

Trial	Drug Therapy	Population	Results	Comments
SMART ¹ 2006 Health Canada Advisory 2003 & 2005	Salmeterol MDI 42ug BID vs Pl. R,DB,PC,Observational n=26,355; 28wks but terminated early (2003)	Asthma ^{>12yrs, Mean 39yr} Non-LABA pts	↑ life threatening experiences & asthma related death ^{37vs22; NNH=909} & asthma related death ^{13vs3; NNH= 1319} in salmeterol group	- study designed as surveillance trial due to previous data suggesting increased harm with B2 agonists - salmeterol monotherapy not adequate & possibly harmful, specifically in blacks & those not on ICS at baseline - "misleading data" to FDA to downplay results discussion ²
Wolfe ³ 2006	Formoterol 24ug vs 12ug BID vs 12ug BID+on demand vs Pl. n=2,085; 16wks	Adult ^{age ≥12, stable} persistent	Exacerbations: 6.3% vs 5.9% vs 4.4% vs 8.8% (NS); formoterol gps ↑ FEV ₁	- high dose formoterol not associated with more asthma exacerbations than lower formoterol doses
Rabe ⁴ 2006	Budesonide 320ug OD+SABA PRN Vs Symbicort bud/form 160/9ug OD + PRN	Asthma ^{mild-moderate} 11-79yrs old 6month follow up n=697	Severe Exacerbations (including PEF falls): 12% vs 27% ^{p<0.01}	- using Symbicort for maintenance and relief reduced risk & rate of severe asthma exacerbations & need for systemic steroids; asthma symptoms also improved. - severe exacerbations: prednisone 30mg po OD x10 days
STAY ⁵ 2005	Budesonide 320ug BID+SABA PRN Vs Symbicort bud/form 80/4.5ug BID + SABA PRN Vs Symbicort 80/4.5ug BID & PRN (Kids 4-11yr only at HS)	Asthma ^{mod-severe} 4-80yrs old 1yr follow up n=2,760	Severe Exacerbations (including PEF falls): 28% vs 27% vs 16% ^{p<0.001}	- using Symbicort for maintenance and relief reduced risk & rate of severe asthma exacerbations & need for systemic steroids; asthma symptoms also improved. - severe exacerbations: prednisone 30mg po OD x10 days
GOAL ⁶ 2004	ADVAIR 50/100 – 50/500ug BID titrated to achieve/maintain goal vs Fluticasone ≥100-500ug BID n=3,421; 1yr	Asthma, ^{uncontrolled} varying severity 12-80yrs old Non-LABA pts	Total Control: 41% vs 28% NNT=8 _{1yr} SAE: 4% vs 3% NNH=100 ^{eg. asthma/pneumonia}	- Advair more effective than fluticasone in achieving control & ↑quality of life (ICS alone & low Advair dose often effective) - drug related ADR: oral candidal inf 3%, hoarseness 3%vs2%) - if not totally controlled after phase 2: prednisone 0.5mg/kg Max 60mg x 10d
Concept ⁷ 2005	ADVAIR 50/250ug BID vs Symbicort bud/form 400/12ug BID n=688; 1yr; Diskus	Asthma, ^{persistent} adults ^{Mean 45yrs}	Symptom-free days 58.8 vs 52.1% ^{p=0.034} for the adjustable Symbicort dose	-stable Advair dose had more symptom-free days & less exacerbations than the adjustable Symbicort dose group (but ↓ dose to OD Symbicort in many pts which is not always effective)
Overbeek ⁸ 2005	budesonide 100ug Bid + pl vs bude 100ug BID + 12ug formoterol	Asthma ^{stable mild} n=40	After 8wks ↑budesonide 400ug BID x another 8 wks: bronchial biopsies done	100ug BID equivalent; no sig. additional anti-inflammatory effects by adding formoterol or ↑budesonide dose 4 fold
START ⁹ 2005	Budesonide 200ug OD (age <11yr) 400ug OD (age ≥11yr) Vs Pl	Asthma-mild, persistent; age5-66 n=7,221 3yr follow up	No difference in death / SAE Fewer asthma related SAE with budes. 319 pregnancies reported.	- OD Budesonide safe & effective in mild, persistent newly detected children & adults. Oral candidiasis 1.2% budes vs 0.5% pl.
Ram ¹⁰ 2005 Cochrane	Systematic Review: LABA+ICS vs LRTA+ICS	Asthma pts on stable dose ICS	≥1 exacerbation requiring systematic steroids: 9% vs 11% NNT=38 ^(CI 23-247)	-LABAs appear preferable to LTRAs for add-on to ICS therapy; however did not assess long-term compliance, seasonal, exercise, age or aspirin sensitive factors
Gibson ¹¹ 2005 Cochrane	Systematic Review: LABA+reduced dose ICS vs mod-high dose ICS	Adults on daily ICS	No difference in need for oral steroids; ICS sparing effect demonstrated	-adding LABA to mod-high dose ICS allows for minimizing ICS dose
Ni ¹² 2005 Cochrane	Systematic Review: LABA+ICS vs ICS	Asthmatics; poor control	Combination reduced likelihood of exacerbation NNT=18/yr	- LABA safe and effective as add-on agents in patients inadequately controlled on ICS
Adams ¹³ 2005 Cochrane	Systematic Review: Fluticasone dose effect in chronic asthma: Low vs medium vs high dose	Children & adults	Low vs medium vs high dose (100-200ug, 400-500ug, 800-1000ug)	- the effect of fluticasone is dose dependent; however its magnitude is small and clinical impact open to interpretation - in moderate disease, mod doses similar to high for control - very high dose (2000ug/d) may lower oral pred requirement
Lasserson ¹⁴ 2005 Cochrane	Systematic Review: Fluticasone vs HFA-beclomethasone dipropionate	predominantly adults	Similar doses had similar lung function	- no significant difference in FEV1 or peak flow at a dose ratio of 1:1; however, data limited
Masoli ²⁰⁰⁴	Meta-analysis ¹⁵ : Fluticasone dose			- most benefit in adolescents/adults with asthma is at 200ug/d
Masoli ²⁰⁰⁴	Meta-analysis ¹⁶ : Budesonide dose			- most benefit at 400ug/d; max effect at 1000ug/d
IMPACT ¹⁷ 2005	Intermittent therapy with action plan vs 200ug budesonide BID vs 20mg zafirlukast BID	Adult ^{age 18-65 mild} persistent asthma n=225; 1yr follow up	Similar increases in PEF and rates of exacerbation despite intermittent group using budesonide only 0.5weeks/yr	- intermittent steroid (800ug budesonide BID x10 days or 0.5mg/kg prednisolone x5d) -secondary endpoints slightly favored daily ICS

- ¹ Health Canada Sep/05 Salmeterol: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/serevent_2_hpc-cps_e.pdf; Health Canada Salmeterol Aug/03 http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/serevent_hpc-cps_e.pdf;
Health Canada Sep/05 Formoterol: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/oxeze_hpc-cps_e.html
GlaxoSmithKline Clinical trial registry SLGA5011: <http://ctr.gsk.co.uk/Summary/salmeterol/studylist.asp> & Nelson HS, et al. The salmeterol multicenter asthma research (**SMART**) trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006 Jan;129(1):15-26. (Martinez FD. Safety of long-acting beta-agonists--an urgent need to clear the air. *N Engl J Med*. 2005 Dec 22;353(25):2637-9.)
- ² Lurie P, Wolfe SM. Misleading data analyses in salmeterol (**SMART**) study. *Lancet*. 2005 Oct 8;366(9493):1261-2; discussion 1262.
- ³ Wolfe J, Laforce C, Friedman B, Sokol W, Till D, Della Cioppa G, van As A, Formoterol, 24 microg bid, and serious asthma exacerbations: similar rates compared with formoterol, 12 microg bid, with and without extra doses taken on demand, and placebo. *Chest*. 2006 Jan;129(1):27-38.
- ⁴ Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Aizenza T, Lier PA, Jorup C. Budesonide/Formoterol in a Single Inhaler for Maintenance and Relief in Mild-to-Moderate Asthma: A Randomized, Double-Blind Trial. *Chest*. 2006 Feb;129(2):246-56.
- ⁵ O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever (Adults: 80/4.5ug bid & prn) medication in asthma. *Am J Respir Crit Care Med*. 2005 Jan 15;171(2):129-36. (**STAY** trial) *Epub* 2004 Oct 22.
- ⁶ Bateman ED, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control Study (**GOAL**). *Am J Respir Crit Care Med* 2004;170:836-44. (Max Diskus dosages were Advair 50/500ug bid vs Flovent 500ug bid)
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- ⁸ Overbeek SE, et al. **Formoterol added** to low-dose budesonide (100ug bid) has no additional antiinflammatory effect in asthmatic patients. *Chest*. 2005;128(3):1121-7.
- ⁹ Sheffer AL, Silverman M, Woolcock AJ, Diaz PV, Lindberg B, Lindmark B. Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study. *Ann Allergy Asthma Immunol*. 2005 Jan;94(1):48-54.
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- ¹¹ Gibson PG, Powell H, Ducharme F. Long-acting beta2-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2005 Oct 19;(4):CD005076.
- ¹² Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, Ducharme FM. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. *Cochrane Database Syst Rev*. 2005 Oct 19;(4):CD005535.
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- ¹⁶ Masoli M, Holt S, Weatherall M, Beasley R. Dose-response relationship of inhaled budesonide in adult asthma: a meta-analysis. *Eur Respir J*. 2004 Apr;23(4):552-8.
- ¹⁷ Boushey HA, Sorkness CA, King TS, et al, for the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. **IMPACT** trial. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005; 352: 1519-528 (Ramey JT, Ledford D. Daily corticosteroids were not better than as-needed corticosteroids in mild persistent asthma. *ACP J Club*. 2005 Nov-Dec;143(3):60.)

O'Byrne PM, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the **OPTIMA** randomized trial (1yr) . *Am J Respir Crit Care Med*. 2001 Oct 15;164(8 Pt 1):1392-7. The 698 corticosteroid free patients (Group A) were assigned to twice daily treatment with 100 microg budesonide, 100 microg budesonide plus 4.5 microg formoterol, or placebo. The 1,272 corticosteroid-treated patients (Group B) were assigned to twice daily treatment with 100 microg budesonide, 100 microg budesonide plus 4.5 microg formoterol, 200 microg budesonide, or 200 microg budesonide plus 4.5 microg formoterol. Thus, in corticosteroid-free patients, low dose inhaled budesonide alone reduced severe exacerbations and improved asthma control, and in patients already receiving inhaled corticosteroid, adding formoterol was more effective than doubling the corticosteroid dose.