CND	CND	CND	Yes	Yes
Edin	2009	NA	Fair	CND	CND	Yes	CND	Yes	Yes
Eid	2010	NCT00316321	Fair	Yes	CND	Yes	CND	CND	Yes
Gappa	2009	VIAPAED	Fair	Yes	CND	Yes	CND	Yes	Yes
Hansel	2006	NA	Fair	Yes	No	Yes	CND	CND	No
Harnest	2008	NA	Fair	Yes	CND	Yes	No	No	No
Huchon	2009	NA	Good	Yes	CND	Yes	CND	Yes	Yes
Kerwin	2008	NA	Fair	CND	CND	Yes	CND	CND	Yes
Knox 2007			Fair	CND	CND	Yes	CND	Yes	Yes
Koenig	2008		Fair	CND	CND	Yes	CND	CND	Yes
Kulus	2010	NA	Poor						
Langdon	1994	NA	Fair	CND	No	Yes	No	No	No
Lanier	2009		Fair	CND	CND	Yes	CND	CND	CND
Lemanske	2010	Best Add-on Therapy Giving Effective Responses (BADGER)	Fair	Yes	CND	Yes	CND	Yes	Yes
Lu	2009	NR	Fair	Yes	CND	Yes	CND	Yes	Yes
Magnussen	2007		Fair	CND	CND	Yes	CND	Yes	Yes
Maspero	2008	PEACE	Fair	Yes	Yes	Yes	CND	Yes	Yes
Massanari	2009	N/A	Fair	CND	CND	Yes	CND	CND	CND
Murphy	2008	NA	Fair	Yes	CND	Yes	CND	Yes	Yes
O'Byrne	2008	NA (FACET for original trial)	Fair	CND	CND	Yes	CND	Yes	Yes
Ohbayashi	2008	NA	Fair	CND	No	Yes	No	No	No

Evidence Table 2. Internal validity: Trials key question 1

Author	Run-in/Washout? Yes, No, CND	Overall attrition high (≥20%)? Yes, No, CND	Loss to follow-up differential high (≥15%)? Yes, No, CND	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, CND, Modified ITT	Post-randomization exclusions? Yes, No, CND
Aalbers	Yes	No	No	Yes	No	Yes
Adachi	Yes	CND	CND	Yes	Yes	No
Bailey	Yes	No	No	Yes	Yes	Yes
Bateman	Yes	No	No	Yes	Modified ITT	Yes
Berger	Yes	No	No	Mixed	Modified ITT	Yes
Boonsawat	Yes	No	No	Yes	Modified ITT	Yes
Boulet	Yes	No	No	Yes	Modified ITT	Yes
Boulet	Yes	CND	CND	Yes	Modified ITT	Yes
Buhl	Yes	No	No	Mixed	Yes	Yes
Chervinsky	Yes	No	No	Mixed	CND	Yes
Chucalin	Yes	No	No	Yes	Yes	Yes
Connolly	Yes	No	No	Mixed	Modified ITT	Yes
Covar	Yes	CND	CND	Yes	CND	CND
Dahl	Yes	No	no	Yes	Yes	No
de Blic	Yes	No	No	Yes	No	Yes
Edin	CND	No	CND	Yes	CND	CND
Eid	Yes	No	no	Yes	Yes	Yes
Gappa	Yes	No	No	Mixed	Modified ITT	Yes
Hansel	Yes	No	No	Yes	Modified ITT	Yes
Harnest	Yes	No	No	Mixed	Modified ITT	Yes
Huchon	Yes	No	No	Yes	Modified ITT	Yes
Kerwin	Yes	No	no	Mixed	Yes	No
Knox	Yes	No	No	Yes	Modified ITT	No
Koenig	Yes	No	No	Yes	Yes	No
Kulus						
Langdon	Yes	No	No	Mixed	No	Yes
Lanier	Yes	No	No	Yes	No	Yes
Lemanske	Yes	No	No	Yes	No	No
Lu	Yes	No	No	Yes	Yes	No
Magnussen	Yes	No	No	Yes	Modified ITT	No
Maspero	Yes	No	No	Yes	CND	CND
Massanari	CND	CND	CND	Yes	Yes	CND
Murphy	Yes	Yes	No	Yes	Yes	Yes
O'Byrne	Yes	No	no	Yes	Yes	CND
Ohbayashi	Yes	No	No	Yes	No	No

Evidence Table 2. Internal validity: Trials key question 1

Author	Year	Trial Name	Efficacy and Effectiveness Outcomes Quality Rating Good, Fair, Poor	Randomization adequate? Yes, No, CND	Allocation concealment adequate? Yes, No, CND	Groups similar at baseline? Yes, No, CND	Outcome assessors masked? Yes, No, CND	Care provider masked? Yes, No, CND	Patient masked? Yes, No, CND
Ohta	2009	NA	Fair	Yes	CND	Yes	CND	Yes	Yes
Pearlman	2004	NA	Fair	CND	CND	Yes	CND	Yes	Yes
Pedersen	2009	NA	Fair	Yes	CND	Yes	CND	Yes	Yes
Pedersen	2006	NA	Fair	Yes	Yes	Yes	CND	Yes	Yes
Peters	2008	NA	Fair	Yes	CND	Yes	CND	Yes	Yes
Renzi	2010	NA	Fair	CND	CND	Yes	CND	CND	CND
Sears	2008	NA	Fair	CND	CND	Yes	No	No	No
Ukena	2007	NA	Fair	CND	CND	Yes	CND	Yes	Yes
Vermeulen	2007	NA	Fair	Yes	CND	Yes	CND	Yes	Yes
von Berg	2007	NA	Fair	CND	CND	Yes	CND	Yes	Yes

Evidence Table 2. Internal validity: Trials key question 1

Author	Run-in/Washout? Yes, No, CND	Overall attrition high (≥20%)? Yes, No, CND	Loss to follow-up differential high (≥15%)? Yes, No, CND	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, CND, Modified ITT	Post-randomization exclusions? Yes, No, CND
Ohta	Yes	No	No	Yes	Modified ITT	Yes
Pearlman	Yes	Yes	Yes	Mixed	CND	Yes
Pedersen	Yes	No	No	Mixed	Yes	No
Pedersen	Yes	No	No	Yes	Yes	No
Peters	Yes	No	No	Yes	CND	Yes
Renzi	Yes	No	No	Mixed	Yes	Yes
Sears	Yes	No	No	Mixed	Yes	No
Ukena	Yes	No	No	Yes	Yes	No
Vermeulen	Yes	No	No	Yes	Modified ITT	CND
von Berg	Yes	No	No	Yes	Modified ITT	Yes

Evidence Table 3. Internal Validity: Trials key question 2

Author	Year	Trial Name	Quality assessment for harms Good, Fair, Poor	Randomization adequate? Yes, No, CND	Allocation concealment adequate? Yes, No, CND	Groups similar at baseline? Yes, No, CND	Outcome assessors masked? Yes, No, CND	Care provider masked? Yes, No, CND	Patient masked? Yes, No, CND	Run-in/Washout? Yes, No, CND
Aalbers	2010	NA	Fair	Yes	Yes	Yes	NR	Yes	Yes	Yes
Adachi	2007	NA	Poor	CND	No	Yes	No	No	No	Yes
Bailey	2008	NA	Fair	CND	CND	Yes	CND	CND	Yes	Yes
Bateman	2008	NA	Fair	Yes	CND	Yes	No	No	No	Yes
Berger	2010	NA	Fair	CND	CND	Yes	CND	Yes	Yes	Yes
Berger	2010	NA	Good	Yes	No	Yes	No	No	No	Yes
Boonsawat	2008	NA	Fair	CND	CND	Yes	Yes	Yes	Yes	Yes
Boulet	2007	NA	Good	Yes	CND	Yes	No	No	No	Yes
Boulet	2006	NA	Fair	Yes	CND	Yes	CND	Yes	Yes	Yes
Buhl	2006	NA	Fair	CND	CND	Yes	CND	Yes	Yes	Yes
Chucalin	2008	NA	Fair	CND	CND	Yes	CND	Yes	Yes	Yes
Chylack	2008	NA	Fair	CND	CND	Yes	CND	CND	Yes	Yes
Connolly	1995	NA	Fair	CND	No	Yes	No	No	No	Yes
Dahl	2010	NA	Fair	Yes	CND	Yes	CND	Yes	Yes	Yes
de Blic	2009	NA	Fair	CND	CND	CND	CND	Yes	Yes	Yes
Eid	2010	NCT00316321	Fair	Yes	CND	Yes	CND	CND	Yes	Yes
Gappa	2009	VIAPAED	Poor	Yes	CND	Yes	CND	Yes	Yes	Yes
Godard	2008	NA	Poor	CND	CND	No	CND	Yes	Yes	Yes
Hansel	2006	NA	Fair	Yes	No	Yes	CND	CND	No	Yes
Harnest	2008	NA	Poor	Yes	CND	Yes	No	No	No	Yes
Huchon	2009	NA	Fair	Yes	CND	Yes	CND	Yes	Yes	Yes
Knox 2007		NA	Fair	CND	CND	No	CND	Yes	Yes	Yes
Koenig	2008	NA	Fair	CND	CND	Yes	CND	CND	Yes	Yes
Langdon	1994	NA	Fair	CND	No	Yes	No	No	No	Yes
Lanier	2009	NA	Fair	CND	CND	Yes	CND	CND	CND	Yes
Li	2010	SFA106484	Fair	Yes	CND	Yes	CND	Yes	Yes	Yes
Lipworth	2005	NA	Fair	CND	CND	Yes	CND	Yes	Yes	No
Lu	2009	NA	Poor	Yes	CND	Yes	CND	CND	CND	Yes
Magnussen	2007	NA	Fair	CND	CND	Yes	CND	Yes	Yes	Yes
Maspero	2008	PEACE	Fair	Yes	Yes	Yes	CND	Yes	Yes	Yes
Massanari	2009	NA	Fair	CND	CND	Yes	CND	CND	CND	CND
Murphy	2008	NA	Fair	Yes	CND	Yes	CND	Yes	Yes	Yes
Ohta	2009	NA	Fair	Yes	CND	Yes	CND	Yes	Yes	CND
Pearlman	2004	NA	Fair	CND	CND	Yes	CND	Yes	Yes	Yes
Pedersen	2009	NA	Fair	Yes	CND	Yes	CND	Yes	Yes	Yes
Pedersen	2006	NA	Fair	Yes	Yes	Yes	CND	Yes	Yes	Yes
Peters	2008	NA	Fair	Yes	CND	Yes	CND	Yes	Yes	Yes
Renzi	2010	NA	Fair	CND	CND	Yes	CND	CND	CND	Yes
Sears	2008	NA	Fair	CND	CND	Yes	No	No	No	Yes
Ukena	2007	NA	Fair	CND	CND	Yes	CND	Yes	Yes	Yes
Vermeulen	2007	NA	Fair	Yes	CND	Yes	CND	Yes	Yes	Yes
von Berg	2007	NA	Fair	CND	CND	Yes	CND	Yes	Yes	Yes

Evidence Table 3. Internal Validity: Trials key question 2

Author	Overall attrition high (≥20%)? Yes, No, CND	Loss to follow-up differential high (≥15%)? Yes, No, CND	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, CND, Modified ITT	Post-randomization exclusions? Yes, No, CND	Adverse events pre-specified and defined? Yes, No, CND	Ascertainment techniques adequately described? Yes, No, CND	Adequate duration of follow-up? Yes, No, CND
Aalbers	No	No	Yes	No	Yes	No	No	Yes
Adachi	CND	CND	Yes	Yes	No	No	No	Yes
Bailey	No	No	Yes	Yes	Yes	No	No	Yes
Bateman	No	No	Yes	Modified ITT	Yes	Yes	Yes	Yes
Berger	Yes	Yes	Yes	Modified ITT	Yes	Yes	Yes	Yes
Berger	No	No	Mixed	Modified ITT	Yes	Yes	Yes	Yes
Boonsawat	No	No	Yes	Modified ITT	Yes	Yes	Yes	Yes
Boulet	No	No	Yes	Modified ITT	Yes	Yes	Yes	Yes
Boulet	CND	CND	Yes	Modfied ITT	Yes	No	Yes	CND
Buhl	No	No	Mixed	Yes	Yes	No	Yes	Yes
Chucalin	No	No	Yes	Yes	Yes	No	Yes	Yes
Chylack	No	No	Yes	Modified ITT	Yes	Yes	Yes	Yes
Connolly	No	No	Mixed	Modified ITT	Yes	Yes	Mixed	Yes
Dahl	No	no	Mixed	Yes	No	No	Mixed	Yes
de Blic	No	No	Yes	No	Yes	Yes	Yes	Yes
Eid	No	no	Yes	Yes	Yes	No	Yes	Yes
Gappa	No	No	Mixed	Modified ITT	Yes	No	No	CND
Godard	No	No	Yes	Yes	No	No	No	Yes
Hansel	No	No	Yes	Modified ITT	Yes	Yes	No	Yes
Harnest	No	No	Mixed	Modified ITT	Yes	No	No	CND
Huchon	No	No	Yes	Modified ITT	Yes	Yes	Yes	Yes
Knox	No	No	Yes	Modified ITT	No	No	Yes	CND
Koenig	No	No	Yes	Yes	No	No	No	CND
Langdon	No	No	Mixed	No	Yes	CND	Mixed	Yes
Lanier	No	No	Yes	No	Yes	No	No	CND
Li	No	No	Yes	Yes	No	Yes	Yes	Yes
Lipworth	No	No	Yes	Yes	No	Yes	Yes	CND
Lu	No	no	Yes	Yes	No	No	No	Yes
Magnussen	No	No	Yes	Modified ITT	No	No	Yes	CND
Maspero	No	No	Yes	CND	CND	No	Yes	Yes
Massanari	CND	CND	Yes	Yes	CND	No	No	Yes
Murphy	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Ohta	No	No	Yes	Modified ITT	Yes	Yes	Yes	Yes
Pearlman	Yes	Yes	Mixed	CND	Yes	Yes	Yes	CND
Pedersen	No	No	Mixed	Yes	No	Yes	Yes	Yes
Pedersen	No	No	Yes	Yes	No	No	Yes	Yes
Peters	No	No	Yes	CND	Yes	CND	Yes	Yes
Renzi	No	No	Mixed	Yes	Yes	No	No	Yes
Sears	No	No	Mixed	Yes	No	No	No	Yes
Ukena	No	No	Yes	Yes	No	No	No	Yes
Vermeulen	No	No	Yes	Modified	CND	Yes	Mixed	Yes
von Berg	No	No	Yes	Modified ITT	Yes	Yes	No	CND

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Adams 2008 Cochrane NHS Research & Development, UK Nederlands Astma Fonds	Inclusion Criteria: Prospective RCTs; double, single or unblinded studies; parallel group design and crossover studies; children and/or adults; clinical diagnosis of chronic asthma; ≥2 years old; treatement settings of primary care, hospital outpatient, or institutional care; FP vs. placebo; treatment duration ≥ 1 wk; Delivery by MDI with or without spacer/chamber or DPI; nominal daily dose of FP had to be stated; concurrent therapy acceptable including use of OCS; Outcomes include FEV1, diary card and clinic PEFR, diurnal PEFR; symptoms; rescue bronchodilator use; health status/ HRQOL; asthma exacerbation; HPA function; orophyngeaql side effects; skin bruising Exclusion criteria: use of nebulisers	N = 86 studies	N = 16, 160	75 studies parallel group design; 12 crossover design; Majority of studies with treatment duration of 12 wk; 21 studies treatment period of 4-8 wks; 6 studies treatment period of 16-24 wks; 4 studies treatment period of 12-24 mo;	Large multicenter trials; Conducted in U.S., Europe, Asia, South Africa; Secondary care/hospital outpatient clinic; 8 studies conducted in children; remaining studies conducted in adult and adolescents. 24 studies recruited patients with mild asthma, 19 mild to moderate; 23 moderate; 3 severe asthma; 8 studies asthma severity could not be estimated	Range of nominal daily doses of FP to placebo; several studies had multiple treatment arms; 21 studies FP 50-100 mcg/d; 42 studies FP 200 mcg/d; 26 studies FP 500 mcg/d; 18 studies FP 1000 mcg/d; 1 study could not determine dose; 7 studies FP 1500-2000 mcg/d vs placebo; 37 studies DPI; 24 studies MDI; 6 studies MDI/spacer combination; Crossover study both devises assessed; 10 studies delivery device could not be determined;	review used for AEs only	FP vs. Placebo: Parallel group studies, No Oral Steroids, ≤ 100 mcg/d Withdrawal due to clinical asthma exacerbation (n/N) Studies = 1 FP: 2/111 Placebo:24/106 OR (95% CI): 0.14 (0.06, 0.32) Withdrawal due to Adverse Events (n) Children Studies = 2 FP: 432 Placebo: 430 OR (95% CI): 0.73 (0.24, 2.20) Adults Studies = 3 FP: 257 Placebo: 259 OR (95% CI): 1.24 (0.30, 5.13) Total Studies = 5 FP: 689 Placebo: 689 OR (95% CI): 0.89 (0.37, 2.12)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Adams 2008 cont'd								Sore Throat or pharyngitis (n) Children Studies = 4 FP: 631 Placebo: 619 OR (95% CI): 1.37 (0.67, 2.91) Adults Studies = 5 FP: 344 Placebo: 334 OR (95% CI): 1.28 (0.58, 2.81) Total Studies = 9 FP: 975 Placebo: 953 OR (95%CI): 1.34 (0.78, 2.29) Hoaresness or Dysphonia (n) Children Studies = 2 FP: 196 Placebo: 199 OR (95% CI): 7.19 (0.74, 69.93) Adults Studies = 5 FP: 417 Placebo: 403 OR (95% CI): 4.36 (1.09, 17.52) Total Studies = 7 FP: 613 Placebo: 602 OR (95% CI): 5.00(1.53, 16.37)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Adams 2008 cont'd								Oral Candidiasis (n) Children Studies = 3 FP: 324 Placebo: 329 OR (95% CI): 1.98 (0.40, 9.85) Adults Studies = 4 FP: 329 Placebo: 316 OR (95% CI): 4.84 (1.39, 16.88) Total Studies = 7 FP: 653 Placebo:645 OR (95% CI): 3.45 (1.29, 9.26) Headaches (n) Children Studies = 2 FP: 392 Placebo: 383 OR (95% CI): 0.75 (0.52, 1.09) Adults Studies = 3 FP: 257 Placebo: 259 OR (95% CI): 1.17 (0.63, 2.17) Total Studies = 5 FP: 649 Placebo: 642 OR (95% CI): 0.84 (0.61, 1.16)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Adams 2008 cont'd								FP vs. Placebo: Parallel group studies, no oral steroids, 200 mcg/d (n) Withdrawal due to clinical asthma exacerbation Children Studies = 2 FP: 123 Placebo: 125 OR (95% CI): 0.18 (0.09, 0.38) Adults Studies = 2 FP: 221 Placebo: 233 OR (95% CI): 0.29 (0.11, 0.79) Total Studies = 4 FP: 344 Placebo: 358 OR (95% CI): 0.22 (0.12, 0.39)
Adams 2008 cont'd								Withdrawals due to adverse events Children Studies = 2 FP: 399 Placebo: 211 OR (95% CI): 2.12 (0.61, 7.41) Adults Studies = 20 FP: 2663 Placebo: 2011 OR (95% CI): 1.15 (0.74, 1.78) Total Studies = 22 FP: 3062 Placebo: 2222 OR (95% CI): 1.23 (0.81, 1.86) Adverse Events Children Studies = 1 FP: 160 Placebo: 81 OR (95% CI): 1.15 (0.66, 2.00) Adults Studies = 11 FP: 1018 Placebo: 1032 OR (95% CI): 1.24 (1.02, 1.50) Total Studies = 12 FP: 1178 Placebo: 1113 OR (95% CI): 1.23 (1.02, 1.47)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Adams 2008 cont'd								Oral Candidiasis Children Studies = 4 FP: 438 Placebo: 316 OR (95% CI): 1.32 (0.55, 3.20) Adults Studies = 13 FP: 1054 Placebo: 1033 OR (95% CI): 4.09 (2.28, 7.35) Total Studies = 17 FP: 1492 Placebo: 1349 OR (95% CI): 2.90 (1.78, 4.72)
Adams 2008 cont'd								Sore Throat or Pharyngitis Children - Studies = 3 FP: 348 Placebo: 265 OR (95% CI): 1.66 (0.75, 3.69) Adults - Studies = 21 FP: 2412 Placebo: 1753 OR (95% CI): 1.79 (1.33, 2.42) Total - Studies = 24 FP: 2760 Placebo: 2018 OR (95% CI): 1.78 (1.34, 2.35) Headaches Children - Studies = 2 FP: 240 Placebo: 159 OR (95% CI): 1.30 (0.64, 2.64) Adults - Studies = 16 FP: 2127 Placebo: 1483 OR (95% CI): 1.16 (0.93, 1.44) Total Studies = 18 FP: 2367 Placebo: 1642

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Adams 2008 cont'd								Hoarseness or Dysphonia Children - Studies = 2 FP: 195 Placebo: 199 OR (95% CI): 8.10 (0.83, 79.01) Adults - Studies = 12 FP: 974 Placebo: 953 OR (95% CI): 3.91 (2.04, 7.49) Total - Studies = 14 FP: 1169 Placebo: 1152 OR (95% CI): 4.13 (2.21, 7.72) Upper Respiratory Tract Infection Children - Studies = 3 FP: 479 Placebo: 279 OR (95% CI): 0.93 (0.61, 1.41) Adults - Studies = 9 FP: 1634 Placebo: 997 OR (95% CI): 1.12 (0.89, 1.40) Total - Studies = 12 FP: 2113 Placebo: 1276 OR (95% CI): 1.07 (0.88, 1.31)
Adams 2008 cont'd								Sinusitis Children - Studies = 2 FP: 240 Placebo: 159 OR (95% CI): 1.96 (0.84, 4.56) Adults - Studies = 10 FP: 1738 Placebo: 1101 OR (95% CI): 1.22 (0.86, 1.73) Total - Studies = 12 FP: 1978 Placebo: 1260 OR (95% CI): 1.30 (0.94, 1.80) FP vs. Placebo: Parallel Group Studies, no oral steroids: 500 mcg/d (n) Withdrawal due to clinical asthma exacerbation Total – Adults Only - Studies =3 FP: 191 Placebo: 203; OR (95% CI): 0.88 (0.42, 1.88)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Bateman 2008 Not abstracted Poor quailty								
Breton 2008 Not abstracted Poor quality								
Castro-Rodriguez 2010 NR None	Inclusion: Studies published Jan 1996 to Nov 2009; children < 18 w/ clinical diagnosis of asthma for > 6 months before study entry; RCTs (parallel group or crossover) without language restriction; >/= 4 wks of treatment with ICS vs MONT or ICS+ MONT (ICS dose maintained throughout intervention period); primary outcome measure AEX requiring PO steroids Exclusion: NR	18 total 13 - ICS vs MONT 3 - ICS + MONT vs ICS 2 - ICS vs MONT vs ICS + MONT	3757	RCTs published January 1996 to November 2009	Children < 18 w/ diagnosis of asthma for >= 6 months before study entry	4+ weeks of treatment with ICS, MONT or ICS + MONT (dose of ICS maintained throughout intervention period)	**ICS vs. MONT** Exacerbations, 7 trials, RR 0.83, 95% CI 0.72 to 0.96, I2=35%, p=0.01) ; 21.3% in ICS group vs 25.6% in MONT group; risk difference 4.3% (95% CI 0.9% to 7.6%); 43 pts out of 1000 benefit from ICS therapy (95% CI 9 to 76); NNT= 24 (95% CI 13 to 110). Mean change from baseline in albuterol use, 6 trials, N = 1823 SMD* 0.34 (0.16 to 0.53) P = 0.002 Mean change from baseline in symptom score, 4 trials, N = 575 SMD* 0.18 (0.01 to 0.34) P = 0.04 Mean rescue medication-free days, 4 trials, N =1904 SMD* 0.16 (0.07 to 0.25) P = 0.0005 Hospitalisations due to exaerbation, 2 trials, N = 533 RR 0.33 (0.03 to 3.15) P =0.34 **ICS vs. ICS + MONT** Mean change from baseline in albuterol use, 2 trials, N = 493 SMD* 0.45 (1.16 to -0.26) P = 0.21 Mean change from baseline in symptom score, 1 trial, N = 63 SMD* 0.20 (0.69 to -0.30) P = 0.43	Overall incidence of adverse effects NS between groups (N = 1767) RR=0.98 (0.86 to 1.11) P = 0.73

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Cates 2008 Cochrane Government	Inclusion: Controlled parallel design with or without blinding; random assignment; patients with chronic asthma (any severity); any delivery device, any dose; placebo and co-interventions allowed, but salmeterol alone had to be the intervention Exclusion: <12 week duration; studies comparing different doses or delivery mechanisms for salemterol; studies in which salmeterol was combined with ICS	32	62630 enrolled; 46501 completed	All double-blind RCTs;	7 pediatric studies (<12 yrs	(1) 26 compared salmeterol to placebo; (2) 8 compared salmeterol to salbutamol; Dose of salmeterol was 50mcg BID in all but 2 studies (those used 100mcg BID in certain participants); 3 studies used either 25mcg or 50mcg BID in children; most studies allowed concurrent use of ICS	NR	All-cause mortality: (1) NSD (OR 1.33; 0.85, 2.08); (2) NSD (OR 1.22; 0.76, 1.96) Non-fatal all-cause SAE: (1): favors control (OR 1.15; 1.02, 1.29) (2): NSD (OR 0.96; 0.81, 1.14) Combined fatal and non-fatal SAE: (1): favors control (OR 1.16; 1.03, 1.30) (2): NSD (OR 0.99; 0.84, 1.16) Asthma mortality: (1) favors control (OR 3.49; 1.31, 9.31) (2) NSD (OR 2.36; 0.78, 7.16) Overall: favors control (OR 2.94; 1.41, 6.14) Cardiovascular mortality: (1) NSD (OR 0.75; 0.32, 1.77) (2) NSD (OR 1.22; 0.64, 2.34) Non-fatal asthma-related SAEs: (1) favors control (OR 1.59; 1.05, 2.41) (1b-GSK US trials) favors control (OR 2.07; 1.36, 3.13) (2) NSD (OR 0.99; 0.54, 1.81)
Cates 2008 cont'd								Non-fatal cardiovascular SAEs: (1) NSD (OR 0.98; 0.73, 1.31) (1b - GSK US trials) NSD (0.90; 0.27, 2.97) (2) NSD (OR 1.06; 0.67, 1.68) Serious drug-related AEs: (1) NSD (OR 0.92; 0.32, 2.65) (2) NSD (OR 0.63; 0.13, 3.07) All AEs: (1) favors control (OR 1.15; 1.00, 1.33) (2) NSD (OR 0.93; 0.77, 1.13) Hospitalizations for asthma (FDA data from GSK USA studies): (1) favors control (OR 2.14; 1.16, 3.93) (2) NR

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Cates 2009 (a) Cochrane NHS R&D, UK	Controlled parallel design clinical trials on patients of any age and severity of asthma were included if they randomised patients to treatment with regular formoterol and inhaled corticosteroids, and were of at least 12 weeks duration.	14	8028	Controlled parallel design clinical trials and were of at least 12 weeks duration.	Any age and severity of asthma	treatment with regular formoterol and inhaled corticosteroids, and were of at least 12 weeks duration.		All cause mortality - No deaths in the trials on children and adolescents (2,788 participants). Adult and adolescent studies (8,028 participants), four deaths which were all in patients taking formoterol with inhaled corticosteroids Pooled Peto Odds Ratio 5.83 (95% CI 0.78 to 43.77) and I2 = zero . Risk differences with a fixed effects model the RD is 0.001 (95% CI -0.001 to 0.003) for adults and adolescents and the RD is zero (95% CI -0.004 to 0.004) in trials on children and adolescents Serious Adverse Events (non-fatal all cause) - All ages Peto Odds Ratio of 1.06 (95% CI 0.81 to 1.39) and I2 was 8% , and the pooled RD for all ages was 0.001 (95% CI -0.004 to 0.007) Adults and Adolescents - 116 out of 4875 (2.4%) participants on regular formoterol with ICS and 86 out of 3153 (2.7%) on ICS alone in whom such events occurred. Peto Odds Ratio was 0.99 (95% CI 0.74 to 1.33) and I2 was zero. The pooled RD was -0.0003 (95% CI -0.007 to 0.007).

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Cates 2009 (a) cont'd								Children and Adolescents - 25 such events amongst young people out of 1719 (1.5%) on regular formoterol with ICS and nine out of 1069 (0.8%) on ICS alone. Peto Odds Ratio 1.62 (95% CI 0.80 to 3.28) and I2 = 32%, and the pooled RD for children was 0.006 (95% CI -0.003 to 0.01). Serious Adverse Events related to Asthma - All Ages - Peto Odds Ratio of 0.68 (95% CI 0.39 to 1.18) and I2 = 21% , and the pooled RD -0.002 (95% CI -0.005 to 0.001) Adults and Adolescents - 15 out of 4875 (0.3%) participants on regular formoterol with ICS and 24 out of 3153 (0.8%) on ICS alone. Peto Odds Ratio 0.53 (95% CI 0.28 to 1.00) and I2 = zero. The pooled RD was -0.003 (95% CI -0.007 to 0.0005). Children and Adolescents - 9 young people out of 1719 (0.5%) on regular formoterol with ICS and four out of 1069 (0.4%) on ICS alone. Peto Odds Ratio 1.49 (95% CI 0.48 to 4.61) and I2 = 60%. The pooled RD 0.002 (95% CI -0.005 to 0.009).
Cates 2009 (b)	Inclusion: Controlled parallel design clinical trials, with or without blinding, in which patients with chronic asthma and 1+ serious AE (any age, unrestricted by disease severity, previous or current treatment) were randomly assigned to regular treatment with formoterol versus salmeterol given regularly for a period of > 12 wks, but not randomised with ICS Exclusion: Studies on acute asthma and exercise induced acute bronchospasm; Studies using adjustable maintenance dosing and single inhaler therapy (for maintenance and relief of symptoms)	4	1272 (1116 adults, 156 children)	All studies were open label and recruited patients who were already taking ICS for their asthma, and all studies contributed data on serious AEs. All compared formoterol 12 mcg vs salmeterol 50 mcg twice daily.	Children 6-17 yrs (mean age 12 yrs); Adults 18 yrs and older (mean age NR); concomitant ICSs used by 100% of patients	G1: Formoterol 12 mcg BID G2: Salmeterol 50 mcg BID Adult studies compared Foradil Aerolizer with Serevent Diskus; Children's studies compared Oxis Turbohaler to Serevent Accuhaler.	NR	Only one death in an adult (unrelated to asthma), and none in children; no significant differences in non-fatal serious AEs comparing formoterol to salmeterol in adults (Peto OR 0.77; 95% CI 0.46 to 1.28), or children (Peto OR 0.95; 95% CI 0.06 to 15.33). 6-month period in studies involving adults, % with serious AEs were 5.1% for formoterol and 6.4% for salmeterol; 3-month period the % of children with serious AEs were 1.3% for formoterol, and 1.3% for salmeterol.

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Cates 2009 (c)	Inclusion Criteria: Controlled parallel design clinical trials, with or without blindicng; SM and ICS randomly assigned to patients with chronic asthma; Clinical diagnosis of asthma; any age group; any disease severity, previous or current treatment; treatment duration ≥ 12wk; any daily dose;delivery by any single or separate device; Outcomes of interest: all cause mortality, all cause non-fatal serious adverse events, asthma-related morality, asthma-related non-fatal serious adverse events, respiratory-realted mortality, respiratory-related non-fata serious adverse events, cardiovascular-related mortality, cardiovascular-related non-fatal serious adverse events, asthma-related non-fatal serious adverse events, respiratory-realted non-fatal life-threatenting events. Exclusion Criteria: Acute asthma; Exercise induced bronchospasm; comparison of different doses of SM or different delivery devices or propellants; compared SM w/ formoterol; SM randomised without an ICS	N = 33 studies	N = 12046	Weighted mean duration: 31 wks for adults; 16 wks for children	10873 adults and adolescents; 1173 children;	FP + SM vs. FP alone; most studies used a single inhaler to combine FP and SM; SM = 50mcg/BID except 3 studies SM dose = 50 mcg/d; FP dose 100 - 1000 mcg/d.	NR	All-cause non-fatal serious adverse events Adults & Adolescents SM + ICS: 5710 ICS: 5163 Peto OR (95%CI): 1.17 (0.90, 1.52) M-H Fixed OR (95% CI): 1.17 (0.90, 1.51) Pooled RD (95%CI): 0.003 (-0.002, 0.009) M-H Random OR (95% CI): 1.14 (0.87, 1.49) Children SM +ICS: 586 ICS: 587 Peto OR (95% CI): 0.75 (0.17, 3.31) M-H Fixed OR (95% CI): 0.75 (0.17, 3.36) Pooled RD (95%CI):-0.002 (-0.01, 0.008) M-H Random OR (95% CI):0.78 (0.13, 4.55) Total SM +ICS: 6296 ICS: 5750 Peto OR (95%CI): 1.16 (0.90, 1.50) M-H Fixed OR (95% CI): 1.15 (0.90, 1.49) M-H Random OR (95% CI): 1.13 (0.87, 1.47)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Cates 2009 (c) cont'd								Asthma-related serious adverse events Adults & Adolescents SM + ICS: 5710 ICS: 5173 OR (95%CI): 0.95 (0.52, 1.73) Pooled RD (95%CI): -0.002 (-0.003, 0.003) Children SM +ICS: 586 ICS: 587 OR (95% CI): 0.14 (0.00, 6.82) Pooled RD (95%CI): -0.002 (-0.008, 0.005) Total SM +ICS: 6296 ICS: 5750 OR (95%CI): 0.91 (0.50, 1.64)
Cates 2009 (c) cont'd								All-cause serious adverse events (fatal and non-fatal) Adults: SM + ICS: 5710 ICS: 5163 Peto OR (95%CI): 1.17 (0.91, 1.51) Children: SM + ICS: 586 ICS: 587 Peto OR (95%CI):0.75 (0.17, 3.31) Total: SM + ICS: 6296 ICS: 5750 Peto OR (95%CI): 1.15 (0.90, 1.48)
Cates 2009 (c) cont'd								All-cause non-fatal serious adverse events (without the lower dose studies) Adults: SM + ICS: 5710 ICS: 5161 Peto OR (95%CI): 1.15 (0.88, 1.49) Children: SM + ICS: 586 ICS: 587 Peto OR (95%CI): 1.95 (0.20, 18.91) Total: SM + ICS: 6296 ICS: 5748 Peto OR (95%CI): 1.15 (0.89, 1.50)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Cates 2010 Cochrane NHS R&D, UK	Controlled clinical trials with a parallel design, recruiting patients of any age and severity of asthma were included if they randomised patients to treatment with regular formoterol versus regular salmeterol (each with a randomised inhaled corticosteroid), and were of at least 12 weeks duration.	8	6163	Controlled clinical trials with a parallel design	patients of any age and severity of asthma	treatment with regular formoterol versus regular salmeterol (each with a randomised inhaled corticosteroid), and were of at least 12 weeks duration.	NR	Mortality - All-cause mortality Peto OR 1.03; 95% CI 0.06 to 16.44, I2 = 50% RD 0.000009; 95% CI -0.002 to 0.002, I2 = 0%). All cause non-fatal serious adverse events - Formoterol and budesonide 77 out of 2,966 adults and adolescents vs salmeterol and fluticason 68 out of 2,969 patients on. Peto OR 1.14; 95% CI 0.82 to 1.59, I2 = 26%) see Figure 3, or as a Risk Difference (RD 0.003; 95% CI -0.005 to 0.011, I2 = 21%). Asthma-related serious adverse events - Formoterol and budesonide 17 adults and adolescents out of 2,966 vs 25 out of 2,969 on salmeterol and fluticasone Peto OR 0.69; 95% CI 0.37 to 1.26, I2 = 33% RD -0.003; 95% CI -0.007 to 0.002, I2 = 0%

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Ducharme 2010 (a) Cochrane NHS R&D, UK	RCTs that compared the combination of inhaled LABA and ICS to a higher dose of inhaled corticosteroids, in children and adults with asthma.	48	15,155 participants including 1155 children and 14,000 adults	RCTs	children and adults with asthma.	Combination of inhaled LABA and ICS to a higher dose of inhaled corticosteroids	LABA+ICs vs higher doses of ICS oral steroid-treated exacerbations (RR 0.88, 95% CI 0.78 to 0.98, P = 0.02; N = 25 studies, 9833 participants) risk difference was -0.01 (-0.02 to -0.00) patients with exacerbation requiring hospitalisation (RR 1.02, 95% CI 0.67 to 1.56, N = 33) adults: RR 0.87, 95% CI 0.54 to 1.38; children: RR 2.21, 95% CI 0.74 to 6.64) Withdrawals due to poor asthma control (RR 0.71, 95% CI 0.56 to 0.91, 29 studies) Overall withdrawals (RR 0.92, 95% CI 0.84 to 1.00, 39 studies. Daytime symptom score (SMD -0.26, 95% CI -0.35 to -0.17, five studies) overall (24 hours) symptom score (SMD -0.23, 95% CI -0.37 to -0.08, random-effects model, six studies); change in percent symptom-free days at endpoint (9.18%, 95% CI 6.02 to 12.33, random-effects model, 12 studies) and % nighttime awakenings at endpoint (-0.40; 95% CI -0.55 to -0.25, fixed-effect model, two studies); all favoured combination therapy.	Risk ratio of serious adverse events (including all cause hospital admission) was 1.12 (95% CI 0.91 to 1.37) (35 studies). Tremor in the LABA group (RR 1.84, 95% CI 1.20 to 2.82, 11 studies) (Analysis 1.53). Ooral thrush on LABA and ICS compared with the higher dose of ICS (RR 0.58, 95% CI 0.40 to 0.86, 14 studies) One study assessed growth in children, with a significantly better short-term rate of growth in the LABA and ICS group over 12 months (0.9 cm, 95% CI 0.20 to 1.60). Overall side effects (RR 0.99, 95% CI 0.95 to 1.03, 30 studies) Adverse cardiovascular events (RR 0.99, 95% CI 0.49 to 2.01, random-effects model, nine studies) Headache (RR 1.02, 95% CI 0.92 to 1.12, 25 studies)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Ducharme 2010 (a) cont'd							Percentage of symptom-free days at endpoint (5.81%, 95% CI -1.14 to 12.76, random-effects model, eight studies); daytime symptoms at endpoint (SMD -0.28, 95% CI -0.67 to 0.11, random-effects model, five studies); nighttime symptoms at endpoint (SMD -0.24, 95% CI -0.49 to 0.01, three studies); change in nighttime symptoms (SMD -0.01, 95% CI -0.04 to 0.01, two studies); percentage of symptom-free nights at endpoint (-2.10%; 95% CI -7.98 to 3.79, two studies) , and in the change from baseline in nighttime awakenings (SMD -0.03, 95% CI -0.10 to 0.04, seven studies) The change in daytime rescue inhalations (-0.48 puffs/d, 95% CI -0.77 to -0.20, random-effects model, five studies); change in nighttime inhalations (SMD -0.13, 95% CI -0.21 to -0.05, random-effects model, four studies), the change in rescue inhalations over 24 hours (-0.20, 95% CI -0.29 to -0.11, 12 studies) and the change in mean percent of rescue-free days at endpoint (11.48%, 95% CI 7.98 to 14.98, fixed-effect model, three studies). Nnumber of daytime rescue inhalations (-0.44, 95% CI -0.94 to 0.06, five studies); nighttime rescue inhalations (-0.09, 95% CI -0.23 to 0.04, random-effects model, four studies): % overall rescue-free days (5.14%, 95% CI -2.79 to 13.08, random-effects model, three studies	Hoarseness (RR 0.95, 95% CI 0.79 to 1.14, nine studies) Tachycardia/palpitations (RR 1.20, 95% CI 0.78 to 1.84, 15 studies) withdrawals due to adverse events (RR 0.99, 95% CI 0.78 to 1.26, 30 studies)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Ducharme 2010 (b) Cochrane NHS R&D, UK	RCTs if they compared the addition of inhaled LABAs versus placebo to the same dose of ICS in children aged two years and above and in adults.	77	21,248 participants (4625 children and 16,623 adults).	RCTs	Adults and children (2 or more) with chronic asthma	LABAs versus placebo to the same dose of ICS i	LABA+ ICS vs ICS exacerbations of asthma requiring oral steroids - The addition of a LABA to ICS therapy led to a 23% reduction (from 15% to 11%) in the relative risk of patients experiencing one or more exacerbations requiring oral corticosteroids (RR 0.77, 95% CI 0.68 to 0.87, P < 0.0001, N = 6808) NNT 41 (29, 72) LABA reduced the risk of overall withdrawals by 20% (all reasons included): RR 0.80 (95% CI 0.75 to 0.87, 53 studies) and reduced the risk of withdrawals due to poor asthma control by 50% (RR 0.50, 95% CI 0.41 to 0.61, 38 studies) Daytime symptoms (SMD -0.33, 95% CI -0.42 to -0.23, eight studies); night-time symptoms (SMD -0.22, 95% CI -0.33 to -0.11, five studies) and overall 24-hour symptoms (SMD -0.23, 95% CI -0.34 to -0.12, six studies) . Percent of symptom-free days during the observation period (WMD 7.31, 95% CI 0.50 to 14.12, random-effects model, six studies); the change from baseline in symptom-free days (11.88%, 95% CI 8.25 to 15.50, random-effects model, 16 studies)and in symptom-free nights (SMD 0.51, 95% CI 0.28 to 0.74, random-effects model, four studies) (Analysis 1.25). Change in "asthma-control" days (15.81%, 95% CI 10.85 to 20.77, four studies). Change in percent nights with no awakening (1.01%, 95% CI -1.06 to 3.08, five studies) and in night-time awakening (SMD -0.10, 95% CI -0.21 to 0.01, five studies)	All-cause serious adverse events (events requiring or prolonging hospital admission or causing death) RR 1.06 (95% CI 0.87 to 1.3) isk of overall adverse effects (RR 1.00, 95% CI 0.97 to 1.04, 41 studies) (Analysis 1.39), meeting our a priori defined limits of equivalence. There was also no group difference in the risk of specific side effects including headache (RR 0.99, 95% CI 0.87 to 1.13, 37 studies) (Analysis 1.40); hoarseness (RR 1.17, 95% CI 0.44 to 3.1, random-effects model, six studies); oral thrush (RR 1.65, 95% CI 0.71 to 3.86, nine studies) (Analysis 1.42); tachycardia or palpitations (RR 2.11, 95% CI 0.83 to 5.37, 12 studies) (Analysis 1.44); cardiovascular adverse effects such as chest pain (RR 0.90, 95% CI 0.32 to 2.54, four studies) or tremor (RR 1.74, 95% CI 0.72 to 4.20, random-effects model, 16 studies).

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Ducharme 2010 (b) cont'd							Use of rescue meds - Daytime use at endpoint (-0.73 puffs/day, 95% CI -1.24 to -0.22, random-effects model, two studies) ; night-time use at endpoint (-0.44 puffs/night, 95% CI -0.81 to -0.07, random-effects model, two studies) ; change in overall 24-hour use (-0.58 puffs/24 hours, 95% CI -0.80 to -0.35, random-effects model, 14 studies); change in night-time use (-0.3 puffs/night, 95% CI -0.48 to -0.11, random-effects model, seven studies; change in rescue-free days (6.43%, 95% CI 1.2 to 11.66, two studies) or change in daytime use (-0.68 puffs/day, 95% CI -0.94 to -0.42, random-effects model, 13 studies) . The change in mean rescue-free days (17.05%, 95% CI 13.75 to 20.35, six studies) and in quality of life (as measured by the AQLQ) 0.26, 95% CI 0.04 to 0.47, random-effects model, three studies) Percent of nights with awakening (WMD -1.37, 95% CI -2.75 to 0.02, fixed-effect model, two studies)	Three studies reporting death (RR 2.46, 95% CI 0.48 to 12.65). However, the wide confidence interval (including the upper limit) for some adverse events was high for tachycardia, palpitations, tremor and death, indicating uncertainty. More dramatic was the scarce documentation of the impact on growth (in children), adrenal function and bone mineral density, preventing any aggregation due to the paucity (0 to 2) of trials measuring or reporting these outcomes. Withdrawal due to adverse events (RR 1.04, 95% 0.86 to 1.26, 52 studies)
Jaeschke 2008 NR NR	treatment allocation by randomization; parallel control groups (crossover studies excluded) with at least 12 weeks of treatment; blinding of patients and care-givers; acceptable follow-up of patients receiving study medication (outcome data for the full duration of planned treatment missing for <20% of patients taking LABA in trials ≤3 mo long, <30% for 3 mo to <1 yr long, <40% for ≥1 yr). Eligible studies involved patients with asthma (excluding children younger than 12 yr); all patients had to be receiving at least some ICS	63 publications describing 65 studies (20 publications formoterol and 43 publications describing 45 studies salmeterol).	29,401	treatment allocation by randomization; parallel control groups (crossover studies excluded) with at least 12 weeks of treatment; blinding of patients and care-givers;	patients with asthma (excluding children younger than 12 yr); all patients had to be receiving at least some ICS	LAB + ICS vs. ICS alone	LONG-ACTING β-AGONIST WITH INHALED CORTICOSTEROIDS VERSUS INHALED CORTICOSTEROIDS ALONE Total mortality events LABA+ICS/ICS 14/8 OR 1.26 (95% CI 0.58–2.74) Asthma-related nonfatal hospitalization LABA+ICS/ICS 66/77 OR 0.74 (95% CI 0 0.53–1.03) SAFETY OF LONG-ACTING β-AGONIST WITH INHALED CORTICOSTEROIDS VERSUS INHALED CORTICOSTEROIDS ALONE IN PATIENTS ON SIMILAR DOSES OF INHALED CORTICOSTEROIDS Total mortality events LABA+ICS/ICS 10/4 OR 1.34 (95% CI 0.53–3.35) Asthma-related nonfatal hospitalization LABA+ICS/ICS 32/42 0.66 (0.41–1.05)	SAFETY OF LONG-ACTING β-AGONIST WITH INHALED CORTICOSTEROIDS VERSUS INHALED CORTICOSTEROIDS ALONE Asthma-related nonfatal SAE events LABA+ICS/ICS 73/83 0.75 (0.54–1.03) Total mortality events LABA+ICS/ICS 14/8 OR 1.26 (95% CI 0.58–2.74) Total nonfatal intubation or death events LABA+ICS/ICS 17/10 OR 1.27 (95% CI 0.62–2.61) Total nonfatal SAE events LABA+ICS/ICS 433/353 OR 1.05 (95% CI 0.91–1.22)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Jaeschke 2008 cont'd							Effects of LABA on total mortality among patients using ICS (only studies with at least one event are presented). Formoterol, dose of ICS similar in both groups OR 1.84 (95% CI 0.44 to 7.72) Formoterol, dose of ICS higher in control group OR 0.71 (95% CI 0.13 to 3.91) Salmeterol, dose of ICS similar in both groups OR 0.92 (95% CI 0.25 to 3.33) Salmeterol, dose of ICS higher in control group OR 3.12 (95% CI 0.38 to 25.49) Total OR 1.26 (95% CI 0.58 to 2.74)	SAFETY OF LONG-ACTING β-AGONIST WITH INHALED CORTICOSTEROIDS VERSUS INHALED CORTICOSTEROIDS ALONE IN PATIENTS ON SIMILAR DOSES OF INHALED CORTICOSTEROIDS Asthma-related nonfatal SAE 19 37/45 OR 0.68 (95% CI 0.44–1.06) Total mortality events LABA+ICS/ICS 10/4 OR 1.34 (95% CI 0.53–3.35) Total nonfatal intubation or death events LABA+ICS/ICS 11/5 OR 1.30 (95% CI 0.54–3.11) Total nonfatal SAE events LABA+ICS/ICS 213/180 OR 1.04 (95% CI 0.85–1.27)
Jaeschke 2008 cont'd							Effects of LABA on asthma-related hospitalizations among patients using ICS (only studies with at least one event are presented) Formoterol, dose of ICS similar in both groups OR 0.49 (95% CI 0.25 to 0.95) Formoterol, dose of ICS higher in control group OR 0.68 (95% CI 0.38 to 1.24) Salmeterol, dose of ICS similar in both groups OR 0.88 (95% CI 0.44 to 1.76) Salmeterol, dose of ICS higher in control group OR 1.12 (95% CI 0.54 to 2.35) Total OR 0.74 (95% CI 0.53 to 1.03	
Joos 2008 NR Government: Institute for Quality and Efficiency in Health Care (Germany)	Inclusion: Montelukast as add-on therapy to ICS; adults and adoescents >=12 yrs; mild to moderate asthma; published in English, German, Dutch, French, Spanish or Portuguese; evaluation of at least one predefined outcomes; duration >=12 weeks. Exclusion: Studies with >=20% of patients having severe asthma	13	NR (5993 found when N-values in Table 1 are added)	All were RCT - 9 double-blind, two open-label, one unclear; duration ranged from 12 to 48 weeks; number of patients ranged from 30-1490.	Mean age ranged from 38-45 yrs; % female ranged from 38-67	3 main protocols: montelukast + constant dose ICS vs. constant dose ICS (N=3); montelukast + tapered ICS vs tapered ICS (N=4); montelukast + constant ICS vs salmeterol + constant ICS (N=6); ICS agents included beclamethasone, budesonide, fluticasone	NR	Montelukast+ICS had a higher rate of SAEs in 12 week studies (RR 1.27 95% CI 0.49 to 3.29) Salmeterol+ICS had a higher rate of SAEs in 48 week studies (RR 0.68; 95% CI 0.49 to 0.94; p=0.021)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

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Lasserson 2008 Cochrane Government	Inclusion: RCTs; single inhaler device (DPI or MDI) use; parallel design; any severity of asthma and any co-intervention allowed; fixed dose of combination products; study duration >=12 weeks Exclusion: Non-parallel study design; studies on acute asthma carried out in emergency departments; non-fixed dose of combination products ("single inhaler therapy" or "adjustable maintenance dosing"); study duration of <12 weeks	5	5537	All RCT; 2 studies reported outcomes from open-label phase, others used double-dummy design; blinding of outcomes assessment was NR	Adults and adolescents (12+); history of chronic asthma, treated with maintenance ICS at moderate to high doses prior to study entry; stable for 1 month prior to run-in; need for frequent reliever inhaler use during run-in ("partly controlled")	G1: fluticasone/salmeterol @ 500/100 mcg/day; G2: budesonide/formoterol @ 400-800/12-24 mcg/day Concomitant reliever med use allowed	NR	Note: reduction in mean or OR<1 represents a lowering for the FP/SAL (G1) compared to BUD/F group (G2) No significant difference between groups for any AEs. **Asthma-related SAE:** NS (OR 1.47; 95% CI 0.75 to 2.86) **Withdrawals due to AE:** NS (0.94; 95% CI 0.60 to 1.46) **AEs:** NS (OR 1.08; 95% CI 0.89 to 1.31) **Headache:** NS (OR 1.08; 95% CI 0.82 to 1.43) **Candidiasis:** NS (OR 1.64; 95% CI 0.68 to 4.00) **Dysphonia:** NS (OR 1.45; 95% CI 0.87 to 2.43)
Lasserson 2008 cont'd								Upper respiratory tract infection: NS (1.09; 0.81, 1.47) Throat irritation: NS (1.39; 0.82, 2.35) Rhinitis: NS (1.35; 0.85, 2.14) Cough: NS (1.15; 0.64, 2.05) Tremor: NS (0.13; 0.02, 1.04)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Lasserson 2010 Cochrane The Netherlands Asthma Fonds	Inclusion: RCTs; Double, single or unblinded studies; Parallell and crossover studies; Adult and children; Diagnosis of chronic asthma; Well and poorly controlled asthma; CFC of HFA-FP vs. extrafine HFA-BDP at a nominal dose ration of 1:1; CFC or HFA-FP vs. extrafine HFA-BDP ata nominal dose ratio of 1:2; CFC or HFa-FP vs extrafine HFA-BDP ata nominal dose raio 2:1; Studies that assessed the effect of FP via either pMDI or DPI with or without spacers; ≥ 2wk duration; Outcomes included lung function, exacerbations, symptoms, rescue medication usage, adverse events, health-related quality of life; Excluded: dose of ICS varied within the treatment groups.	N = 9 studies	N = 1,324	3 were crossover trials; 6 were parallel group design; Open label design for 6 studies; Double-dummy design for 3 studies;	Majority of participantw adults; Baseline symptoms and lung function indicate moderate asthma. 2 studies recruited children.	Assessed the relative effects of FP and HFA-BDP at nominal dose rations of 1:1; Trial duration 3-12 wk; Hfa-BdP delivered by MDI; FP delivered via MDI in 5 of 9 studies; 4 of 9 studies FP delivered via DPI; Spacers provided in 1 study.	Parallel Group Trials: Beta-agonist use (puffs/day), Mean (SD): Studies = 1 FP: N= 84, -1 (3.67) HFA-BDP: N = 88, -1.3 (7.5) Mean Difference (95% CI): 0.30 (-1.45, 2.05) Beta-agonist use (% reduction in days using beta-agonist), Mean (SD): Studies = 1 FP: N = 97, -18.89 (39.89) HFA-BDP: N = 101, -23.96 (43.11) Mean Difference (95% CI): 5.07 (-6.49, 16.63) Change in rescue medication usage, Mean (SD): Studies = 1 FP: N = 148, -0.5 (1) HFA-BDP: N = 145, -0.6 (1.2) Mean Difference (95%CI): 0.10 (-0.15, 0.35) Change in asthma-free days per week, Mean (SD): Studies = 1 FP N = 141, 3.7 (2.9) HFA-BDP: N = 139, 3.3 (3) Mean Difference (95% CI): 0.40 (-0.29, 1.09)	Parallel Group Trials: Withdrawals (any reason): Studies = 6 FP: N = 501 HFA-BDP = 510 RR (95%CI): N = 1011; 0.73 (0.47, 1.14) Dysphonia: Studies = 2; FP: N= 246 HFA-BDP: N = 250 RR (95%CI): N = 496; 1.53 (0.92, 2.54) Headache n/N: Studies = 1 FP: 0/97 HFA-BDP: 2/101 RR (95%CI): 0.21 (0.01, 4.28)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Lasserson 2010 cont'd							Change in % days without asthma symptoms, Mean (SD): Studies = 1 FP: N = 97, 18.2 (39.4) HFA-BDP: N = 101, 24.32 (44.12) Mean Difference: -6.12 (-17.76, 5.52) Change in AQLQ, Mean (SD): Studies = 1 FP: N = 84, 0.41 (0) HFA-BDP: N = 88, 0.47 (0) Mean difference (95%CI): 0.0 (0.0, 0.0) Change in ACQ, Mean (SD): Studies = 1 FP: N = 148, -0.8 (1) HFA-BDP: N = 145, -1 (1) Mean Difference (95%CI): 0.20 (-0.03, 0.43) Increased Asthma Symptom, n/N: FP: 1/97 HFA-BDP: 1/1010	Oral Candidiasis, n/N: Studies = 1 FP: 3/97 HFA-BDP: 4/101 RR (95%CI): 0.78 (0.18, 3.40) Any Adverse Event,N: Studies = 3 FP: 334 HFA-BDP: 334 RR (95%CI): 0.88 (0.72, 1.08)
Lasserson 2010 cont'd							Admissions to hospital for asthma, n/N: Studies = 1 FP: 0/9 HFA-BDP: 2/20 RR (95%CI): 0.42 (0.02, 7.96) Crossover Trials: Asthma Control Questionnaire: Studies = 1 Mean Difference (95%CI): -0.13 (-0.47, 0.21) Growth (cm): Studies = 1 Mean Difference 0.34 (-0.28, 0.96)	

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Ni Chroinin 2009 (a) Cochrane Government	Inclusion: RCTs in which the combination of ICS + LABA was compared to a similar dose of ICS alone and to a higher dose of ICS alone; patients had to be steroid-naïve; adults and children >=2 years with persistent asthma; medication administered for >=4 weeks Exclusion: Cross-over trials, non-fixed dose treatment arms	28	8050	All RCTS; two main comparisons: (1)ICS + LABA vs. similar dose of ICS (N=24) and (2) ICS+LABA vs. higher dose of ICS (N=4) Duration ranged from 4 weeks to 52 weeks.	5 studies of children (mean range 8-12 years); 23 of adults (mean range 26-45) % female range 49% to 75% All naïve to LABA and ICS and had inadequate asthma control with ongoing symptoms and use of rescue SABA	LABA was either salmeterol (N-22) or formoterol (N=6); ICS included beclomethasone , budesonide, triamcinolone and fluticasone; 15 used single inhaler and 13 used two separate inhalers.	Exacerbations requiring systemic corticosteroids (dichotomous): (1) NSD (RR 1.04; 95% CI 0.73 to 1.47); (2) favors ICS alone (RR 1.24; 95% CI 1.00 to 1.53) Exacerbations requiring hospitalization (dichotomous): (1) NSD (RR 0.38, 95% CI 0.09 to 1.65); (2) NSD (RR 1.00; 95% CI 0.31 to 3.25) Change in % symptom free days @ endpoint: (1) favors ICA+LABA (MD 8.72; 3.75, 13.68) (2) Change in symptom score @ endpoint: (1) favors ICS+LABA (SMD -0.26; -0.37, -0.14)	Risk of SAEs: (1) NSD (RR 1.15; 95% CI 0.64 to 2.09); (2) NSD (RR 1.03; 95% Ci 0.63 to 1.69) Risk of any AEs: (1) NSD (RR 1.02; 95% CI 0.96 to 1.09); (2) NR Risk of withdrawals due to poor asthma control: (1) NSD (RR 0.94; 95% CI 0.63 to 1.41); (2) NSD (RR 0.99; 0.25, 3.95) Risk of withdrawal due to AEs: (1) NSD (RR 1.07; 95% CI 0.67 to 1.71);

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Ni Chroinin 2009 (a) Cont'd							Change in nighttime symptoms @ endpoint: (1) favors ICS+LABA (SMD -0.16; -0.32, 0.00) Change in % nights with no awakenings @ 12 weeks: (1) NSD (MD 3.53; -2.98, 10.05) Change in mean % rescue-free days @ 12 weeks: (1) favors ICS+LABA (MD 9.29; 4.52, 14.05) Change in awakenings requiring SABA/nt: (1) NSD (MD 0.0; -0.11, 0.11) Change in use of rescue fasst-scting b-agonists (puffs/24 hrs) @ endpoint: (1) favors ICS+LABA (MD -0.41; -0.73, -0.09) Change in rescue inhalations/24 hours @ endpoint: (1) NR (2) NSD (SMD 0.06; -0.03,0.15) Change in daytime rescue medication (puffs): (1) NSD (MD -0.20; -0.41, 0.01) Change in nighttime rescue medication (puffs): (1) NSD (MD -0.20; -0.41, 0.01) Change in AQLQ score @ 12 weeks: (1) NSD (MD 0.10; -0.04, 0.24)	Oral thrush: (1) NSD (RR 0.39, 2.12) Hoarseness: (1) NSD (RR 1.97; 0.49, 7.88) (2) NSd (RR 2.01; 0.37, 10.87) Tremor: (1) favors ICS alone (RR 4.71; 1.38, 16.08) Tachycardia or palpitations: (1) NSD (RR 2.77; 0.12, 64.76) Adverse cardiovascular events: (1) NSD (RR 2.77; 0.12, 64.76) Growth (pedatric only): (1) NR (2) favors ICS (cm -0.06; -0.12, 0.00) Deaths: (1) NSD (RR 0.0, 0.0, 0.0)

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Ni Chroinin 2009 (b) Cochrane University	Inclusion: RCTs; children age 2-18; LABA + ICS	31	5572	All RCTS; two main comparisons: (1)ICS + LABA vs. similar dose of ICS (N=24) and (2) ICS+LABA vs. higher dose of ICS (N=7) (1) Duration ranged from <=8 weeks to 52 weeks; (2) duration ranged from 6 weeks to 52 weeks	(1) mean age = 10 years; 36% female; mostly (but not all) inadequately controlled (2) mean age = 10 years; 23% female; almost all inadequately controlled	(1) LABA was either salmeterol (N=10) or formoterol (N=14); ICS was BDP equivalent; 12 used single inhaler and 12 used two separate inhalers. (2) LABA was either salmeterol (4) or formoterol (3); ICS was BDP equivalent; 4 used single inhaler; 3 used separate	Exacerbations requiring systemic corticosteroids: (1) NSD (RR 0.92; 95% CI 0.60 to 1.40); (2) NSD (RR 1.5; 95% CI 0.65 to 3.48) Exacerbations requiring hospitalization: (1) NSD (RR 1.65; 95% CI 0.83 to 3.25); (2) NSD (RR 2.21; 95% CI 0.74 to 6.64) Mean change in symptom score: (1) NSD (SMD -0.04; 95% CI -0.16 to 0.08); (2) NR Change in daytime rescue inhalations @ endpoint: (1) NSD (MD -0.07 puffs/day; 95% CI -0.14 to 0.01); (2) NSD (MD 0.02 puffs/day; -0.16, 0.20) Change in nighttime rescue inhalations @ endpoint: (1) NSD (MD -0.04; -0.36, 0.28)	Risk of serious SAEs: (1) NSD (RR 1.16; 95% CI 0.73 to 1.85); (2) NSD (RR 1.45; 0.63, 3.33) Risk of overall AEs: (1) NSD (RR 1.04; 95% CI 0.98 to 1.10); (2) NSD (RR 1.05; 95% CI 0.9 to 1.23) Risk of withdrawals due to poor asthma control: (1) NSD (RR 0.79; 95% CI 0.42 to 1.48); (2) NSD (RR 0.33; 0.01, 8.02) Withdrawal due to AE: (1) NSD (RR 0.78; 95% CI 0.52 to 1.19); (2) NSD (RR 1.44; 95% CI 0.25 to 8.42) Withdrawal for any reason: (1) Lower risk with ICS+LABA (RR 0.79; 95% CI 0.67 to 0.93); (2) NSD (RR 0.71; 0.42, 1.20) Risk of oral candidiasis: (1) NSD (RR 3.78; 95% CI 0.63 to 22.75) (2) NR

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Ni Chroinin 2009 (b) cont'd							Change in nighttime awakening (# nights) @ endpoint: (1) NSD (MD 0.20; -2.21, 2.61) Change in symptom-free days @ endpoint: (1) NSD (WMD 1.30%; 95% CI -3.12 to 5.71); (2) NR	Risk of tremor: (1) NSD (RR 3.07; 95% CI 0.38 to 25.05) (2) NR Risk of tachycardia or palpitations: (1) NSD (RR 0.40; 95% CI 0.05 to 3.25) (2) NR Risk of adverse cardiovascular events: (1) NSD (0.31; 0.01, 7.49) (2) NR Risk of headache: (1) NSD (RR 1.10; 95% CI 0.90 to 1.33); (2) NSD (RR 1.37; 95% CI 0.98 to 1.90) Change in height (cm) at one year: (1) NSD (MD 0.60; -0.34, 1.54) (2) favors ICS+LABA (1.2 cm/yr; 95% CI 0.72 to 1.7)
Rodrigo 2009 NR None	(1) Children and adults with a clinical diagnosis of asthma for at least 6 months prior to study entry. (2) Inhaled LABA (delivered via metered dose or dry powder inhalers) as monotherapy vs. placebo or LABA added to ICS (one or two separate inhalers) vs. similar or higher dose of ICS (with the same ICS in both arms), (3) Studies of at least 4 weeks of duration. (4) Randomized (parallel group or cross-over) controlled trials without language restriction. (5) Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed.	92	74,092	RCTs	Children and adults with a clinical diagnosis of asthma for at least 6 months prior to study entry	LABA vs. placebo Laba + ICS vs. ICS	ICS vs placebo rate of withdrawals in LABA patients (2.9%) compared with placebo (4.4%) (RR 0.68; 95% CI, 0.61–0.76, I2 ¼0%, *P* < 0.0001, fixed-effect model) with a NNT = 68 (95% CI, 53–93), Asthma related deaths in studies that had any 3.83 (95% CI, 1.21–12.14, I2 ¼ 0%, p ¼ 0.02, fixed-effects model) which represents one excess of death for every 1226 LABA treated patients (95% CI, 703–10.585). When all trials with and without deaths were incorporated in the analysis, the incidence was 0.071% in the LABA group and 0.016% in the placebo group, with a NNH of 1824 (95% CI, 1020–19.261). LABA plus ICS compared with ICS	ICS vs placebo life-threatening events between LABA and placebo (LABA rate 0.37% and placebo 0.24%) Severe AE cumulative incidence was 14.0% in the LABA group and 18.2% in the placebo group, with a RR = 0.80; 95% CI, 0.73–0.88, I2 = 16%, *P* < 0.0001, fixed-effects model (NNT= 24; 95% CI,17–39). LABA plus ICS compared with ICS Incidence of AEwas 11.1% in the LABA plus ICS group and 16.1% in the ICS group, with a RR = 0.73; 95% CI, 0.67– 0.79, I2 = 0%, *P* < 0.00001, fixed-effects model (NNT=20; 95% CI, 16–26). Withdrawals due to AEs (3.0% in the LABA group and 4.6% in the placebo group) (RR = 0.64; 95% CI, 0.52–0.78, I2 = 7%, *P* < 0.0001, fixed-effects model) with a NNT of 91

Evidence Table 4. Systematic Reviews: Key questions 1 and 2

Author Year Research Group Funding	Eligibility Criteria (Inclusion and Exclusion)	Number of studies included	Total number of patients	Characteristics of included studies	Characteristics of included populations	Characteristics of Interventions	Main efficacy and effectiveness outcomes and results	Main Harms Outcomes and Results
Rodrigo 2009 cont'd							Hospitalization incidence was 1.2% in the LABA group and 2.0% in the placebo group (NNT = 135; 95% CI, 90–282), incidence of asthma-related deaths (0.11% LABA/ICS group and 0% in the ICS group, RR = 2.96; 95% CI, 0.50–17.57, I2 = 0%, P = 0.23, fixed-effects model). LABA plus inhaled corticosteroids (ICS) with ICS Asthma exacerbations requiring hospitalization Adults vs. children RR 0.52 (95% CI 0.40–0.66) vs. RR 3.38 (95% 0.94–12.15) P = 0.004	Asthma exacerbations requiring oral CCS use Formoterol vs. Salmeterol RR 0.69 (95% CI 0.62–0.77) vs. RR 0.85 (95% CI 0.74–0.99) P = 0.02 LABA plus inhaled corticosteroids (ICS) with ICS Withdrawals due to asthma exacerbations Adults vs. children 0.69 (0.53–0.90) vs. RR 0.69 (95% CI 0.48–0.98) P = 0.99 Life-threatening asthma exacerbations Adults vs. Children RR 0.95 (95% CI 0.51–1.76) vs. RR 0.79 (95% CI 0.35–1.79) P = 0.72 Asthma exacerbations requiring oral CCS use Adults vs. children RR 0.75 (95% CI 0.69–0.82) vs. RR 0.73 (95% CI 0.43–1.26) P = 0.92

Evidence Table 5. Internal Validity: Systematic reviews key questions 1 and 2

Author	Year	Trial or Reseach Group Name	Quality Rating Good, Fair, Poor	Is the review based on a focused question of interest? Yes, No, CND	Did the search strategy employ a comprehensive, systematic, literature search? Yes, No, CND	Are eligibility criteria for studies clearly described? Yes, No, CND
Bateman	2008	NA	Poor	Yes	Yes	Yes
Breton	2008	NA	Poor	No	Yes	Yes
Jaeschke	2008	NA	Fair	Yes	Yes	Yes
Lasserson	2010	Cochrane	Good	Yes	Yes	Yes
Ni Chroinin	2009	Cochrane	Good	Yes	Yes	Yes
Ni Chroinin	2009	Cochrane	Good	Yes	Yes	Yes
Key Question 1						
Castro-Rodriguez	2010	None	Good	Yes	Yes	Yes
Ducharme	2010	Cochrane	Good	Yes	Yes	Yes
Ducharme	2010	Cochrane	Good	Yes	Yes	Yes
Rodrigo	2009	NA	Good	Yes	Yes	Yes
Key Question 2						
Adams	2008	Cochrane	Good	Yes	Yes	Yes
Cates	2008	Cochrane	Good	Yes	Yes	Yes
Cates	2008	Cochrane	Good	Yes	Yes	Yes
Cates	2010	Cochrane	Good	Yes	Yes	Yes
Cates	2009	Cochrane	Good	Yes	Yes	Yes
Cates	2009	Cochrane	Good	Yes	Yes	Yes
Joos	2008	Cochrane	Fair	Yes	Yes	Yes
Lasserson	2010	Cochrane	Good	Yes	Yes	Yes

Evidence Table 5. Internal Validity: Systematic reviews key questions 1 and 2

Author	Did at least 2 people independently review studies? Yes, No, CND	Did authors use a standard method of critical appraisal before including studies? Yes, No, CND	Was publication bias assessed? Yes, No, CND	Was heterogeneity assessed and addressed? Yes, No, CND	Was the approach used to synthesize information adequate and appropriate? Yes, No
Bateman	Yes	No	Yes	Yes	Yes
Breton	Yes	No	No	No	No
Jaeschke	Yes	No	No	Yes	Yes
Lasserson	Yes	Yes	CND	Yes	Yes
Ni Chroinin	Yes	Yes	Yes	Yes	Yes
Ni Chroinin	Yes	Yes	Yes	Yes	Yes
Key Question 1					
Castro-Rodriguez	Yes	Yes	CND	Yes	Yes
Ducharme	Yes	Yes	Yes	Yes	Yes
Ducharme	Yes	Yes	Yes	Yes	Yes
Rodrigo	Yes	Yes	Yes	Yes	Yes
Key Question 2					
Adams	Yes	Yes	CND	Yes	Yes
Cates	Yes	Yes	Yes	Yes	Yes
Cates	Yes	Yes	Yes	Yes	Yes
Cates	Yes	Yes	Yes	Yes	Yes
Cates	Yes	Yes	Yes	Yes	Yes
Cates	Yes	Yes	Yes	Yes	Yes
Joos	Yes	No	No	Yes	Yes
Lasserson	Yes	Yes	Yes	Yes	Yes

Evidence Table 6. Observational studies key questions 2 and 3

Author Year Trial Name Country	Aim(s) of Study	Study Design Study Duration Setting	Inclusion criteria Exclusion criteria	Asthma severity	Overall Sample Size	Comparison Groups - Sample Sizes	Comparison Groups - Medications/ Interventions Received
Blais 2009	To investigate the association between doses of ICS during the first trimester of pregnancy and the risk of congenital malformations among women with asthma.	Cohort 12 years	Inclusion Criteria: Having at least 1 pregnancy from a woman with asthma ending in a delivery (live birth or still birth) between 1990 and 2002; 13-50 years old at conception; at least 1 diagnosis of asthma (ICD-9 code 493); at least 1 prescription for an asthma medication at any time in the previous 2 years or during pregnancy; covered by the RAMQ Drug Insurance Plan for at least 1 year before and throughout the duration of the pregnancy	All	13,280 pregnancies, 10,099 women	G1 (no ICS use): N = 8, 734 pregnancies G2 (>0-1000 micg ICS daily during 1st trimester): N = 4,392 pregnancies G3 (>1,000 micg ICS daily during 1st trimester): N = 154 pregnancies	G1: no ICS use G2: >0 - 1,000 micg ICS daily during 1st trimester (mean daily dose 185.5ug+/- SD 192.7) G3: >1,000 micg ICS daily during 1st trimester (mean daily dose 1469.4ug +/- SD 434.0)

Evidence Table 6. Observational studies key questions 2 and 3

Author Year Trial Name Country	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)	Smokers (%)	Method and timing of adverse event assessment	Adverse events	Funding source
Blais 2009	G1: age 13-18 = 6.6%, age 19-34 = 87.1%, age 35-45 = 6.3% ethnicity NR; 100% female G2: age 13-18 = 7.2%, age 19-34 = 85.8%, age 35-45 = 5.8% ethnicity NR; 100% female G3: age 13-18 = 6.5%, age 19-34 = 80.5%, age 35-45 = 13.0% ethnicity NR; 100% female	NR	All cases of a congenital malformation were identified within the cohort using ICD-9 diagnosis codes specific to congenital malformations recorded in the RAMQ and MED-ECHO databases. An infant was identified as a case if the infant had at least 1 diagnosis of a congenital malformation at birth or during the first year of life recorded in the databases. The geneticist also classified the malformations as either minor or major. A congenital malformation was classified as major if it could be life-threatening or caused major cosmetic defects and if there was at least 1 hospitalization related to the malformation during the first year of life. All and major congenital malformations were the outcomes under study.	1633 congenital malformations in 1257 infants 1125 major malformations in 782 infants Crude prevalence of malformations: G1: All malformations = 9.6% (n=841), major malformations = 5.9% (n=519) G2: all malformations = 9.0% (n=394) major malformations = 5.7% (n=248) G3: all malformations = 14.3% (n=22), major malformations = 9.7% (n=15)	FRSQ (Fonds de la recherche en sante du Quebec), Canadian Insitutes of Health Research, Canadian Foundation for Innovation

Evidence Table 6. Observational studies key questions 2 and 3

Author Year Trial Name Country	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)	Smokers (%)	Method and timing of adverse event assessment	Adverse events	Funding source
Blais 2009 cont'd				Adjusted RRs, all malformations (Table II): G1: 1.08 (0.94-1.24) G2: Reference G3: 1.66 (1.02-2.68) Adjusted RRs, major malformations (Table II): G1: 1.06 (0.89-1.26) G2: Reference G3: 1.67 (0.91-3.06) The 154 women who used more than 1000ug/d ICS were significantly more likely to have a baby with a malformation that the 4392 women who used >0-1000ug/d (RR 1.63, 95% CI 1.02-2.60)	

Evidence Table 6. Observational studies key questions 2 and 3

Author Year Trial Name Country	Aim(s) of Study	Study Design Study Duration Setting	Inclusion criteria Exclusion criteria	Asthma severity	Overall Sample Size	Comparison Groups - Sample Sizes	Comparison Groups - Medications/ Interventions Received
Kelly 2008 CAMP USA	To assess further the potential effects of both bursts of OCSs and long-term use of ICSs on bone mineral accretion in the CAMP cohort followed prospectively.	Cohort Median of 7 years Primary Care	Inclusion Criteria Mild-to-moderate asthma, as defined by the presence of symptoms or by the use of an inhaled bronchodilator at least twice weekly or the use of daily medication for asthma. Airway responsiveness to methacholine, as indicated by the concentration of the drug that caused a 20 percent decrease in the FEV1, was 12.5 mg per milliliter or less. All included patients had a baseline BMD determination and at least 1 follow-up BMD. Exclusion Criteria FEV1 less than 65% of normal when not taking b2-agonists for greater than 4 hours and theophylline for greater than 24 hours, (2)any other active pulmonary diseases, (3)pulmonary function suggesting a restrictive defect or irreversible lung disease, (4)severe chronic sinusitis or nasal polyposis, (5) change in allergy immunotherapy in the month before interview, (6) used more than 4 sprays of nasal steroids (beclomethasone) daily at the time of randomization, (7) were currently using antigastroesophygeal reflux medication, or (8) were currently participating in another pharmaceutical, immunotherapy, respiratory, or asthma study. Also, pregnancy, the inability to perform acceptable spirometry, inability to complete the methacholine challenge test, or evidence that the child's family might not adhere to protocol requirements. Prednisone bursts more than 5 times over the prior year, had more than 1 hospitalization for asthma in the year before their initial interview, or required intubation for asthma at any time. Patients were also excluded if they had an initial DEXA from one study center that could not be standardized.	Mild to Moderate	1041 patients enrolled in CAMP 941 elected to continue in the follow-up study 877 were included in this analysis	Boys: n = 531 Girls: n = 346 Cumulative OCS courses (boys): 0: n = 108 >0 and <5: n = 268 ≥5: n= 155 Cumulative OCS courses (girls): 0: n = 66 >0 and <5: n = 168 ≥5: n = 112 Cumulative ICS, mg (boys): 0: n = 189 1-437: n = 126 ≥ 438: n = 216 Cumulative ICS, mg (girls): 0: n = 118 1-437: n = 84 ≥ 438: n = 144 Passive smoking (boys): No: n = 318 Yes: n = 213 Passive smoking (girls): No: n = 178 Yes: n = 168 Active smoking (boys): No: n = 503 Yes: n = 28 Active smoking (girls): No: n = 320 Yes: n = 26	Participants received budesonide 200 micg bid, nedocromil 4 mg bid, or placebo for 4 to 6 years, followed by a 4-year posttrial follow-up study. Patients could receive predisone bursts and open-label ICS during the trial, and medication during the posttrial follow-up was directed by primary care physicians. Numbers of patients receiving each treatment are not reported for the various study groups. For this analysis, ICSs include the blinded budesonide and un-blinded ICSs during the CAMP treatment phase nad then any ICS that the patients' primary care physicians prescribed during the follow-up study.

Evidence Table 6. Observational studies key questions 2 and 3

Author Year Trial Name Country	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)	Smokers (%)	Method and timing of adverse event assessment	Adverse events	Funding source
Kelly 2008 CAMP USA	Boys: median age 8.8 (baseline visit), 16.6 (last follow-up visit); 75.5% white/other, 13.2% black, 11.3% hispanic Girls: median age 8.9 (baseline visit), 16.6 (last follow-up visit); 78.3% white/other, 14.4% black, 7.2% hispanic	Boys: 28/531 (5.3%) Girls: 26/346 (7.5%)	BMD measurements made at baseline, yearly during the treatment phase, and twice during the follow-up study, at 7 and 9 years after randomization. Lumbar spine BMD measrued by DEXA using either the Hologic QDR-1500 (6 centers) or the Lunar DPX at 2 centers initially. Density measures on an anthropomorphic spine Phantom were obtained annually at each clinical center; these density measures were used to derive equations for converting density measurements to a Hologic fan-beam equivalent. BDM z scores were calculated using CAMP internal references, mean, and SDD of patients in the lowest to medium category for cumulative oral and inhaled corticosteroid dosages. Fractures were prospectively collected on the data history forms.	Growth rate (g/cm^2) By cumulative ICS, mg (boys): 0: 0.051 (reference) 1-437: 0.046 (p=0.0040) > 438: 0.048 (p=0.0300) Growth rate (g/cm^2) By cumulative ICS, mg (girls): 0: 0.052 (reference) 1-437: 0.052 (p=0.9400) >438: 0.051 (p=0.5400) Fractures: Boys: 40 fractures (11 per 1000 person-years) Girls: 27 fractures (12 per 1000 person-years). Neither OCS nor ICS use was related to time of first fracture in boys or girls.	Contracts with the National Heart, Lung, and Blood institute; General Clinical Research Center grants; National Center for Research Resources grant

Evidence Table 7. Internal Validity: Observational studies key questions 2 and 3

Author	Year	Trial Name	Quality Rating for Harms Good, Fair, Poor	Were comparison groups selected from the same source population? Yes, No, CND	Were subjects recruited over the same time period? Yes, No, CND	Were measurements equal, valid, and reliable? Yes, No, Mixed	Were outcome assessors masked? Yes, No, CND	Were outcomes presepecified and defined? Yes, No, CND
Blais	2009		Fair	Yes	Yes	Yes	CND	Yes
Kelly	2008	CAMP	Fair	Yes	Yes	Yes	CND	Yes

Evidence Table 7. Internal Validity: Observational studies key questions 2 and 3

Author	Was time of follow-up equal for all groups? Yes, No, CND	Overall attrition high? (≥20%) Yes, No, CND	Was differential attrition high? (≥15%) Yes, No, CND	Did the study design and/or statistical analyses account for confounding? Yes, No, CND	Was the length of followup adequate? Yes, No, CND	Methods of harms assessment
Blais	Yes	No	No	Yes	Yes	All cases of a congenital malformation were identified within the cohort using ICD-9 diagnosis codes specific to congenital malformations recorded in the RAMQ and MED-ECHO databases. An infant was identified as a case if the infant had at least 1 diagnosis of a congenital malformation at birth or during the first year of life recorded in the databases. The geneticist also classified the malformations as either minor or major. A congenital malformation was classified as major if it could be life-threatening or caused major cosmetic defects and if there was at least 1 hospitalization related to the malformation during the first year of life. All and major congenital malformations were the outcomes under study.
Kelly	CND	No	CND	CND	Yes	BMD measurements made at baseline, yearly during the treatment phase, and twice during the follow-up study, at 7 and 9 years after randomization. Lumbar spine BMD measrued by DEXA using either the Hologic QDR-1500 (6 centers) or the Lunar DPX at 2 centers initially. Density measures on an anthropomorphic spine Phantom were obtained annually at each clinical center; these density measures were used to derive equations for converting density measurements to a Hologic fan-beam equivalent. BDM z scores were calculated using CAMP internal references, mean, and SDD of patients in the lowest to medium category for cumulative oral and inhaled corticosteroid dosages. Fractures were prospectively collected on the data history forms.