Evidence Table 15. Pharmacologic Therapy: Bronchodilators—Safety of Long-Acting Beta$_2$-Agonists

Abbreviations used in table:

AE	**adverse event**
AG	**adrenoceptor agonists**
AQLQ	**Asthma Quality of Life Questionnaire**
AUC	**area under the curve**
COPD	**chronic obstructive pulmonary disease**
DAE	**discontinuation due to adverse event**
DPI	**dry powder inhaler**
ED	**emergency department**
$FEF_{25\%–75\%}$	**forced expiratory flow between 25% and 75% of vital capacity**
FEV_1	**forced expiratory volume in 1 sec.**
FVC	**forced vital capacity**
ICS	**inhaled corticosteroid**
IGCS	**inhaled glucocorticosteroid**
ITT	**intent-to-treat**
LABA	**long-acting beta$_2$-agonists**
MDI	**metered-dose inhaled**
OCS	**oral corticosteroid**
PEF	**peak expiratory flow**
RR	**relative risk**
SABA	**short-acting beta-agonist**
SAE	**serious adverse event**

*** indicates primary outcome**

Evidence Table 15. Pharmacologic Therapy: Bronchodilators—Safety of Long-Acting Beta$_2$-Agonists

Citation (Sponsor)	Study Design	Purpose/ Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
Lipworth et al. Effects of adding a leukotriene antagonist or a long-acting beta(2)-agonist in asthmatic patients with the glycine-16 beta(2)-adrenoceptor genotype. Am J Med 2000;109(2): 114–121.	Randomized placebo-controlled crossover study	To compare the effects of regular treatment with inhaled formoterol or oral zafirlukast on bronchial hyperrespon-siveness and on airway inflammation in patients who were homozygous for the glycine-16 allele and who were already being treated with inhaled corticosteroids	24 (24)	**Age** 19–66 yr, mean = 39 yr **Gender** 37% male, 63% female	Mild-to-moderate asthma Homozygous for glycine-16 allele and being treated with ICS FEV_1 % pred. mean = 76 FEV_1 mean = 2.42 L FEV_1 reversibility mean = 13.3% ICS mean = 592 mcg, median 400 mcg	**Arm 1** Formoterol fumarate with placebo tables twice daily **Arm 2** Zafirlukast tablets with placebo inhaler twice daily **Arm 3** Placebo inhaler and placebo tablets both twice daily	12 mcg 20 mg	5 weeks (each treatment 1 week with 1-week wash out between treatments) after 1-week run-in period Two puffs of inhaled ipratropium bromide (Atrovent Foirte 40 mcg/puff) used as first-line rescue with albuterol as second-line rescue.	*No difference in geometric mean methacholine provocative doses between formoterol (1.9-fold) and zafirlukast (1.5-fold) groups after 1 week of treatment Compared with placebo, zafirlukast produced 1.7-fold difference in geometric mean exhaled nitric oxide ($p < 0.05$), and formoterol produced a 1.2-fold difference ($p > 0.05$). No difference between formoterol and zafirlukast in improvement in PEF			
Bensch et al. A randomized, 12-week, double-blind, placebo-controlled study comparing formoterol dry powder inhaler with albuterol metered-dose inhaler. Ann Allergy Asthma Immunol 2001;86(1):19–27.	Multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study (26 clinical sites in the United States)	To evaluate two doses of formoterol administered via the Aerolizer inhaler in patients with mild to moderate persistent asthma	541 (458 completed; 535 in efficacy analysis; 541 in ITT analysis)	**Age** >12 yr, mean = 35.5 yr **Gender** 41% male, 59% female **Ethnicity** 88% Caucasian, 6% Black, 7% Other	Mild-to-moderate persistent asthma Duration of asthma mean = 18.9 yr 51% ICS 17% maintenance theophylline FEV_1 % pred. mean = 66 FEV_1 mean = 2.2 L FVC mean = 3.4 L $FEF_{25\%–75\%}$ mean = 1.6 L/s PEF mean = 342 L/min	**Arm 1:** Formoterol (F-12) (n=136) **Arm 2:** Formoterol (F-24), (n=135) **Arm 3:** Albuterol (n=134) **Arm 4:** Placebo (n=136), Overall, 83 withdrew from study.	12 mcg twice daily via Aerolizer 24 mcg twice daily via Aerolizer 180 mcg 4 times daily via metered-dose inhaler	12 weeks after 2-week single-blind, placebo lead-in period All patients received labeled albuterol for use as rescue medication. Post spirometric data at 4, 8, and 12 weeks at intervals throughout a 12-hour observation period	*After 12 weeks, all FEV_1 % pred. values for both formoterol groups were higher than those for placebo ($p < 0.001$) except for 0-hour value for F-12. F-12 and F-24 groups did not differ in FEV_1 % pred. Morning and evening PEF favored each formoterol group compared with placebo ($p < 0.003$) and albuterol ($p < 0.001$).	Patients in each group had either little change or a decrease in mean number of premature ventricular beats per hour. No clinically significant changes in mean blood pressure or pulse rate Clinical laboratory test results indicated no clinically significant mean changes and no significant differences among the groups.	Greater percentage of symptom-free treatment days for F-12 (52%) and F-24 (53%) vs. placebo (33%), $p < 0.001$. Albuterol and placebo groups differed ($p=0.008$). Percentage of days without nocturnal awakenings greater for F-12 (72%) and F-24 (59%) vs. placebo (53%) and albuterol (59%), $p < 0.001$. Daily and nocturnal asthma scores were better for F-12 and F-24 than for placebo. Significantly less rescue medication used by formoterol and albuterol groups than by placebo group; no difference for F-12 vs. F-24 groups.	No difference in AE reported: 68% of F-12, 76% of F-24, 70% of albuterol, and 71% of placebo groups. 3 withdrew from F-12, 6 from F-24, 5 from albuterol, and 6 from placebo for asthma-related AE.

Citation (Sponsor)	Study Design	Purpose/ Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
Hirono et al. Left ventricular diastolic dysfunction in patients with bronchial asthma with long-term oral beta$_2$-adrenoceptor agonists. Am Heart J 2001; 142(6):E11. (Ministry of Education, Science, Sports, and Culture, Japan)	One retrospective chart review and two prospective observation studies	To describe clinical features and cardiac pump function of patients with bronchial asthma during long-term oral administration of beta$_2$-adrenoceptor agonists (AG)	**Study 1:** Retrospec-tive, 143 patients **Study 2:** Prospective, 48 of the 143 patients + 20 controls **Study 3:** 11 of the 48 in a withdrawal study	**Study 1:** **Age** mean = 54 yr **Study 2:** **Age** mean = 47 yr **Gender** 51% male, 49% female	**Study 1** FEV_1 % pred. mean = 64 FVC mean = 3.1 **Study 2** FEV_1 % pred. mean = 75 FEV_1 mean = 3.3 L Among 48 patients, 50% used theophylline, 69% corticosteroids, 40% inhaled beta$_2$-agonists	**Study 1** Chart Review: 74 cases treated with oral beta$_2$-AG and 69 without oral beta$_2$-AG **Study 2** **Group 1** 26/74 cases treated with oral beta$_2$-AG **Group 2** 22/69 without oral beta$_2$-AG **Group 3 (control)** 21 healthy volunteers		**Study 3:** 2-week cessation of beta$_2$-AG (n=11/26)	**Study 2:** FEV_1 significantly lower in group 1 than in group 3 (control).	**Study 1:** No differences in angina, ventricular arrhythmia, hypertension between groups **Study 2:** No difference in right ventricular function between groups Group 1 (oral beta$_2$-AG group) showed higher heart rate, lower left ventricular E/A, longer DT, and lower plasma norepinephrine concentration than those in groups 2 & 3 ($p < 0.05$). **Study 3:** Cessation for 2 weeks improved left ventricular E/A by 50%, shortened DT by 18%, increased %FS by 6%, and increased plasma level of norepinephrine by 64% ($p < 0.01$).	**Study 1:** No difference in remedies for asthma between those with and without oral beta$_2$-AG.	**Study 1:** Incidence of nonfatal heart failure associated with oral nitrates was more frequent in oral beta$_2$-AG group ($p < 0.05$).
Martin & Shakir. Age- and gender-specific asthma death rates in patients taking long-acting beta$_2$-agonists: prescription event monitoring pharmacosurveillance studies. Drug Saf 2001;24(6): 475–481. (GlaxoWellcome & AstraZeneca)	Surveillance cohort study (general practice patients in England)	To determine age- and gender-specific asthma death rates in patients prescribed the LABAs salmeterol and bambuterol	23,504 (Sample is 51% of those receiving prescription between December 1990 and May 1991)	**Prescribed Salmeterol** (n=15,406) **Age** Median = 55 yr **Gender** 51% male, 49% female **Prescribed Bambuterol** (n=8,098) **Age** Median = 60 yr **Gender** 55% male, 45% female	**Prescribed Salmeterol** Asthma/wheeze, 70.2% Chronic obstructive airways disease, 11.8% Other, 2.8% Unknown, 15.2% **Prescribed Bambuterol** Asthma/wheeze, 59.2% Chronic obstructive airways disease, 14.9% Other, 10.9% Unknown, 15.0%	**Salmeterol** patients, n=15,406 (55.0%) of 28,019 patients with prescription **Bambuterol** patients, 8,098 (45.0%) of 18,013 patients with prescription		At least 1 prescription between December 1990 and May 1991				In the cohorts combined, the death rate was 2.33 (95% CI 1.84 to 2.84) per 10,000 patient-months of observation: 2.40 (95% CI 1.74 to 3.40) for males and 3.08 (95% CI 2.21 to 3.98) for females per 10,000 patient-months of observation. Rate ratio 0.78, p=0.26. Rates highest for those 60–69 and 80–89 yr.

Citation (Sponsor)	Study Design	Purpose/ Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
Shrewsbury & Hallett. Salmeterol 100 microg: an analysis of its tolerability in single- and chronic-dose studies. Ann Allergy Asthma Immunol 2001;87(6): 465–473. (GlaxoSmithKline UK Limited)	Pooled analysis of 19 studies (14 published and 5 from clinical development)	To examine the systemic effects of single and chronic doses of salmeterol 100 mcg	10 single-dose studies (141 subjects) and 9 chronic-dose studies (1,504 subjects)		6 chronic-dose studies enrolled patients with persistent asthma; single-dose studies enrolled healthy volunteers (3 studies) or patients with asthma (7 studies)	**Single dose studies** Salmeterol compared with placebo and/or albuterol **Chronic dose studies** Salmeterol twice daily compared with placebo, albuterol administered 4 times/day and/or salmeterol twice daily	**Single dose studies** 12.4–400 **mcg** on separate days **Chronic dose studies** Salmeterol 100 mcg	**Single dose studies** Monitored over 4–36 hours **Chronic dose studies** Minimum of 7 days		**Single dose salmeterol 100 mcg studies** Mean change in heart rate of +2.3 beats/min, mean change in systolic blood pressure +0.4 mm Hg, maximum change in systolic blood pressure +13.9 mm Hg. **Chronic dose studies salmeterol 50 mcg twice daily** Mean change in heart rate +1.2 beats/min, mean change in systolic blood pressure –0.35 mm Hg		**Single dose 100 mcg studies** 5.7% with tremors, 2.8% with palpitations, 2.1% with decreased K+ concentration, 17.0% with ECG events, most from one study. **Chronic dose studies salmeterol 50 mcg twice daily** 1.7% with tremor, 0.9% with palpitations
Bensch et al. One-year efficacy and safety of inhaled formoterol dry powder in children with persistent asthma. Ann Allergy Asthma Immunol 2002;89(2): 180–190. (Novartis)	Multinational, multicenter, randomized, double-blind, placebo-controlled study (42 centers)	To examine the effectiveness of inhaled formoterol over a period of 12 months in children with asthma who were still symptomatic despite anti-inflammatory treatment	518 (407 completed; ITT analysis)	**Age** 5–12 yr, mean = 9 yr **Gender** 63% male, 37% female **Ethnicity** 87% Caucasian, 7% African-American, 6% other	Persistent asthma Duration of asthma mean = 5.2 yr FEV_1 % pred. mean = 71 FEV_1 reversibility 29.7% FEV_1 mean = 1.66 L Required daily use of inhaled albuterol to control symptoms Receiving sodium cromoglycate, nedocromil sodium, and/or ICS at stable dose	**Arm 1:** Formoterol dry powder twice daily (n=171; 134 completed) **Arm 2:** Formoterol dry power twice daily (n=171; 141 completed) **Arm 3:** Placebo (n=176; 135 completed)	12 mcg delivered by Aerolizer inhaler (F-12) Arm 2: 24 mcg delivered by Aerolizer inhaler (F-24)	12 months following 2-week run-in period (evaluated monthly) Anti-inflammatory and other anti-asthmatic medications were maintained at stable doses throughout the study. Rescue medication with inhaled salbutamol was allowed.	*In FEV_1 both F-12 and F-24 were always significantly superior to placebo ($p < 0.0062$), with no difference between F-12 and F-24. Average increase in morning PEF was 16.3% in F-24 and 14.5% in F-12 vs. 8.6% in placebo. Both F-24 and F-12 were always superior to placebo ($p < 0.001$).		Reduction in daytime symptom scores was greater in F-24 (–0.27) and F-12 (–0.27) than placebo (–0.17). F-12 vs. placebo significant during first 3 months of treatment (p=0.03). Median nocturnal symptom score decreased in F-12 (–0.02) and F-24 (–0.05) but increased in placebo (+0.11). All 3 groups reduced use of rescue medication. F-12 favored placebo during first 3 months ($p < 0.05$). F-24 superior to placebo over 12 months ($p < 0.01$). No difference in number of patients with exacerbations	Number of patients with SAE and AE was 43% in F-24, 42% in F-12, and 45% in placebo. Asthma-related SAE for 6% of F-24 and 5% of F-12 vs. 0% for placebo Frequency of nonserious asthma-related AE greater in placebo than in F-24 and F-12 among least reversible patients Time to first asthma-related AE shorter in placebo than F-24 and F-12

Citation (Sponsor)	Study Design	Purpose/ Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
Ind et al. Safety of formoterol by Turbuhaler as reliever medication compared with terbutaline in moderate asthma. Eur Respir J 2002;20(4): 859–866. (AstraZeneca , Lund, Sweden)	Multicenter randomized, double-blind, reference-controlled parallel groups trial (42 centers in 5 countries)	To investigate the safety of as-needed formoterol as an alternative to a conventional SABA reliever	357 (296 completed; ITT analysis)	**Age** >18 yr, mean = 47 yr **Gender** 40% male, 60% female **Ethnicity** Not reported	Stable on adequate dose of ICS Duration of asthma mean = 14.9 yr FEV_1 % pred. mean = 76 FEV_1 mean = 2.2 L FEV_1 reversibility mean = 13.3% ICS 200–3200 mcg, mean = 1032 mcg Oral steroid use 3% Xanthines use 15%	**Arm 1** Formoterol (n=176; 146 completed) **Arm 2** Terbutaline (n=181;150 completed)	Formoterol 9 mcg bid + formoterol 4.5 mcg as needed Formoterol 9 mcg bid + terbutaline 0.5 mg as needed	12 weeks after single-blind 2-week run-in during which all patients received formoterol 9 mcg bid and terbutaline 0.5 mg as needed	Morning and evening PEF did not change in either group from run-in period. No difference between groups in development of tolerance	*Mean changes in serum potassium level, pulse rate, systolic and diastolic blood pressure, and PR interval did not differ between groups. Terbutaline group had greater increases in cardiac frequency (2.6 beats/min, p=0.03). Cardiac frequency-adjusted QTc did not differ between groups (p=0.82). No changes in mean hematology or clinical chemistry laboratory values for either reliever	Formoterol group decreased reliever use by 0.21 inhalations/ day compared with terbutaline group (not significant). Mean reduction in daytime reliever use (0.21 inhalations) was greater with formoterol compared with terbutaline (p <0.05). Nocturnal reliever use did not differ between groups. Severe exacerbation for 34 in formoterol group and 39 in terbutaline group	7 SAE in formoterol group and 1 in terbutaline. Only 1 in formoterol group possibly related to study drug. 14 in each group discontinued study due to AE.
Ankerst et al. Tolerability of a high dose of budesonide/formoterol in a single inhaler in patients with asthma. Pulm Pharmacol Ther 2003;16(3): 147–151.	Randomized, double-blind, double-dummy, cross-over, placebo-controlled study	To assess the acute tolerability of a high dose of budesonide/formoterol compared with placebo	14 (14)	**Age** 21–59 yr, mean = 39.6 yr **Gender** 43% male, 57% female **Smoking** 64.3% nonsmokers, 35.7% ex-smokers	Stable asthma Duration 3–52 yr, mean = 21.7 yr Regular treatment with budesonide (400–800 mcg/day or equivalent) for at least 30 days	**Arm 1** Budesonide/ formoterol **Arm 2** Formoterol **Arm 3** Placebo	1,600/45 mcg 45 mcg	Up to 12 weeks (1–4 weeks between test days) All received maintenance dose of budesonide/formoterol 160/4.5 mcg twice daily		*Mean serum potassium levels remained within normal range for all treatments. Changes in serum potassium, pulse rate, blood pressure, QTc, blood glucose, and plasma lactate with budesonide/formoterol vs. placebo were significant but not clinically meaningful. No clinically relevant differences between active treatments		AE similar after each treatment and generally mild. No SAE reported.

Citation (Sponsor)	Study Design	Purpose/ Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
Boonsawat et al. Formoterol (OXIS) Turbuhaler as a rescue therapy compared with salbutamol pMDI plus spacer in patients with acute severe asthma. Respir Med 2003;97(9): 1067–1074.	Multicenter, randomized, double-blind, double-dummy, parallel-groups study (5 emergency departments in Thailand)	To compare the efficacy and safety of maximum recommended dose of formoterol with predicted equivalent dose of salbutamol in patients presenting to an ER with acute severe bronchoconstriction	86 (84; ITT analysis)	**Age** 18–67 yr, mean = 44 yr **Gender** 27% male, 73% female **Ethnicity** Not reported	Acute severe asthma FEV_1 % pred. 17–60, mean = 44 FEV_1 0.38–2.00 L, mean = 1.07 L FVC mean = 3.4 L Pulse rate 60–137, mean = 102 SaO_2 91–100, mean = 96 SABA use 73% IGCS use 37% IGCS dose at entry 400–1600 mcg, mean = 867 mcg	**Arm 1** Formoterol via Turbuhaler (n=44; 42 completed) **Arm 2** Salbutamol via pMDI plus spacer (n=44)	18 mcg at 0, 30 and 60 min (54 mcg) 800 mcg at 0, 30 and 60 min (2400 mcg)	4 hours	*Mean increase in FEV_1 higher for formoterol than salbutamol at all time points. Adjusted mean increase at 75 min was 37% in formoterol and 28% in salbutamol group (p=0.18). Maximal effect between 75 and 240 min was 51% in formoterol and 36% in salbutamol group (p <0.05). Average effect was 43% in formoterol and 28% in salbutamol group (p <0.05).	Adjusted mean minimum serum potassium was lower in formoterol than in salbutamol group (3.2 vs. 3.5 mmol/l, p <0.001). Adjusted mean average serum potassium was lower with formoterol than salbutamol (p=0.002). No differences in decrease in systolic and diastolic blood pressure No difference in heart rate or QTc	Difference in subjective symptom score (3.04) was not significant between groups. Mean Acute AQLQ score increased from 2.67 to 5.88 for formoterol group and from 2.49 to 5.69 for salbutamol group (p >0.05).	Ten patients reported a total of 13 mild AEs.
Ostrom. Tolerability of short-term, high-dose formoterol in healthy volunteers and patients with asthma. Clin Ther 2003;25(11): 2635–2646. (Novartis Pharma AG, Basel, Switzerland)	Review article of 1 open-label, non-comparative study (S1); 1 placebo-controlled, dose-escalation study (S2); and 3 comparative studies (S3–S5)	To assess the safety profile of short-term use of high doses of formoterol delivered via MDI or single-dose DPI in healthy volunteers or patients with stable asthma	S1: 12 S2: 20 S3: 13 S4: 12 S5: 9	S1: mean age = 29 yr; 8 men, 4 women S2: mean age = 30 yr; 11 men, 9 women S3: mean age = 47.2 yr; 12 men, 1 woman S4: mean age = 27 yr; 4 men, 8 women S5: mean age = 10 yr; 4 boys, 5 girls	**S1**: healthy volunteers, no history of asthma **S2**: mild-to-moderate asthma **S3**: stable, reversible asthma **S4**: healthy nonsmoking volunteers **S5**: stable, moderate asthma	**Study 1:** Formoterol via DPI **Study 2:** Single dose of formoterol or placebo **Study 3:** Formoterol or albuterol via MDI **Study 4:** Formoterol, albuterol, fenoterol, or placebo by MDI **Study 5:** Formoterol or albuterol	**Study 1:** 120 mcg **Study 2:** 12, 24, 48, or 96 mcg **Study 3:** Cumulative daily doses of 12–228 mcg formoterol or 200–3800 mcg albuterol **Study 4:** Formoterol 24 mcg, albuterol 400 mcg, or fenoterol 400 mcg **Study 5:** Escalating doses formoterol (6, 18, 54 mcg) or albuterol (100, 300, 900 mcg)	**Study 1:** Single dose with measurements for 48 hours **Study 2:** Single dose with measurements for 9 hours **Study 3:** Doses increased at 1-hour intervals up to 6 hours; cross over after ≥1 day washout **Study 4:** 5 doses at 30 min intervals; cross over to each of other treatments after 3–7 days washout **Study 5:** 2 study days separated by at least 1 week		**Study 1:** Metabolic and cardiovascular effects were small and not clinically relevant. **Study 2:** Metabolic and cardiovascular effects were dose dependent and single doses < 96 mcg. **Study 3:** Heart rate increased at high doses with no difference between treatments; mean serum potassium decreased at maximal doses with no difference between treatments. **Study 4:** High dose formoterol exerted inotropic, chronotropic, and electrophysiologic effects smaller than those of fenoterol and comparable to those of albuterol. **Study 5:** No between-group differences in heart rate. Neither treatment had effect on blood pressure.		**Study 1:** 11 of 12 subjects reported mild and transient AE. **Study 2:** Single doses of formoterol <96 mcg are unlikely to cause clinically relevant adverse effects.

Citation (Sponsor)	Study Design	Purpose/ Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
Pauwels et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. Eur Respir J 2003;22(5): 787–794.	Multicenter, open, randomized, parallel-group study (1,139 centers in 24 countries)	To assess the safety and effectiveness of formoterol as reliever medication, compared with salbutamol in people with asthma over a wide age range with different degrees of asthma severity and receiving a variety of other maintenance medications	18,124 (16,935 completed study; ITT analysis for 17,862)	**Age** 4–91 yr, mean = 39 yr Children ≤11 yr, 9% Adolescents 12–17 yr, 9% Adults 18–64 yr, 72% Elderly ≥65 yr, 10% **Gender** 43% male, 57% female **Ethnicity** 76% Caucasian, 16% Oriental, 8% other	Severity judged by medication level: Intermittent, 16% Mild, 35% Moderate, 35% Severe, 15% At entry: 76% ICS, 31% LABA, 9% Leukotriene modifiers, 13% xanthines/oral beta$_2$-agonists, 4% oral OCS, 10% others	**Arm 1** Formoterol via Turbuhaler® (n=9,064; 8,260 completed) **Arm 2** Salbutamol via pMDI or equivalent (n=9,060; 8,413 completed)	4.5 mcg per dose as needed 200 mcg per dose as needed	6 months Investigators could change maintenance treatment according to clinical judgment.			Fewer in formoterol (28.6%) experienced exacerbation vs. salbutamol (32.4%). Time to first exacerbation longer in formoterol vs. salbutamol, with 14% reduction in relative risk (p <0.001) and 12% reduction for first severe exacerbation (p <0.0013). Patients in each age group and each level of baseline asthma medication had longer times to first exacerbation with formoterol compared with salbutamol. Significant reduction in percent of days with symptoms for formoterol vs. salbutamol (p <0.03)	*AE for 42% of each group. Fewer asthma-related AE in formoterol (12.3%) than salbutamol (13.5%), p=0.018. *No difference in number of asthma-related SAE: formoterol 1.2% vs. salbutamol 1.4%, p=0.39 *More DAE and asthma-related DAE in formoterol (2.4% & 1.0%) vs. salbutamol (1.3% & 0.5%), p <0.001
Perera. Salmeterol multicentre asthma research trial (SMART): interim analysis shows increased risk of asthma related deaths. Ceylon Med J 2003;48(3):99. (GlaxoSmithKline)	Multicenter, randomized, double-blind, parallel-group, placebo-controlled study	To compare respiratory and asthma event outcomes in subjects receiving usual asthma pharmacotherapy (plus placebo) with event outcomes in subjects receiving usual pharmacotherapy plus salmeterol	26,355 (26,355) Study terminated early after planned interim analysis of 26,355 of planned 60,000 patients had been enrolled.	**Age** ≥12 yr, mean = 39 yr **Gender** Not reported **Ethnicity** 71% Caucasian, 18% African-American, 8% Hispanic, 3% other/not reported	Clinical diagnosis of asthma Currently taking prescription asthma medications No previous or current use of LABAs	**Arm 1** Salmeterol (n=13,176) **Arm 2** Placebo (n=13,179)	42 mcg (2 puffs of 21 mcg/puff) twice daily 2 puffs twice daily	Data collected at 4-week intervals for 28 weeks. All continued usual asthma therapy.				Note: RR based on Life Table Analysis. *The relative risk for the overall incidence of primary safety outcome events (combined respiratory-related death or life-threatening experience) in Arm 1 relative to Arm 2 was 1.40 (95% CI 0.91–2.14). Relative risk of respiratory-related death (2.16, 95% CI 1.06–4.41), asthma-related death (RR 4.37, 95% CI 1.25–15.34), and combined asthma-related death or life-threatening experiences (RR 1.71 95% CI 1.01–2.89) were higher in Arm 1 relative to Arm 2. In African-American subpopulation, the RR for combined respiratory-related death or life-threatening experiences (RR 4.10 95% CI 1.54–10.90), combined all cause death or life-threatening experiences (RR 2.17, 95% CI 1.06–4.41), and asthma-related death or life-threatening experiences (RR 4.92, 95% CI 1.68–14.45) were higher for Arm 1 relative to Arm 2.

Citation (Sponsor)	Study Design	Purpose/ Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
von Berg et al. Efficacy and tolerability of formoterol Turbuhaler in children. Int J Clin Pract 2003;57(10): 852–856.	Multicenter, randomized, double-blind, placebo-controlled study (32 centers in 5 countries in Europe)	To investigate the efficacy and tolerability of maintenance treatment with formoterol Turbuhaler® at two different doses in children with mild to moderate asthma	248 (225 completed; ITT analysis)	**Age** 6–17 yr, mean = 11.1 yr **Gender** 65% male, 35% female **Ethnicity** Not reported **Smoke Exposure** 42% yes	Mild-to-moderate asthma Duration 1–16 yr, mean = 6.3 yr 82% received ICS FEV_1 % pred. mean = 80.8 FEV_1 mean = 2.12 L FEV_1 reversibility mean = 10.8%	**Arm 1** Formoterol (n=83; 77 completed) **Arm 2** Formoterol (n=81; 74 completed) **Arm 3** Placebo (n=84; 74 completed)	9 mcg twice daily 4,5 mcg twice daily	12 weeks after 2-week run-in Terbutaline 0.025 mg used as relief medication. Normal anti-inflammatory medication or immunotherapy continued throughout the study. No other asthma medication permitted.	*Increase in morning PEF over 12 weeks was greater for formoterol 9 mcg vs. placebo (13.01 L/min, p=0.02); no difference for formoterol 4.5 mcg vs. placebo (11.1 L/min, p=0.051). Average FEV_1 over 12 weeks was higher in formoterol 4.5 mcg (5.2%) and 9 mcg (6.7%) than placebo (p <0.05). Mean FEV_1 reversibility was greater in placebo from a lower treatment baseline: 9.9% and 9.7% in formoterol 4.5 mcg and 9 mcg vs. 15.1% in placebo.		Decrease in symptom scores were not different between groups. Formoterol groups reduced daytime use of terbutaline during study (p <0.04). Formoterol 9 mcg dose reduced number of nocturnal inhalations (p=0.02) and number of awakenings due to asthma (p=0.04 vs. placebo).	Total of 107 AE during placebo vs. 84 and 104 in formoterol 4.5 and 9 mcg twice daily. Most mild or moderate. Nine SAE: 3 in formoterol 4.5 mcg, 5 in formoterol 9 mcg, and 1 in placebo; none were related to study drug.
Pohunek et al. Dose-related efficacy and safety of formoterol (Oxis) Turbuhaler compared with salmeterol Diskhaler in children with asthma. Pediatr Allergy Immunol 2004;15(1):32–39. (AstraZeneca, Lund, Sweden)	Multicenter, single-dose randomized, double-blind, double-dummy, placebo-controlled, cross-over study	To compare the efficacy of single doses of formoterol Turbuhaler® with that of salmeterol Diskhaler® and placebo in children in order to fully evaluate the potential role of formoterol in children	68 (64 completed)	**Age** 7–17 yr, mean = 11.9 yr 53% 7–12 yr, 47% 13–17 yr **Gender** 68% male, 32% female **Ethnicity** Not reported	Moderate-to-severe asthma 82% received ICS FEV_1 % pred. mean = 71 FEV_1 mean = 1.97 L FEV_1 reversibility mean = 25%	**Arm 1** Formoterol (n=43) **Arm 2** Formoterol (n=41) **Arm 3** Formoterol (n=44) **Arm 4** Formoterol (n=44) **Arm 5** Salmeterol (n=42) **Arm 6** Placebo (n=42)	4.5 mcg 9 mcg 18 mcg 36 mcg 50 mcg	12-hour study period Measurements at 32, 10, 20, 30 min and 1, 2, 4, 6, 8, 10, and 12 hours after drug administration. Six visits with treatments at visits 2–5 and poststudy safety followup at visit 6, 3 days after last treatment day. Each patient received 4 of the 6 possible treatments in random order. To maintain blinding, patients received 1 of the 6 treatments and 4 placebo inhalations at visits 2–5 with 3 days of washout between visits.	*All treatments had better effects than placebo in average 12-hour serial FEV_1, mean. FEV_1, at 12 hours, and maximal FEV_1 for 12-hour period Formoterol 4.5 mcg and salmeterol did not differ on efficacy parameters. Improvement in effect was dose-related for formoterol 9, 18, and 36 mcg vs. salmeterol. Formoterol at doses 9, 18, and 36 mcg provided better effects for 7–12 year olds than salmeterol (p <0.05) with relatively steep dose-response curve. Less steep dose-response effect for 13–17 year olds with 36 mcg significant vs. 4.5–18 mcg doses (p=0.05). Formoterol dose corresponding to salmeterol 50 mcg for efficacy estimated to be 2.6–3.3 mcg.	Dose-dependent effects for formoterol on pulse, heart rate, and QTc. Salmeterol 50 mcg was estimated to correspond to 7.8–13.5 mcg delivered dose of formoterol.		AE was generally mild or moderate with no difference between treatments.

Citation (Sponsor)	Study Design	Purpose/ Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
Salpeter et al. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. Chest 2004;125(6): 2309–2321.	Meta-analysis of 33 randomized placebo-controlled trials	To evaluate the cardiovascular effects of $beta_2$-agonist use in patients with asthma or chronic obstructive pulmonary disease (COPD)	13 single-dose trials with 232 participants; 20 longer duration trials with 6,623 participants	**Single dose trials:** Mean age = 56.6 yr **Longer duration trials**: Mean age = 52.2 yr						*Single dose of $beta_2$-agonist increased heart rate by 9.12 beats/min (95% CI 5.32–12.92) compared to placebo and reduced potassium concentration by 0.36 mmol/L (95% CI 0.18–0.54) compared to placebo.		For trials 3 days to 1 year, $beta_2$-agonist increased risk for cardiovascular event (relative risk 2.54, 95% CI 1.59–4.05) compared to placebo. Relative risk for sinus tachycardia was 3.06 (95% CI 1.70–5.50).
Kruse et al. Safety and tolerability of high-dose formoterol (Aerolizer) and salbutamol (pMDI) in patients with mild/moderate, persistent asthma. Pulm Pharmacol Ther 2005; 18(3):229–234.	Randomized, double-blind, double-dummy, active-comparator controlled, two-period cross-over study	To compare the safety and tolerability of high-dose formoterol and salbutamol over a 3-day period in patients with asthma, specifically to confirm that there is an acceptable safety margin for formoterol at high doses that may be taken by patients suffering from worsening asthma symptoms over several days	16 (16)	**Age** 21–49 yr, mean = 32 yr **Gender** 81% male, 19% female **Ethnicity** Not reported **Weight** 78–102 kg, mean = 75.6 kg	Mild (87.5%) or moderate (122.5%) persistent asthma FEV_1 2.04–4.48 L, mean = 3.36 L FEV_1 % pred. 78–102, mean = 89.6 QTc interval, 352–440 ms, mean = 399 ms Serum potassium, 3.96–5.22 mmol/L, mean = 4.51 mmol/L Blood glucose, 3.68–6.13 mmol/L, mean = 4.84 mmol/L	Patients randomly assigned to treatment sequence; n=16 **Arm 1 (F)** Formoterol **Arm 2 (S)** Salbutamol (n=16)	36 mcg (dry powder for inhalation) via Acrolize® 3 times daily at 5-hour intervals 600 mcg via pressurized MDI 3 times daily at 5-hour intervals	3 consecutive days with 3- to 7-day wash-out period between drugs; 21-day screening period	Similar peak FEV_1 values for F and S (p=0.613) F vs. S had higher mean AUC of FEV_1 over 72-hour period (302.2 L vs. 277.4 L, p <0.001). Higher mean 24-hour AUC FEV_1 for F vs. S for each day (102.3 vs. 93.9 L for 0–24 hours; 101.6 vs. 91.5 L for 24–48 hours; 98.3 vs. 92.1 L for 48–72 hours; all p <0.01)	Plasma potassium concentration means during F vs. S were 3.4 and 3.6 mmol/L (p <0.001). Mean AUC for 72-hour period was lower during F vs. S (284.3 vs. 296.6 mmol/L, p <0.001). Difference between F and S during 0–24 hours was 90.8 vs. 96.6 mmol/L, p <0.001; and 24–48 hours was 93.3 vs. 97.9 mmol/L, p <0.001, with no difference for 48–72 hour period (p=0.13). Mean AUC for blood glucose over 72 hours was higher for F than S (421.2 vs. 410.8 mmol/L, p=0.009), with only difference in 0–24 hour period (147.6 vs. 139.9 mmol/L, p=0.001). QTc was greater for F vs. S over 72 hours (p <0.001), with maximum values higher for F vs. S (428.8 vs. 417.4 ms, p <0.001).		47 mild AEs and 2 moderate AEs: 23 reports (8 patients) with F and 26 reports (9 patients) with S. No SAE reported.

Citation (Sponsor)	Study Design	Purpose/ Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
Nelson et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;29(1): 15–26. (SMART trial)	Randomized, double-blind, placebo-controlled, observational study (6,163 sites in the Unites States; 1,316 investigators randomized subjects into trial)	To compare the safety of salmeterol xinafoate or placebo added to usual asthma care	26,355 (26,355 ITT)	**Age** 9–100 yr, mean = 39.1 yr **Gender** 36% male, 64% female **Ethnicity** 71% Caucasian, 18% African-American, 8% Hispanic, 1% Asian, 2% other	Diagnosis of asthma Mean duration of asthma = 16.3 yr Currently receiving prescription asthma medication No previous use of inhaled LABAs PEF mean = 355.3 L/min PEF % pred. mean = 83.9 In previous 12 months: 26% asthma ED visits, 8% hospitalization, 61% weekly symptoms of nocturnal asthma ICS use: 47% overall, 49% of Caucasians, and 38% of African-Americans	**Arm 1 (S)** Salmeterol via MDI (n=13,176) **Arm 2 (P)** Placebo MDI (n=13,179)	42 mcg twice daily	28 weeks Single clinic visit when subjects were given a 28-week supply of student medication, instructed on proper use of MDI, and instructed to continue use of current asthma medications. Study medications to be taken approximately 12 hours apart, and a new inhaler to be used every 4 weeks. Subjects contacted every 4 weeks by telephone for data collection. Compliance not reinforced during study contact.				*No difference in number of subjects with respiratory-related death or life-threatening experiences over 28-week period (RR 1.395, 95% CI 0.91 to 2.14). Difference between S and P in number of respiratory related deaths (24 vs. 11, RR 2.16, 95% CI 1.06 to 4.41), asthma-related deaths (13 vs. 3, RR 4.37, 95% CI 1.25 to 15.34), and combined asthma-related deaths or life-threatening experiences (37 vs. 22, RR 1.71, 95% CI 1.01 to 2.89). No differences among Caucasians, but among African-Americans, differences between S and P for number of respiratory-related deaths (20 vs. 5, RR 4.10, 95% CI 1.54 to 10.90) and combined asthma-related deaths or life-threatening experiences (19 vs. 4, RR 4.92, 95% CI 1.68 to 14.45). Differences for S vs. P in time to first SAE causing discontinuation (S survival rate, 95.6%; P survival rate, 96.2%; p=0.022)
Wolfe et al. 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;129(1):27–38.	Multicenter, placebo-controlled, parallel-group study (194 outpatient asthma clinics in the United States)	To determine whether high-dose formoterol, 24 mcg bid, was associated with more asthma exacerbations compared with lower formoterol doses in patients with stable persistent asthma	2,085 (2,085 ITT)	**Age** 12–82 yr, mean = 38.1 yr; 15% 12–18 yr, 79% 19–64 yr, 5% 65–74 yr, 1% >74 yr **Gender** 45% male, 55% female **Ethnicity** 79% Caucasian, 13% African-American, 2% Oriental, 6% other	Persistent stable asthma Duration of asthma 0–80 yr, mean = 20.5 yr FEV_1 0.67–5.01 L, mean = 2.37 L FEV_1 % pred. 35.2–123.6, mean = 68.8	**Arm 1 (F-24)** Formoterol high dose (n=527) **Arm 2 (F/D)** Open-label formoterol plus on demand (n=517) **Arm 3 (F-12)** Formoterol low dose (n=527) **Arm 4 (P)** Placebo (n=514)	24 mcg bid 12 mcg bid, with 2 additional 12 mcg daily doses as needed 12 mcg bid	16 weeks Medications administered by inhalation from a single-dose DPI between 6 and 9 a.m. and between 6 and 9 p.m. Patients in double-blind groups were allowed rescue medication; patients in F/D were allowed up to 4 puffs/day of albuterol as rescue medication after receiving 2 additional 12 mcg doses on demand.	All three formoterol groups achieved significant ($p < 0.0001$) and clinically relevant treatment differences of 270–320 mL compared with P in FEV_1 at 2 hours after first dose and after 16 weeks of treatment. After first dose, difference of 50 mL favored F-24 vs. F-12 (p=0.0065) with no difference at the end of 16 weeks.	No clinically meaningful differences between groups in pulse rate and blood pressure	*No differences between groups in serious exacerbation (p >0.21) Lower proportion in F/D vs. P with serious exacerbation requiring systemic corticosteroids (4.4% vs. 8.8%, p=0.006). No other groups differed. No difference in proportion experiencing serious exacerbation or discontinuing due to asthma-related AE or having an asthma-related ED visit (p >0.25)	Proportion with any asthma-related AE was similar in F-24 and F-12 and not different from P (13.7% and 14.0% vs. 15.8%, p >0.38); fewer had asthma-related AE in F/D vs. P (10.3% vs. 15.8%, p=0.009).