

Evidence Table 15. Pharmacologic Therapy: Bronchodilators—Safety of Long-Acting Beta₂-Agonists

Abbreviations used in table:

AE	adverse event	ICS	inhaled corticosteroid
AG	adrenoceptor agonists	IGCS	inhaled glucocorticosteroid
AQLQ	Asthma Quality of Life Questionnaire	ITT	intent-to-treat
AUC	area under the curve	LABA	long-acting beta₂-agonists
COPD	chronic obstructive pulmonary disease	MDI	metered-dose inhaled
DAE	discontinuation due to adverse event	OCS	oral corticosteroid
DPI	dry powder inhaler	PEF	peak expiratory flow
ED	emergency department	RR	relative risk
FEF_{25%-75%}	forced expiratory flow between 25% and 75% of vital capacity	SABA	short-acting beta-agonist
FEV₁	forced expiratory volume in 1 sec.	SAE	serious adverse event
FVC	forced vital capacity		

* indicates primary outcome

Evidence Table 15. Pharmacologic Therapy: Bronchodilators—Safety of Long-Acting Beta₂-Agonists

Citation (Sponsor)	Study Design	Study Population		
		Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)
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	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
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)	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
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	Study 1: Retrospective, 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

Citation (Sponsor)	Study Design	Study Population		
		Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)
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)	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%
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)	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)
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)	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
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)	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%

Citation (Sponsor)	Study Design	Study Population		
		Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)
Ankerst et al. Tolerability of a high dose of budesonide/formoterol in a single inhaler in patients with asthma. <i>Pulm Pharmacol Ther</i> 2003;16(3):147–151.	Randomized, double-blind, double-dummy, cross-over, placebo-controlled study	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
Boonsawat et al. Formoterol (OXIS) Turbuhaler as a rescue therapy compared with salbutamol pMDI plus spacer in patients with acute severe asthma. <i>Respir Med</i> 2003;97(9):1067–1074.	Multicenter, randomized, double-blind, double-dummy, parallel-groups study (5 emergency departments in Thailand)	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
Ostrom. Tolerability of short-term, high-dose formoterol in healthy volunteers and patients with asthma. <i>Clin Ther</i> 2003;25(11):2635–2646. (Novartis Pharma AG, Basel, Switzerland)	Review article of 1 open-label, noncomparative study (S1); 1 placebo-controlled, dose-escalation study (S2); and 3 comparative studies (S3–S5)	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
Pauwels et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. <i>Eur Respir J</i> 2003;22(5):787–794.	Multicenter, open, randomized, parallel-group study (1,139 centers in 24 countries)	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

Citation (Sponsor)	Study Design	Study Population		
		Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)
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	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
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)	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%
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	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%
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	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	

Citation (Sponsor)	Study Design	Study Population		
		Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if Reported)
Kruse et al. Safety and tolerability of high-dose formoterol (Aerolizer) and salbutamol (pMDI) in patients with mild/moderate, persistent asthma. <i>Pulm Pharmacol Ther</i> 2005;18(3):229–234.	Randomized, double-blind, double-dummy, active-comparator controlled, two-period cross-over study	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 (12.5%) 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
Nelson et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. <i>Chest</i> 2006;29(1): 15–26. (SMART trial)	Randomized, double-blind, placebo-controlled, observational study (6,163 sites in the United States; 1,316 investigators randomized subjects into trial)	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
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. <i>Chest</i> 2006;129(1):27–38.	Multicenter, placebo-controlled, parallel-group study (194 outpatient asthma clinics in the United States)	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

Citation/ Sponsor	Study Characteristics			Findings			
	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.	Purpose/Objective: To compare the effects of regular treatment with inhaled formoterol or oral zafirlukast on bronchial hyperresponsiveness and on airway inflammation in patients who were homozygous for the glycine-16 allele and who were already being treated with inhaled corticosteroids			*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			
	Arm 1 Formoterol fumarate with placebo tables twice daily	12 mcg	5 weeks (each treatment 1 week with 1 week wash out between treatments) after 1 week run-in period				
	Arm 2 Zafirlukast tablets with placebo inhaler twice daily	20 mg	Two puffs of inhaled ipratropium bromide (Atrovent Foirte 40 mcg/puff) used as first-line rescue with albuterol as second-line rescue.				
	Arm 3 Placebo inhaler and placebo tablets both twice daily						

Citation/ Sponsor	Study Characteristics			Findings			
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
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.	Purpose/Objective: To evaluate two doses of formoterol administered via the Aerolizer inhaler in patients with mild to moderate persistent asthma			*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.
	Arm 1 Formoterol (F-12) (n=136)	12 mcg twice daily via Aerolizer	12 weeks after 2-week single-blind, placebo lead-in period				
	Arm 2 Formoterol (F-24) (n=135)	24 mcg twice daily via Aerolizer	All patients received labeled albuterol for use as rescue medication.				
	Arm 3 Albuterol (n=134)	180 mcg 4 times daily via metered-dose inhaler	Post spirometric data at 4, 8, and 12 weeks at intervals throughout a 12-hour observation period				
	Arm 4 Placebo (n=136) Overall, 83 withdrew from study.						

Citation/ Sponsor	Study Characteristics			Findings			
	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)	<p>Purpose/Objective: To describe clinical features and cardiac pump function of patients with bronchial asthma during long-term oral administration of beta₂-adrenoceptor agonists (AG)</p> <p>Study 1 Chart Review: 74 cases treated with oral beta₂-AG and 69 without oral beta₂-AG</p> <p>Study 2 Group 1 26/74 cases treated with oral beta₂-AG</p> <p>Group 2 22/69 without oral beta₂-AG</p> <p>Group 3 (control) 21 healthy volunteers</p>		<p>Study 3: 2 week cessation of beta₂-AG (n=11/26)</p>	<p>Study 2: FEV₁ significantly lower in group 1 than in group 3 (control).</p>	<p>Study 1: No differences in angina, ventricular arrhythmia, hypertension between groups</p> <p>Study 2: No difference in right ventricular function between groups</p> <p>Group 1 (oral beta₂-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).</p> <p>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).</p>	<p>Study 1: No difference in remedies for asthma between those with and without oral beta₂-AG.</p>	<p>Study 1: Incidence of nonfatal heart failure associated with oral nitrates was more frequent in oral beta₂-AG group (p <0.05).</p>

Citation/ Sponsor	Study Characteristics			Findings			
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
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 & Astra Zeneca)	Purpose/Objective: To determine age- and gender-specific asthma death rates in patients prescribed the LABAs salmeterol and bambuterol						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.
	Salmeterol patients, n=15406 (55.0%) of 28,019 patients with prescription		At least 1 prescription between December 1990 and May 1991				
Shrewsbury & Hallett. Salmeterol 100 mcg: an analysis of its tolerability in single- and chronic-dose studies. Ann Allergy Asthma Immunol 2001;87(6): 465-473. (GlaxoSmithKline UK Limited)	Purpose/Objective: To examine the systemic effects of single and chronic doses of salmeterol 100 mcg				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
	Single dose studies Salmeterol compared with placebo and/or albuterol	Single dose studies 12.4-400 mcg on separate days	Single dose studies Monitored over 4-36 hours				
	Chronic dose studies Salmeterol twice daily compared with placebo, albuterol administered 4 times/day and/or salmeterol twice daily	Chronic dose studies Salmeterol 100 mcg	Chronic dose studies Minimum of 7 days				

Citation/ Sponsor	Study Characteristics			Findings			
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
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)	<p>Purpose/Objective: 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</p> <p>Arm 1 Formoterol dry powder twice daily (n=171; 134 completed)</p> <p>Arm 2 Formoterol dry powder twice daily (n=171; 141 completed)</p> <p>Arm 3 Placebo (n=176; 135 completed)</p>	<p>12 mcg delivered by Aerolizer inhaler (F-12)</p> <p>24 mcg delivered by Aerolizer inhaler (F-24)</p>	<p>12 months following 2 week run-in period (evaluated monthly)</p> <p>Anti-inflammatory and other anti-asthmatic medications were maintained at stable doses throughout the study. Rescue medication with inhaled salbutamol was allowed.</p>	<p>*In FEV₁ both F-12 and F-24 were always significantly superior to placebo (p <0.0062), with no difference between F-12 and F-24.</p> <p>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).</p>		<p>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).</p> <p>Median nocturnal symptom score decreased in F-12 (-0.02) and F-24 (-0.05) but increased in placebo (+0.11).</p> <p>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).</p> <p>No difference in number of patients with exacerbations</p>	<p>Number of patients with SAE and AE was 43% in F-24, 42% in F-12, and 45% in placebo.</p> <p>Asthma-related SAE for 6% of F-24 and 5% of F-12 vs. 0% for placebo</p> <p>Frequency of nonserious asthma-related AE greater in placebo than in F-24 and F-12 among least reversible patients</p> <p>Time to first asthma-related AE shorter in placebo than F-24 and F-12</p>

Citation/ Sponsor	Study Characteristics			Findings			
	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)	Purpose/Objective: To investigate the safety of as-needed formoterol as an alternative to a conventional SABA reliever			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.
	Arm 1 Formoterol (n=176; 146 completed)	Formoterol 9 mcg bid + formoterol 4.5 mcg 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				
	Arm 2 Terbutaline (n=181;150 completed)	Formoterol 9 mcg bid + terbutaline 0.5 mg as needed					

Citation/ Sponsor	Study Characteristics			Findings			
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
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.	Purpose/Objective: To assess the acute tolerability of a high dose of budesonide/formoterol compared with placebo				*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.
Arm 1 Budesonide/formoterol	1600/45 mcg	Up to 12 weeks (1–4 weeks between test days)					
Arm 2 Formoterol	45 mcg	All received maintenance dose of budesonide/formoterol 160/4.5 mcg twice daily					
Arm 3 Placebo							

Citation/ Sponsor	Study Characteristics			Findings			
	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. Turbuhaler as a rescue therapy compared with salbutamol pMDI plus spacer in patients with acute severe asthma. Respir Med 2003; 97(9):1067–1074.	Purpose/Objective: 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			*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.
	Arm 1 Formoterol via Turbuhaler (n=44; 42 completed)	18 mcg at 0, 30 and 60 min (54 mcg)	4 hours				
	Arm 2 Salbutamol via pMDI plus spacer (n=44)	800 mcg at 0, 30 and 60 min (2400 mcg)					

Citation/ Sponsor	Study Characteristics			Findings			
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
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)	Purpose/Objective: 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						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.
	Study 1: Formoterol via DPI	Study 1: 120 mcg	Study 1: Single dose with measurements for 48 hours		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 2: Single dose of formoterol or placebo	Study 2: 12, 24, 48, or 96 mcg	Study 2: Single dose with measurements for 9 hours				
	Study 3: Formoterol or albuterol via MDI	Study 3: Cumulative daily doses of 12–228 mcg formoterol or 200–3800 mcg albuterol	Study 3: Doses increased at 1-hour intervals up to 6 hours; cross over after ≥1 day washout				
	Study 4: Formoterol, albuterol, fenoterol, or placebo by MDI	Study 4: Formoterol 24 mcg, albuterol 400 mcg, or fenoterol 400 mcg	Study 4: 5 doses at 30 min intervals; cross over to each of other treatments after 3–7 days washout				
Study 5: Formoterol or albuterol	Study 5: Escalating doses formoterol (6, 18, 54 mcg) or albuterol (100, 300, 900 mcg)	Study 5: 2 study days separated by at least 1 week					

Citation/ Sponsor	Study Characteristics			Findings			
	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.	<p>Purpose/Objective: 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</p> <p>Arm 1 Formoterol via Turbuhaler® (n=9,064; 8,260 completed)</p> <p>Arm 2 Salbutamol via pMDI or equivalent (n=9,060; 8,413 completed)</p>	<p>4.5 mcg per dose as needed</p> <p>200 mcg per dose as needed</p>	<p>6 months</p> <p>Investigators could change maintenance treatment according to clinical judgment.</p>			<p>Fewer in formoterol (28.6%) experienced exacerbation vs. salbutamol (32.4%).</p> <p>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).</p> <p>Patients in each age group and each level of baseline asthma medication had longer times to first exacerbation with formoterol compared with salbutamol.</p> <p>Significant reduction in percent of days with symptoms for formoterol vs. salbutamol (p <0.03)</p>	<p>*AE for 42% of each group. Fewer asthma-related AE in formoterol (12.3%) than salbutamol (13.5%), p=0.018.</p> <p>*No difference in number of asthma-related SAE: formoterol 1.2% vs. salbutamol 1.4%, p=0.39</p> <p>*More DAE and asthma-related DAE in formoterol (2.4% & 1.0%) vs. salbutamol (1.3% & 0.5%), p <0.001</p>

Citation/ Sponsor	Study Characteristics			Findings			
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
Perera. Salmeterol multicentre asthma research trial (SMART): interim analysis shows increased risk of asthma related deaths. Ceylon Med J 2003;48(3):99. (GlaxoSmithKline)	Purpose/Objective: 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						<p>Note: RR based on Life Table Analysis.</p> <p>*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).</p> <p>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.</p> <p>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.</p>
	Arm 1 Salmeterol (n=13,176)	42 mcg (2 puffs of 21 mcg/puff) twice daily	Data collected at 4-week intervals for 28 weeks. All continued usual asthma therapy.				
	Arm 2 Placebo (n=13,179)	2 puffs twice daily					
von Berg et al. Efficacy and tolerability of formoterol Turbuhaler in children. Int J Clin Pract 2003;57(10):852–856.	Purpose/Objective: To investigate the efficacy and tolerability of maintenance treatment with formoterol Turbuhaler® at two different doses in children with mild to moderate asthma			*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		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	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.
	Arm 1 Formoterol (n=83; 77 completed)	9 mcg twice daily	12 weeks after 2-week run-in Terbutaline 0.025 mg used as relief medication. Normal anti-inflammatory medication or				
	Arm 2 Formoterol (n=81; 74 completed)	4,5 mcg twice daily					

Citation/ Sponsor	Study Characteristics			Findings			
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
	<p>Arm 3 Placebo (n=84; 74 completed)</p>		<p>immunotherapy continued throughout the study. No other asthma medication permitted.</p>	<p>in formoterol 4.5 mcg (5.2%) and 9 mcg (6.7%) than placebo (p <0.05). Mean FEV₁ 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.</p>		<p>inhalations (p=0.02) and number of awakenings due to asthma (p=0.04 vs. placebo).</p>	

Citation/ Sponsor	Study Characteristics			Findings			
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
Pohunek et al. Dose-related efficacy and safety of formoterol (Oxis) Turbuhaler compared with salmeterol Diskhaler in children with asthma. <i>Pediatr Allergy Immunol</i> 2004;15(1):32–39. (AstraZeneca, Lund, Sweden)	Purpose/Objective: 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			*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.
	Arm 1 Formoterol (n=43)	4.5 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.				
	Arm 2 Formoterol (n=41)	9 mcg					
	Arm 3 Formoterol (n=44)	18 mcg					
	Arm 4 Formoterol (n=44)	36 mcg	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.				
	Arm 5 Salmeterol (n=42)	50 mcg					
Arm 6 Placebo (n=42)							

Citation/ Sponsor	Study Characteristics			Findings			
	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.	Purpose/Objective: To evaluate the cardiovascular effects of beta ₂ -agonist use in patients with asthma or chronic obstructive pulmonary disease (COPD)				*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).

Citation/ Sponsor	Study Characteristics			Findings			
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
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.	Purpose/Objective: 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			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.
	Patients randomly assigned to treatment sequence; n=16 Arm 1 (F) Formoterol	36 mcg (dry powder for inhalation) via Acrolize® 3 times daily at 5-hour intervals	3 consecutive days with 3- to 7-day wash-out period between drugs; 21-day screening period				
	Arm 2 (S) Salbutamol (n=16)	600 mcg via pressurized MDI 3 times daily at 5-hour intervals					

Citation/ Sponsor	Study Characteristics			Findings			
	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;129(1):15–26. (SMART trial)	Purpose/Objective: To compare the safety of salmeterol xinafoate or placebo added to usual asthma care						<p>*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).</p> <p>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).</p> <p>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)</p>
	<p>Arm 1 (S) Salmeterol via MDI (n=13,176)</p> <p>Arm 2 (P) Placebo MDI (n=13,179)</p>	42 mcg twice daily	<p>28 weeks</p> <p>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.</p> <p>Subjects contacted every 4 weeks by telephone for data collection.</p> <p>Compliance not reinforced during study contact.</p>				

Citation/ Sponsor	Study Characteristics			Findings			
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Vital Signs/ Cardiovascular/ Clinical Laboratory Values	Exacerbations/ Symptoms	Safety
Wolfe et al. Formoterol, 24 microg bid, and serious asthma exacerbations: similar rates compared with formoterol, 12 micro bid, with and without extra doses taken on demand, and placebo. Chest 2006;129(1): 27–38.	<p>Purpose/Objective: 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</p> <p>Arm 1 (F-24) Formoterol high dose (n=527)</p> <p>Arm 2 (F/D) Open-label formoterol plus on demand (n=517)</p> <p>Arm 3 (F-12) Formoterol low dose (n=527)</p> <p>Arm 4 (P) Placebo (n=514)</p>	<p>24 mcg bid</p> <p>12 mcg bid, with 2 additional 12 mcg daily doses as needed</p> <p>12 mcg bid</p>	<p>16 weeks</p> <p>Medications administered by inhalation from a single-dose DPI between 6 and 9 a.m. and between 6 and 9 p.m.</p> <p>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.</p>	<p>All three formoterol groups achieved significant ($p < 0.0001$) and clinically relevant treatment differences of 270–320 mL compared with P in FEV₁ 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.</p>	<p>No clinically meaningful differences between groups in pulse rate and blood pressure</p>	<p>*No differences between groups in serious exacerbation ($p > 0.21$)</p> <p>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.</p> <p>No difference in proportion experiencing serious exacerbation or discontinuing due to asthma-related AE or having an asthma-related ED visit ($p > 0.25$)</p>	<p>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%, $p=0.009$).</p>