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Salmeterol/Fluticasone Propionate

A Review of its Use in Asthma

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Data Selection

Sources: Medical literature published in any language since 1980 on 'salmeterol/fluticasone', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'salmeterol/fluticasone propionate' or 'fluticasone/salmeterol' and 'asthma'. Searches were last updated 3 August 2009.

Selection: Studies in patients with asthma who received salmeterol/fluticasone propionate. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Salmeterol, fluticasone propionate, salmeterol/fluticasone propionate, asthma, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary

Abstract

Salmeterol/fluticasone propionate (Seretide/Advair Diskus® [dry powder inhaler] or Seretide/Advair® inhalation aerosol [metered-dose inhaler]) is a fixed-dose combination inhalation agent containing a long-acting β_2-adrenoceptor agonist (LABA) plus a corticosteroid. In patients with symptomatic asthma, twice-daily salmeterol/fluticasone propionate maintenance therapy improves lung function and asthma symptoms to a greater extent than monotherapy with inhaled corticosteroids (ICS), such as fluticasone propionate, oral montelukast with or without fluticasone propionate, or sustained-release theophylline plus fluticasone propionate. The greater efficacy achieved with salmeterol/fluticasone propionate versus fluticasone propionate alone was sustained for 1 year in a well designed trial. Salmeterol/fluticasone propionate is also associated with a corticosteroid-sparing effect. Results of studies comparing fixed dosages of salmeterol/fluticasone propionate with formoterol/budesonide in adults and adolescents are equivocal. Twice-daily salmeterol/fluticasone propionate is associated with clinically meaningful improvements from baseline in health-related quality of life (HR-QOL), and improvements were greater than those reported with fluticasone propionate alone. Salmeterol/fluticasone propionate is generally well tolerated in adults, adolescents and children aged 4–11 years, and the fixed-combination inhaler ensures the appropriate use of a LABA in combination with an ICS. In cost-utility analyses in patients with uncontrolled asthma, salmeterol/fluticasone propionate compares favourably with fluticasone propionate alone or oral montelukast. Thus, salmeterol/fluticasone propionate provides an effective, well tolerated and cost-effective option for maintenance treatment in patients with asthma.

Pharmacological Properties

Salmeterol is a selective LABA, which causes bronchodilation and inhibition of the release of hypersensitivity mediators from mast cells. The corticosteroid fluticasone propionate inhibits eosinophil activation and the subsequent release of inflammatory mediators. Coadministration of inhaled salmeterol and fluticasone propionate produce similar effects to those observed when the two agents are administered separately, and *in vitro* studies suggest beneficial additive or synergistic effects.

The pharmacokinetics of concomitant salmeterol and fluticasone propionate are generally similar to those recorded following individual administration, with no systemic pharmacokinetic interaction. The action of inhaled salmeterol or fluticasone propionate is local to the lung, so plasma levels are not an indication of therapeutic effect. Salmeterol is extensively metabolized via hydroxylation, and fluticasone propionate is principally metabolized to an inactive metabolite by the cytochrome P450 (CYP) isoenzyme CYP3A4.

Therapeutic Efficacy

Salmeterol/fluticasone propionate maintenance therapy improves lung function and asthma symptoms to a greater extent than monotherapy with ICS or montelukast in adults, adolescents and children aged 4–11 years with symptomatic asthma. In well designed, long-term studies of up to 1 year, twice-daily salmeterol/fluticasone propionate achieved better asthma control than twice-daily fluticasone propionate alone. The combination of salmeterol/fluticasone

propionate has a corticosteroid-sparing effect, with twice-daily salmeterol/fluticasone propionate 50 μg/100 μg maintaining a level of control that was not significantly different to that achieved with twice-daily fluticasone propionate 250 μg. Twice-daily salmeterol/fluticasone propionate in a single inhaler was as effective as the same dosages of twice-daily salmeterol plus fluticasone propionate administered concurrently in separate inhalers.

Results of studies comparing salmeterol/fluticasone propionate with formoterol/budesonide maintenance therapy in adults and adolescents have been mixed, with some showing similar efficacy and others demonstrating greater efficacy with either agent. Twice-daily salmeterol/fluticasone propionate provided more effective control of asthma symptoms than twice-daily sustained-release theophylline plus fluticasone propionate. Clinically meaningful improvements from baseline in HR-QOL have been observed in asthmatics treated with twice-daily salmeterol/fluticasone propionate. Asthma quality-of-life questionnaire scores were improved more with salmeterol/fluticasone propionate than with fluticasone propionate alone or oral montelukast, but results from HR-QOL studies comparing salmeterol/fluticasone propionate with formoterol/budesonide were mixed.

In patients with uncontrolled asthma, salmeterol/fluticasone propionate was cost effective compared with monotherapy with fluticasone propionate or oral montelukast, with regard to the incremental cost per quality-adjusted life-year gained, per symptom- or rescue-free day, or cost per 12% improvement in forced expiratory volume in 1 second, but results of studies comparing salmeterol/fluticasone propionate with formoterol/budesonide were mixed.

Tolerability

Salmeterol/fluticasone propionate is generally well tolerated in adults, adolescents and children and, overall, the most frequent treatment-related adverse effects include upper respiratory tract infection, pharyngitis, headaches and throat irritation/cough. In clinical trials, the incidence of treatment-related effects was generally similar to that of comparators, including fluticasone propionate alone, montelukast or formoterol/budesonide.

In a well designed, 12-week study in asthmatic children aged 6–14 years, the most common adverse event associated with salmeterol/fluticasone propionate or oral motelukast was headache. The incidence of treatment-related adverse effects was 2% in each treatment group, with serious events reported in zero and three patients, respectively. Urinary cortisol excretion over 24 hours remained within normal limits after 12 weeks of treatment with salmeterol/fluticasone propionate 50 μg/100 μg in children aged 4–11 years.

1. Introduction

Asthma is a chronic disease of the airways characterized by bronchoconstriction, inflammation and remodelling.[1] The disease is estimated to affect 300 million people of all ages worldwide, placing a considerable burden on healthcare systems.[2]

Treatment options include reliever (i.e. used as required with a fast onset of action) and controller (i.e. taken daily to maintain asthma control) medication.[3] Inhaled short-acting β_2-adrenoceptor agonists (SABAs) [e.g. salbutamol, terbutaline] are the first-line options for fast relief of bronchospasm during acute asthma attacks, if break-through symptoms occur, or for exercise-induced asthma.[3] The long-acting β_2-adrenoceptor agonist (LABA) formoterol also has a role as reliever medication. The most effective controller medications available currently are inhaled corticosteroids (ICS) [e.g. fluticasone propionate], which achieve control primarily via their anti-inflammatory effects. Low-dose ICS should be combined with as-required SABAs in

patients not adequately controlled with SABAs alone. If adequate control is not achieved, other controller medications may be indicated, including inhaled LABAs, systemic corticosteroids, leukotriene modifiers (e.g. montelukast) and sustained-release theophylline. LABAs are most effective when combined with ICS, and should not be used as monotherapy in asthma.

This article focuses on the therapeutic use of the fixed-dose combination of salmeterol/fluticasone propionate (Seretide/Advair Diskus® [dry powder inhaler; DPI] or Seretide/Advair® inhalation aerosol [metered-dose inhaler; MDI]), which was reviewed previously in *Drugs*.[4] Unless stated otherwise throughout, all medication was administered via inhalation.

2. Pharmacodynamic Properties

The pharmacodynamic properties of salmeterol/fluticasone propionate have been reviewed in detail previously.[5,6] This section provides a brief summary, with a focus on recently published data.

Salmeterol is a selective LABA, which causes relaxation of the bronchial smooth muscles leading to bronchodilation, and inhibits the release of hypersensitivity mediators from mast cells.[7] The corticosteroid fluticasone propionate inhibits eosinophil activation and the subsequent release of inflammatory mediators. In patients with asthma, the drug also appears to reduce bronchial hyper-responsiveness.[7]

Coadministration of inhaled salmeterol and fluticasone propionate produces similar effects to those observed when the two agents are administered separately, with no systemic pharmacodynamic interaction.[8] *In vitro* studies suggest beneficial additive or synergistic effects on the enhancement of glucocorticoid-inducible gene expression and upregulation of the β-receptor when salmeterol and fluticasone propionate are coadministered.[9]

Adding salmeterol to fluticasone propionate in asthmatics led to a significant ($p = 0.001$) improvement in size selectivity of plasma protein permeation across the respiratory membrane, but did not affect markers of allergen-induced bronchial inflammation.[10] Furthermore, salmeterol/fluticasone propionate reduced airway resistance more markedly than fluticasone propionate alone, as determined by plethysmography 12 hours post-dose, in mild asthmatics.[11]

Significantly greater bronchodilation with salmeterol/fluticasone propionate than with placebo was evident at 15 minutes post-dose ($p < 0.001$), as measured by mean forced expiratory volume in 1 second (FEV_1) from 0 to 15 minutes, in a randomized, crossover study in asthmatics.[12] The onset of bronchodilation was faster with formoterol/budesonide (4.5 μg/160 μg or 9 μg/320 μg) than with salmeterol/fluticasone propionate (50 μg/250 μg), as measured by mean FEV_1 at 3 minutes post-dose and by mean FEV_1 from 0 to 15 minutes ($p < 0.001$ for both).[12]

In children aged 4–11 years, salmeterol/fluticasone propionate (50 μg/100 μg) achieved significantly greater bronchodilation than placebo for at least 20 hours after evening inhalation, as determined by peak expiratory flow (PEF), in a double-blind, crossover study ($p < 0.01$ at 24 hours).[13]

Genetic studies in asthmatics suggested that variability in response to LABAs may be due to differing *ADRB2* (the gene coding for the β_2-adrenergic receptor) polymorphisms at codon 16, characterized by substitution of glycine for arginine (Gly16Arg).[14] However, studies in patients with asthma demonstrated that Gly16Arg genotypes had no effect on therapeutic outcome.[14-16] Moreover, withdrawals from salmeterol/fluticasone propionate treatment were similar in Caucasian and African American patients, irrespective of the ADRB2 genotype variant.[17]

Ethnicity did not have an effect on therapeutic response in a crossover study.[18] In Japanese ($n = 18$) and Caucasian ($n = 17$) asthmatics, treatment with salmeterol/fluticasone propionate or with the concurrent administration of both individual agents led to a similar significant bronchodilator response throughout 14 days of treatment, as measured by plethysmography. Furthermore, in a long-term (1-year), randomized, double-blind trial in African-American asthmatics, who experience greater asthma prevalence than Caucasians, a similar low rate of exacerbations was achieved with salmeterol/fluticasone

propionate and fluticasone propionate alone (see also section 4.1.2).[19]

3. Pharmacokinetic Properties

Pharmacokinetic data on the use of salmeterol and fluticasone propionate administered individually have been reviewed previously.[5,6] This section provides a summary of relevant properties, using data obtained from a study in 28 healthy volunteers,[8] supplemented with data from the manufacturer's prescribing information.[20,21]

The pharmacokinetics of concomitant salmeterol and fluticasone propionate are generally similar to those recorded following individual administration, with no systemic pharmacokinetic interaction.[8] The peak plasma concentration (C_{max}) and time to C_{max} (t_{max}) for each agent was not significantly different when given alone or in combination. However, following concomitant administration, the fluticasone propionate area under the plasma concentration-time curve was ≈8% higher ($p < 0.05$) than that recorded after fluticasone propionate alone.[8]

The action of inhaled salmeterol or fluticasone propionate is local to the lung, so plasma levels are not an indication of therapeutic effect.[20,21] Plasma salmeterol concentrations following repeated doses are low, and there is no accumulation of the drug. In patients with asthma receiving multiple doses of inhaled salmeterol 50 μg twice daily, mean C_{max} was 167 pg/mL and t_{max} 20 minutes.[20] Following inhalation of fluticasone propionate 500 μg via a Diskus® device in patients with asthma, steady-state mean C_{max} ranged from undetectable to 266 pg/mL, with a mean plasma concentration of 110 pg/mL. In healthy volunteers, the absolute bioavailability of fluticasone propionate following administration via Diskus® device was 5.5%.[20]

Fluticasone propionate is highly lipid soluble with a high first-pass metabolism; therefore, any part of the dose that is swallowed contributes minimally to systemic exposure (<1%).[21] In plasma, the drug is approximately 91% protein bound,[21] and the volume of distribution is about 4.2 L/kg.[20]

Both salmeterol and fluticasone propionate are metabolized by the liver.[20,21] Salmeterol is extensively metabolized via hydroxylation and primarily eliminated in the faeces. Fluticasone propionate is principally metabolized to an inactive carboxylic acid metabolite by the cytochrome P450 (CYP) isoenzyme CYP3A4 and excreted in the faeces, with renal elimination accounting for <5% of the dose.[20,21] The mean terminal elimination half-lives of salmeterol and fluticasone propionate when coadministered via the Diskus® device were ≈5.5 and 5.6 hours, respectively.

Formal pharmacokinetic studies on the use of salmeterol/fluticasone propionate in patients with renal or hepatic impairment have not been performed. As both agents are hepatically metabolized, patients with hepatic dysfunction should be closely monitored for drug accumulation.[20] Coadministration of salmeterol/fluticasone/propionate with the potent CYP3A4 inhibitor ritonavir is not recommended, as this combination led to markedly increased plasma concentrations of fluticasone propionate and reduced serum cortisol levels.[20] Similar but less pronounced effects were reported when salmeterol/fluticasone propionate was coadministered with ketoconazole.[20]

4. Therapeutic Efficacy

This section focuses on large (n >80), well designed studies that compared the efficacy of salmeterol/fluticasone propionate with several other recommended agents, used alone or in combination, for the treatment of asthma. Most studies were carried out in adults and adolescents, although several evaluated only adults aged ≥18 years[22-30] or children aged 4–17 years,[31-36] with a history of asthma and reversible airways obstruction. Some retrospective analyses of the pivotal GOAL (Gaining Optimal Asthma controL) study,[37,38] observational studies[39-46] and meta-analyses[47-51] are also discussed.

Prior to randomization, patients were receiving SABAs alone as required,[22,33,52-58] ICS,[19,23,26,27,31,32,34,36,55,59-75] ICS with or without a SABA or LABA,[25,26,29,30,35,71,76-80] or oral sustained-release theophylline.[28] In most studies, patients continued to receive SABAs as required, but in three studies, formoterol/

budesonide was administered for asthma maintenance and relief.[71,72,75]

Primary efficacy endpoints included lung function measures (mean predose FEV_1, area under the serial FEV_1-time curve over 12 hours [$AUC_{12}FEV_1$], or the change in mean PEF),[23,25,28,29,31-33,35,36,52-54,56-60,62,64-70,74,76,77,79,80] or various measures evaluating symptom control.[19,22,24,26,27,34,44-46,55,61,71-73,75,78] Where stated, analyses were performed in the intent-to-treat population, which generally included randomized patients who had received at least one dose of study medication;[19,22-24,26,27,31-34,36,52-62,64-78,80] per-protocol analyses were also performed in non-inferiority studies.[25,28,31,36,74,79]

All prospective studies included a screening period, at the end of which eligible patients were required to be symptomatic,[19,22-24,26-28,31-33,35,36,52-60,62,64-78] based on lung function measurements compared with expected values and/or based on symptom assessment, or were considered well controlled,[25,30,34,61,79,80] based on Global Initiatives for Asthma (GINA) guidelines[3] or on measures of lung function.

Salmeterol/fluticasone propionate was administered via a Diskus® DPI in all studies except for three that used an MDI.[53,59,77] The two delivery devices have demonstrated clinical equivalence in adults,[81] adults and adolescents,[82,83] and children aged 4–11 years.[84]

Throughout the studies, patients recorded PEF measurements, symptom scores, use of rescue medication and night-time awakenings in a diary. Daily symptoms were generally assessed on a scale of 0 (no symptoms) to 5 (symptoms severely interfered with daily activities). Asthma exacerbations were generally defined as mild, moderate or severe, based on morning PEF measurements and need for oral corticosteroids; an event requiring hospital admission was classified as severe.

Health-related quality of life (HR-QOL) was assessed using the asthma quality-of-life questionnaire (AQLQ), a well established, disease-specific, self-administered, 32-item assessment tool, which assesses four domains (activity limitation, symptoms, emotional function and environmental exposure) on a scale of 1 (most impairment) to 7 (no impairment), with a change of ≥0.5 points considered clinically meaningful.[57,85,86] One recent study evaluated HR-QOL using the asthma treatment satisfaction measure (ATSM), a validated, self-administered, 11-item tool that also assesses four domains (expectations of treatment, treatment preference, treatment outcome and overall treatment satisfaction), with scores scaled from 0 to 100 (a higher score indicates greater patient satisfaction).[87] Most major comparative studies were sponsored by the manufacturer of one of the agents included in the study.

4.1 Compared with Fluticasone Propionate, Other Inhaled Corticosteroids or Salmeterol Monotherapy

4.1.1 Initial Maintenance Therapy

Salmeterol/fluticasone propionate maintenance therapy improves lung function and asthma symptoms to a greater extent than monotherapy with fluticasone propionate. In 12- or 24-week, randomized, double-blind, multicentre trials, twice-daily salmeterol/fluticasone propionate 50 μg/100 μg, 42 μg/220 μg or 50 μg/250 μg generally achieved significantly greater improvements in measurements of lung function and symptom assessment (including primary efficacy measures) than twice-daily inhaled fluticasone propionate 100–500 μg, salmeterol 42 μg or 50 μg (monotherapy with LABAs such as salmeterol is no longer approved by the US FDA), or placebo in patients with asthma previously treated with SABAs alone as required, ICS, or ICS and/or SABAs (table I). In one study[58] that compared twice-daily salmeterol/fluticasone 50 μg/100 μg with a higher-strength, once-daily regimen (50 μg/250 μg), greater efficacy was achieved with the twice-daily regimen for one efficacy parameter, although the once-daily regimen was more effective than once-daily fluticasone propionate alone for several parameters (table I).

Corticosteroid-Sparing Effect in Adults and Adolescents

The combination of salmeterol/fluticasone propionate achieves a corticosteroid-sparing effect.[30,61]

Patients aged ≥12 years (n = 558)[61] or ≥18 years (n = 88)[30] who required fluticasone propionate 250 μg twice daily for asthma stability (determined during a run-in period) were randomized to twice-daily salmeterol/fluticasone propionate 50 μg/100 μg or fluticasone propionate 250 μg in double-blind, multicentre , 24-week studies. In the larger trial,[61] the proportion of patients who withdrew from the study in the first 12 weeks because of lack of efficacy (primary endpoint) was not different between treatment groups (5% vs 7%), and only an additional 1% in each group were withdrawn during weeks 13 to 24. Thus, asthma control was maintained in the combined therapy group with a 60% reduction in the total daily ICS dose.[61] This study also demonstrated that at week 24, twice-daily salmeterol/fluticasone propionate 50 μg/100 μg was associated with greater improvements in mean change from baseline in FEV_1 (0.10 vs 0.00 L; baseline measurements [2.74 and 2.8 L] were 80% of predicted values), evening PEF (49.4 vs 31.3 L/min) and use of rescue medication (14.9 vs 8.3 rescue-free days) than twice-daily fluticasone propionate 250 μg ($p < 0.05$ for all comparisons).[61]

Similarly, in the second study,[30] which primarily evaluated biopsy data, there were no significant differences between treatment groups in secondary clinical endpoints, including mean change from baseline in FEV_1, PEF and percentage of symptom-free days. The mean change from baseline in the daily asthma symptom score in the combination therapy group versus the fluticasone propionate group was –0.23 (baseline 0.85) versus –0.20 (baseline 0.87) [$p = 0.05$].[30]

Similarly, salmeterol/fluticasone propionate 50 μg/250 μg was associated with better lung function and symptom control than doubling the dose of fluticasone propionate to 500 μg in another well designed study in symptomatic moderate asthmatics (table I).[23]

Exercise-Induced Asthma in Adults and Adolescents

Salmeterol/fluticasone propionate was more effective than fluticasone propionate alone in providing protection from exercise-induced asthma.[62] Patients (n = 292) aged 12–50 years who were treated with twice-daily fluticasone propionate 250 μg for a 2- to 5-week run-in period and experienced a decrease in FEV_1 of ≥20% from baseline after two exercise challenge tests were included in a randomized, double-blind, 4-week study. The mean maximal decline in FEV_1 (primary endpoint) after exercise challenge was significantly lower with twice-daily salmeterol/fluticasone propionate 50 μg/250 μg than with twice-daily fluticasone propionate 250 μg on the first day of treatment at 1 hour (11.4% vs 20.0%; $p < 0.001$), but not at 8.5 hours (11.6% vs 12.6%) after study drug administration (mean baseline FEV_1 measurements [2.72 L in both groups] were 78% of predicted values).[62] After 4 weeks, there was a significant difference in the mean maximal decline in FEV_1 after exercise challenge between treatment groups in favour of combined therapy at both timepoints (10.9% vs 18.4% and 8.9% vs 12.9%, respectively; $p \leq 0.01$ for both).[62] More patients in the salmeterol/fluticasone propionate group than in the fluticasone propionate group were able to complete the exercise challenge test 8.5 hours post-treatment on day 1 (82% vs 64%) or at week 4 (82% vs 67%; $p \leq 0.01$ for both).

Recovery times (i.e. time taken to return to within 5% of the pre-exercise baseline FEV_1 value from the time of maximal decline) were shorter with twice-daily salmeterol/fluticasone propionate 50 μg/250 μg than with twice-daily fluticasone propionate 250 μg except for 8.5 hours post-treatment on day 1.[62] On the first day of treatment, respective recovery times at 1 hour were 19.7 versus 33.7 hours ($p < 0.005$) and at 8.5 hours, 22.4 vs 28.0 hours. At week 4, corresponding values at 1 and 8.5 hours post-treatment were 18.5 vs 31.7 hours ($p < 0.01$) and 17.1 vs 28.6 hours ($p < 0.05$).[62]

Treatment in Children

Treatment with salmeterol/fluticasone propionate was at least as effective as twice the dose of fluticasone propionate in two randomized, non-inferiority trials in asthmatic children not well controlled with ICS (one reported in an abstract[36]).[31] Twice-daily salmeterol/fluticasone propionate 50 μg/100 μg improved mean morning PEF significantly more from baseline (baseline

Table I. Efficacy of salmeterol/fluticasone propionate (S/FP) compared with fluticasone propionate (FP), salmeterol (SAL) or placebo (PL) monotherapy in patients (pts) with asthma.[a] Results are shown for the intent-to-treat populations in randomized, double-blind, multicentre, 12-week trials (except for one trial of 24 weeks[22]), which assessed efficacy using lung function tests in adults[22,23] or adults and adolescents.[52-54,58-60,76,77] S/FP was administered twice daily via a single Diskus® dry powder[22,23,52,54,58,60,76] or metered-dose[53,59,77] inhaler. In all but three studies,[22,54,58] the co-primary efficacy endpoints were mean predose morning forced expiratory volume in 1 second (FEV_1) and area under the serial FEV_1-time curve over 12 hours ($AUC_{12}FEV_1$) relative to day 1

Study	Regimen (μg bid unless stated otherwise) [no. of pts]	$AUC_{12}FEV_1$ [day 1 value] (L/h)	Mean change from baseline					
			morning FEV_1 (L)	morning PEF (L/min)	evening PEF (L/min)	symptom-free days (%)	SABA use (puffs/day)	nights with no awakenings (%)
Pts previously treated with SABAs alone as required								
Kerwin et al.[58][b]	S/FP 50/100 [210]		0.48	57	49‡			
	S/FP 50/250 od [210]		0.49¥	52¥¥	39¥			
	FP 250 od [212]		0.36††	34††	28†			
	PL [212]		0.18	13	16			
Murray et al.[52]	S/FP 50/100 [88]	8.4* [5.3]	0.51	68*	51*	41*	−2.8*	30
	FP 100 [89]	7.0 [2.7]	0.50	37	30	25	−1.8	21
	SAL 50 [90]	6.2 [4.8]	0.38	33	24	26	−2.6	26
Nelson et al.[53]	S/FP 50/100 [95]	10.6* [7.2]	0.69	67*	52*	30	−2.4	20
	FP 100 [97]	7.2 [2.9]	0.51	43	30	25	−1.8	21
	SAL 50 [91]	8.2 [7.6]	0.47	29	22	30	−1.6	17
Rojas et al.[54]	S/FP 50/250 [182]			72***c		78**d		
	FP 250 [180]			51c		61d		
Strand and	S/FP 50/100 [78]			56**	40*	60*c,e		27
Luckow[22]	FP 100 [72]			23	14	47c,e		19
Pts previously treated with ICS								
Bergmann	S/FP 50/250 [170]			52*c	46*	49**	−1.6***	
et al.[23]	FP 500 [177]			36c	29	38	−1.0	
Nathan et al.[59]	S/FP 42/220 [92]	7.0* [5.4]	0.41***	50***	36***	19††	−1.6***	4††
	FP 220 [89]	3.6 [2.1]	0.19	14	9	15	−0.5	−1
	SAL 42 [92]	5.3 [6.1]	0.15	13	5	14	−0.9	−1
	PL [87]	1.4 [0.6]	−0.12	−16	−14	−9	1.6	−15
Shapiro et al.[60]	S/FP 50/250 [81]	7.3* [5.0]	0.48*	54*	45*	34*	−2.3*	7*
	FP 250 [81]	4.5 [1.2]	0.25†	15†	8†	15†	−0.9†	3†
	SAL 50 [84]	4.4 [3.9]	0.05†	−12	−14	2	0.0†	−8
	PL [90]	3.3 [0.7]	−0.11	−14	−16	−8	0.9	−12
Pts previously treated with ICS and/or SABAs								
Kavuru et al.[76]	S/FP 50/100 [87]	8.9* [5.8]	0.51*	53*	35*	23*	−1.9*	5§
	FP 100 [85]	5.4† [2.3]	0.28†	17†	18†	7	−0.4†	2†
	SAL 50 [86]	6.4† [5.2]	0.11	−2†	−7	8†	−0.3†	−5†
	PL [77]	3.0 [1.7]	0.01	−24	−13	−4	1.7	−17
Pearlman	S/FP 50/100 [92]	9.0** [6.7]	0.58**	58**	48**	40**		9**
et al.[77]	FP 100 [89]	5.6 [2.7]	0.36	27	20	10		5
	SAL 50 [92]	6.5 [6.1]	0.25	25	16	16		2
	PL [87]	2.6 [2.0]	0.14	1	3	5		−4

Continued next page

Table I. Contd

a Mean baseline FEV_1 values were approximately 64%,[76] 66%[52,53] 68%,[59,60,77] 72%,[54] 74%[58] or 75%[23] of predicted values, or baseline morning PEF was approximately 390 L/min.[22]

b The primary endpoint was the change from baseline in the percentage of predicted evening PEF, which was 10.1% with S/FP 50 μg/100 μg bid ($p < 0.05$ vs S/FP 50 μg/250 μg od), 8.3% with S/FP 50 μg/250 μg od ($p \leq 0.001$ vs FP 250 μg od), 5.5% with FP 250 μg od ($p < 0.05$ vs PL) and 3.2% with PL. Baseline values ranged from 75.8% to 78%.[58]

c Primary endpoint.

d Median value.

e 24-hour period.

bid = twice daily; **ICS** = inhaled corticosteroids; **od** = once daily; **PEF** = peak expiratory flow; **SABA** = short-acting β_2-adrenoceptor agonist; * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs all comparators; † $p < 0.05$, †† $p < 0.001$ vs PL; ‡ $p < 0.05$ vs S/FP od; ¥ $p < 0.05$, ¥¥ $p \leq 0.001$ vs FP od; § $p < 0.05$ vs SAL.

measures were 270.8 vs 265.3 L/min) than twice-daily fluticasone propionate 200 μg over 12 weeks in children aged 4–11 years in the per-protocol population (figure 1) [treatment difference of 9.3 L/min; 95% CI 3.2, 15.3; $p < 0.01$].[31] Thus, the non-inferiority of salmeterol/fluticasone 50 μg/100 μg versus double the fluticasone propionate dose alone was established, based on the predetermined lower limit of the 95% confidence interval being greater than −12 L/min.[31] Similar results were achieved in the intent-to-treat population (treatment difference of 7.6 L/min; 95% CI 1.7, 13.5; $p < 0.05$), and the lower limit of the 95% confidence interval was also greater than zero. Subsequent testing demonstrated statistically significant advantages for salmeterol/fluticasone propionate over fluticasone propionate for both the per-protocol and intent-to-treat populations ($p < 0.05$ for both).[31] Patients receiving twice-daily salmeterol/fluticasone propionate showed greater improvements at week 12 in mean pre-bronchodilator maximal-expiratory flow (0.33 vs 0.16 L/sec; $p < 0.05$) and percentage of rescue-free days (95% vs 94%; $p < 0.05$) than those receiving twice-daily fluticasone propionate, whereas similar improvements from baseline in both treatment groups were recorded for symptom scores, rescue medication use and lung function assessments.[31]

The noninferiority of twice-daily salmeterol/fluticasone 50 μg/100 μg versus twice-daily fluticasone propionate 200 μg was also established in an 8-week study in 283 children aged 4–16 years.[36] The study was terminated after an interim analysis confirmed noninferiority. The mean change in morning PEF from baseline was 29.6 versus 18.3 L/min (mean difference 11.3 L/min; 95% CI 3.4, ∞).

Twice-daily salmeterol/fluticasone propionate 50 μg/100 μg provided greater protection from exercise-induced asthma than twice-daily fluticasone propionate 100 μg in a randomized, double-blind, multicentre, 4-week study in children (n = 248) aged 4–17 years with persistent asthma.[35] The mean maximum fall in FEV_1 after exercise challenge 8.5 hours after treatment (primary

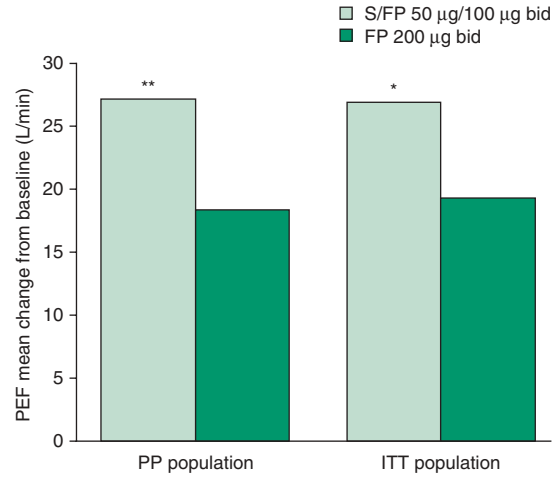

Fig. 1. Mean change in morning peak expiratory flow (PEF) over weeks 1–12 in asthmatic children (aged 4–11 years). Results are from a randomized, double-blind, double-dummy, multicentre, non-inferiority study, in which patients received twice-daily (bid) salmeterol/fluticasone propionate (S/FP) 50 μg/100 μg or bid fluticasone propionate (FP) 200 μg.[31] Baseline PEF measurements were 270.8 and 265.3 L/min, respectively. Noninferiority of FP to S/FP was established in the per-protocol (PP) population (n = 265), and superior efficacy with S/FP vs FP was established in the intent-to-treat (ITT) population (n = 303). * $p < 0.05$, ** $p < 0.01$ vs FP.

endpoint) on day 28 in the combination therapy group was significantly less than that with fluticasone propionate (9.5% vs 12.7%; $p < 0.05$). The difference between treatment groups for rescue-free and symptom-free days did not reach significance.[35]

4.1.2 Longer-Term (≥1 Year) Therapy

Salmeterol/fluticasone propionate maintenance therapy achieved better longer-term asthma control than fluticasone propionate alone in three randomized, double-blind, 1-year studies in patients with symptomatic asthma,[19,24,55] one of which was conducted exclusively in African Americans.[19]

In the large GOAL study in 3421 patients, efficacy was assessed via a composite, guideline-based control measure comprising seven criteria: PEF, rescue medication use, symptoms, night-time awakenings, exacerbations, emergency visits and adverse events. Totally controlled asthma was achieved if the patients experienced ≥7 of 8 consecutive weeks with no asthma features, and well controlled asthma was achieved if only a low level of symptoms and rescue medication use were recorded during ≥7 of 8 consecutive weeks. Asthma control was not achieved in the advent of an exacerbation, emergency room visit or adverse event, irrespective of how well asthma was controlled at other timepoints.[55]

Patients were stratified according to previous corticosteroid use: stratum 1 (no ICS); stratum 2 (≤500 μg/day beclomethasone dipropionate or equivalent); and stratum 3 (501–1000 μg/day).[55] During phase 1, treatment dosage was increased every 12 weeks, with dosage 'step-ups' depending on strata, until total asthma control was achieved or the maximum dose of study drug was reached (twice-daily salmeterol/fluticasone propionate 50 μg/500 μg or fluticasone propionate 500 μg). In phase 2 (maintenance phase), patients continued to receive the maximum dosage or the dosage at which they had achieved total asthma control until study end.[55]

Significantly higher proportions of patients in all three strata receiving twice-daily salmeterol/fluticasone propionate achieved totally and well controlled asthma during phase 1 than those receiving twice-daily fluticasone propionate alone (table II). The cumulative proportion of patients achieving totally and well controlled asthma at the end of phase 2 was also significantly greater with combination therapy than with fluticasone propionate.[55] During phase 1, more patients in the combination therapy group than in the fluticasone propionate group achieved control at the same or lower dosages of ICS than used perviously. Asthma control was achieved significantly faster with salmeterol/fluticasone propionate than with fluticasone propionate alone.[55]

Asthma control was sustained, with most patients who achieved control in phase 1 maintaining control throughout phase 2. At the end of phase I, 77–83% of salmeterol/fluticasone propionate recipients and 75–77% of fluticasone propionate recipients who were well controlled maintained this level of control throughout phase 2, and 69–70% and 62–74%, respectively, who achieved total asthma control in phase 1 maintained this control throughout phase 2.[55]

Significantly greater improvements in FEV_1 were achieved with twice-daily salmeterol/fluticasone propionate than with twice-daily fluticasone propionate alone in both phases and in all three strata (table II). Asthma exacerbation rates requiring either oral corticosteroids and/or hospitalization or emergency room visits also improved more in the combination therapy group than in those receiving fluticasone propionate alone in each of the three strata ($p \leq 0.009$).[55]

Retrospective analyses of the GOAL study have further examined these data for guidance on asthma treatment.[37,38] In a protocol-defined analysis, the magnitude of change in single specific endpoints was evaluated.[37] Mean morning PEF (table II), asthma symptom score, rescue medication use, symptom-free days, night-time awakenings and annual rate of exacerbations requiring corticosteroids and/or hospitalization or emergency room visits were all improved more with twice-daily salmeterol/fluticasone propionate than with twice-daily fluticasone propionate alone over 1 year in all three strata ($p < 0.05$). In a pooled analysis of all strata, the mean improvement from baseline in morning PEF with salmeterol/fluticasone propionate compared with fluticasone propionate alone was 58.2 versus 33.9 L/min ($p < 0.001$).

Table II. Effect of salmeterol/fluticasone propionate (S/FP) vs fluticasone propionate (FP) on asthma control and lung function in the GOAL study.[37,55] In this randomized, double-blind, multicentre study, adults and adolescents (aged ≥12 years) received twice-daily S/FP or FP for 1 year and were stratified according to inhaled corticosteroid (ICS) use at randomization: stratum 1 (no ICS); stratum 2 (≤500 μg/day beclomethasone dipropionate or equivalent); and stratum 3 (501–1000 μg/day). In phase 1, the ICS dose was increased every 12 weeks until total asthma control was achieved or until the maximum dose was reached. In phase 2, patients (pts) remained at the dosage at which they achieved totally controlled asthma or the maximum dosage. Results shown are for the intent-to-treat population

Regimen (no. of pts)	Asthma control[a] (% of pts)				Mean change from baseline[b]			
	phase 1		phase 2		FEV_1 (L)		morning PEF (L/min)[c]	
	well controlled	total control	well controlled	total control	phase 1	phase 2	weeks 1–12	weeks 1–52
Stratum 1								
S/FP (548)	71*	42**	78*	50**	0.45**	0.52**	55.8	71.1
FP (550)	65	31	70	40	0.31	0.34	32.0	49.2
Stratum 2								
S/FP (585)	69**	32**	75**	44**	0.35**	0.37**	42.5	57.1
FP (578)	52	20	60	28	0.22	0.24	15.7	30.0
Stratum 3								
S/FP (576)	51**	19**	62**	29**	0.29**	0.32**	31.8	45.7
FP (579)	31	8	47	16	0.17	0.18	10.3	21.6

a Based on a multifactorial endpoint comprising morning PEF, rescue β_2-adrenoceptor agonist use, daytime symptoms, night-time awakenings, exacerbations, emergency visits and adverse events. Pts achieving total asthma control also achieved well controlled asthma.

b Mean baseline FEV_1 measurements ranged from 2.3–2.5 L (75–79% of predicted values), and baseline mean morning PEF ranged from 344–349 L/min.

c Results are from a protocol-defined, retrospective analysis of pt diary records. Individual p-values not reported, but for the comparison of pooled data from all strata: S/FP 58.2 vs FP 33.9 L/min; $p < 0.001$.[37]

FEV_1 = forced expiratory volume in 1 second; **PEF** = peak expiratory volume; * $p < 0.05$, ** $p < 0.001$ vs FP.

Corresponding values for the adjusted mean change in asthma symptom scores were −1.0 versus −0.8; median percentage of symptom-free days 72.5% versus 54.5%; median percentage of rescue-free days 87.3% versus 74.7%; proportion of patients with no night-time awakenings 31% versus 22%; and the mean annualized exacerbation rate was 0.02 versus 0.03 visits per year ($p < 0.001$ for all pooled comparisons).[37]

A further retrospective analysis identified factors that influenced treatment response in the GOAL study.[38] The factors that were found to be most predictive of not achieving at least well controlled asthma were smoking status and treatment. The odds ratio (OR) for current smoker versus never smoked was 2.76 (95% CI 2.06, 3.69; $p < 0.0001$), and for fluticasone propionate versus salmeterol/fluticasone propionate, the OR was 1.97 (95% CI 1.69, 2.31; $p < 0.0001$).[38] Other factors affecting the probability of not achieving asthma control included being male, a former smoker, and having a history of ICS use. Of those patients who did not achieve at least well controlled asthma in all strata, 93% of salmeterol/fluticasone propionate recipients and 90% of fluticasone propionate recipients had improvement in at least one of the criteria used to assess the composite endpoint.[38]

In a second study in 282 patients with mild to moderate asthma, the efficacy of salmeterol/fluticasone propionate 50 μg/250 μg was compared with fluticasone propionate 250 μg or salmeterol 50 μg (all administered twice-daily).[24] Medication was increased or decreased to maintain asthma control based on treatment guidelines. The percentage of patients requiring an increase in study medication (primary endpoint) over 1 year was significantly lower with salmeterol/fluticasone propionate (10.5%) than with fluticasone propionate (34.8%) or salmeterol (61.1%) [$p < 0.001$ for both]. Furthermore, the proportion of patients experiencing at least two exacerbations was significantly lower in the combination therapy group (4.2% vs 17.4% [$p < 0.01$] and 40% [$p < 0.001$]).[24] Airway hyper-responsiveness after 1 year of treatment, as measured by methacholine

PC_{20} tests, was improved significantly more with salmeterol/fluticasone propionate (from 0.5 to 1.8 mg/mL) than with fluticasone propionate (from 0.6 to 1.1 mg/mL; $p < 0.05$) or salmeterol (deteriorated from 0.9 to 0.7 mg/mL; $p < 0.001$). Similarly, significant improvements were achieved with combination therapy versus fluticasone or salmeterol alone in mean change in morning PEF (38 vs 21 and 7 L/min; $p < 0.01$ for both), but not FEV_1 (0.09 vs 0.02 and –0.05).[24]

Another randomized, double-blind, multicentre, 1-year study was conducted exclusively in African American asthmatics (n = 475).[19] The annualized exacerbation rate (primary endpoint) was not significantly different between patients receiving twice-daily salmeterol/fluticasone propionate 50 μg/100 μg or fluticasone propionate 100 μg after 1 year (0.45 vs 0.53). However, in secondary analyses, combined therapy was associated with greater improvements in lung function, as determined by FEV_1 and PEF measurements (all $p \leq 0.01$), than fluticasone propionate. Similarly, night-time awakenings per night improved more from baseline with combination therapy than with fluticasone propionate alone ($p = 0.05$).[19]

Observational Studies in Adults and Adolescents

One prospective[39] and several retrospective[40,41,44-46] observational studies have compared salmeterol/fluticasone propionate with fluticasone propionate (or other ICS) or salmeterol (no longer approved for single-agent use) in a clinical practice setting for periods of up to 4 years in adults[39,41] or adults and adolescents;[40,44-46] one study also included children aged >5 years.[45]

Following 1 year of double-blind treatment with salmeterol/fluticasone propionate 50 μg/250 μg or fluticasone propionate 250 μg or salmeterol 50 μg (all administered twice daily) in 282 patients with mild to moderate asthma (described earlier in section 4.1.2),[24] patients were followed-up for a further 2 years (n = 229 completed 3 years) during which they continued open-label treatment.[39] As in the first year, medication was increased or decreased to maintain asthma control based on treatment guidelines. Increases in treatment at any time in the 3 years were required by 25% of patients randomized to salmeterol/fluticasone propionate, 47% of patients randomized to fluticasone propionate and 81% of patients randomized to salmeterol. At the end of the study, the proportion of patients maintaining asthma control with combined therapy versus fluticasone propionate or salmeterol was 73% versus 21% and 5%. The OR for requiring increased treatment in the fluticasone or salmeterol groups compared with the combined-therapy group was 2.66 (95% CI 1.43, 4.96; $p = 0.002$) and 9.38 (95% CI 4.68, 18.80; $p < 0.0001$).[39] Patients who had used ICS prior to the study were more likely to require a treatment increase than patients who had not.

In large (n = 1013–58 270) retrospective cohort analyses, the use of twice-daily salmeterol/fluticasone propionate was generally associated with better outcomes than twice-daily fluticasone propionate[40,41,44,46] or salmeterol.[45] In the largest of these analyses (n = 58 270), which used pharmacy and medical claims data in the US in patients with at least one prescription for either agent between 2001 and 2005, the adjusted OR of requiring hospitalization or an emergency department visit in the salmeterol/fluticasone propionate group compared with the fluticasone propionate group was 0.80 (95% CI 0.73, 0.88).[40] When the endpoints were assessed separately, there was a significant difference in favour of combined therapy for asthma-related emergency visits (OR 0.79; 95% CI 0.72, 0.87) but not for hospitalizations (OR 0.80; 95% CI 0.62, 1.02).

Similar results were observed in smaller retrospective analyses using medical claims data.[41,44,46] The OR of requiring hospitalization or an emergency department visit was significantly lower with salmeterol/fluticasone propionate compared with fluticasone propionate (OR 0.75; 95% CI 0.61, 0.93) in one analysis (n = 1013),[41] and in a second analysis in patients not well controlled on ICS (n = 1904), the risk of experiencing an asthma exacerbation was reduced by 36% in patients who had salmeterol added to fluticasone propionate compared with those whose fluticasone propionate dose was doubled (OR 0.64; 95% CI 0.51, 0.81; $p < 0.001$) [data reported in an abstract].[44] Adding salmeterol to fluticasone propionate in a fixed-dose combination or to beclomethasone in a separate inhaler for concurrent use improved

outcomes and the difference between treatment groups did not reach significance for the primary endpoint of hospitalizations or emergency department visits, but did reach significance in favour of salmeterol/fluticasone propionate for secondary endpoints, including SABA use and the need for oral corticosteroids (n = 2426).[46] One of these analyses also revealed that patients receiving twice-daily fixed-dose salmeterol/fluticasone propionate were less likely to require hospitalization or an emergency department visit than those receiving dual therapy with twice-daily salmeterol plus fluticasone propionate in separate inhalers (OR = 0.69; 95% CI 0.51, 0.95).[41]

Salmeterol combined with an ICS was also associated with better outcomes than salmeterol alone.[45] In a large (n = 33 339), case-control, retrospective cohort study of patients hospitalized for asthma (extracted from MEDSTAT's MarketScan database) over 1 year (333 hospitalizations in the year 2001), the use of concomitant salmeterol plus ICS was associated with a 32% risk reduction for hospitalization due to asthma compared with salmeterol without ICS.[45]

In a meta-analysis of observational studies, which included >80 000 asthmatic adults, salmeterol/fluticasone propionate was associated with a lower risk of asthma-related hospitalization (OR 0.85; 95% CI 0.74, 0.97) and asthma-related emergency department visits (OR 0.84; 95% CI 0.76, 0.94) than ICS alone.[51]

Observational Studies in Children

In inner-city children aged 4–17 years with a history of frequent emergency department visits or hospitalizations over the previous 2 years, salmeterol/fluticasone propionate 100 or 250 μg twice daily maintained better asthma control than usual care (predominantly ICS alone) over 1 year in a small (n = 50) prospective, open-label study.[42] The rate of hospitalizations and/or emergency department visits for each treatment group was compared with the mean recorded in the previous 2 years. Patients receiving salmeterol/fluticasone propionate had a 24% reduction in emergency department visits compared with an increase in the group continuing usual care ($p < 0.01$). Both groups had significant reductions in hospitalizations compared with treatment history, but the 69% reduction recorded in the combination therapy group was not significantly greater than the reduction recorded in the usual care group.[42]

Salmeterol/fluticasone propionate twice daily was associated with significantly fewer asthma-related emergency department event rates (41.4 vs 46.8) and hospitalization event rates (8.0 vs 11.0) [$p < 0.001$ for both] than ICS alone over 4.25 years in a large (n = 751 001), retrospective cohort study of asthmatic children aged 4–11 years (reported in an abstract).[43]

In a meta-analysis of observational studies, which included >43 000 asthmatics aged 2–17 years, salmeterol/fluticasone propionate was associated with a lower risk of asthma-related hospitalization or emergency department visits (OR 0.91; 95% CI 0.86, 0.97) than ICS alone.[51] In a similar analysis including 3790 children or adolescents, salmeterol/fluticasone propionate was associated with a lower risk of asthma-related hospitalization or emergency department visits than ICS plus montelukast (OR 0.46; 95% CI 0.27, 0.76).[51]

4.1.3 Meta-Analysis

A meta-analysis of pooled data from four, randomized, controlled trials[52,53,55,77] of up to 1 year's duration in adults and adolescents with persistent asthma (discussed in sections 4.1.1 and 4.1.2) aimed to identify patients on SABAs alone who would benefit from therapy with twice-daily salmeterol/fluticasone propionate 50 μg/100 μg or twice-daily fluticasone propionate 100 μg alone.[47] The proportion of patients achieving well controlled asthma was calculated according to GINA-defined criteria including, moderate to severe airflow limitations (FEV_1 or PEF ≤80% predicted normal), daily symptom assessment (symptom score ≥1 every day during the run-in period) and daily use of rescue medication (rescue medication used at least once during every day of the run-in period).

Results suggest that patients exhibiting two or three features of uncontrolled asthma at baseline were more likely to benefit from twice-daily salmeterol/fluticasone propionate than from twice-daily fluticasone propionate, with the greatest difference reported in patients with three baseline

features (43% vs 23% achieved well controlled asthma; OR 2.60; 95% CI 1.87, 3.62; $p < 0.001$).[47] When subgroup analyses evaluated patients with three baseline features, treatment with salmeterol/fluticasone propionate was associated with significantly greater improvements than fluticasone propionate in mean morning PEF, percentage of symptom-free days, nights with no awakenings, rescue-free days and the time to the first week of well controlled asthma (all $p < 0.001$). Among patients with two baseline features, these same endpoints were improved significantly more in the combination-therapy group than in the fluticasone propionate group ($p < 0.05$ for all), except for nights with no awakenings.[47]

4.2 Compared with Concurrent Salmeterol Plus Fluticasone Propionate

The combination of twice-daily salmeterol/fluticasone propionate (50 μg/100 μg,[66] 50 μg/250 μg[65] or 50 μg/500 μg[64]) in a single inhaler was as effective as the same dosages of twice-daily salmeterol plus fluticasone propionate administered concurrently using separate inhalers in three randomized, double-blind, multicentre, 12-[66] or 28-week[64,65] trials in adults or adolescents with asthma (table III). There were no significant differences in improvements from baseline in mean morning PEF (primary endpoint in all trials) or FEV_1 in either treatment group in each of the studies, but in one study, mean evening PEF improved significantly more from baseline in patients receiving the fixed combination compared with patients receiving concurrent therapy ($p < 0.01$).[65]

As demonstrated in adults and adolescents,[66] the combination of twice-daily salmeterol/fluticasone propionate 50 μg/100 μg in a single inhaler was as effective as the same dosages of twice-daily salmeterol plus fluticasone propionate administered concurrently using separate inhalers in a randomized, double-blind, multicentre, 12-week trial in children aged 4–11 years with persistent asthma while receiving ICS (table III).[32] There were no significant differences between-treatment groups in mean morning PEF (primary endpoint), evening PEF, FEV_1, number of symptom-free or rescue-free days.[32]

In a meta-analysis of the three adult studies[64-66] and one in children,[32] the between-treatment group difference in mean morning (5.4 L/min; $p < 0.01$) and evening (6.1 L/min; $p < 0.001$) PEF was found to be significant in favour of salmeterol/fluticasone propionate compared with concurrent therapy of each agent at the same dosage.[49]

4.3 Compared with Budesonide or Formoterol/Budesonide

Twice-daily salmeterol/fluticasone propionate was more effective than twice-daily budesonide monotherapy in symptomatic adults and adolescents previously treated with ICS in two randomized, double-blind, double-dummy, multicentre trials.[69,70] In a 12-week study, twice-daily salmeterol/fluticasone propionate 50 μg/100 μg was compared with twice-daily budesonide 400 μg ($n = 349$),[70] and in a 24-week study, twice-daily salmeterol/fluticasone propionate 50 μg/250 μg was compared with twice-daily budesonide 800 μg ($n = 338$).[69] The mean morning increase from baseline in PEF (primary endpoint) was 45 versus 19 L/min ($p < 0.001$), respectively, in the lower-dosage study,[70] and 43 versus 33 L/min ($p < 0.05$), respectively, in the higher-dosage study.[69]

Results of studies comparing salmeterol/fluticasone propionate with formoterol/budesonide have been mixed. A similar level of asthma control, according to primary efficacy endpoints, was demonstrated in two randomized, double-blind,[27,71] and two open-label,[73,78] multicentre studies of about 6 months' duration comparing salmeterol/fluticasone propionate with formoterol/budesonide (table IV). However, in three further 6-[72] or 12-month[26,75] studies (two were double-blind[26,72] and one was open-label[75]), asthma control was improved to a greater extent with salmeterol/fluticasone propionate in one study,[26] and with formoterol/budesonide in the other two studies.[72,75] Worthy of note in these studies are the dosages selected for comparison. Only one study compared the maximum recommended daily dosages of each agent (i.e. twice-daily salmeterol/fluticasone propionate 50 μg/500 μg with twice-daily formoterol/budesonide 9 μg/320 μg),[71] whereas the other studies compared a lower dosage of salmeterol/fluticasone propionate (50 μg/250 μg twice-daily) with the maximum

Table III. Efficacy of salmeterol/fluticasone propionate (S/FP) compared with concurrently administered salmeterol (SAL) plus fluticasone propionate (FP) in patients (pts) with persistent asthma[a] previously treated with inhaled corticosteroids. Results are from randomized, double-blind, multicentre trials of 12[32,66] or 28[64,65] weeks' duration. The primary endpoint in all studies was the mean improvement from baseline in morning peak expiratory flow (PEF) and analyses were in the intent-to-treat population. S/FP was administered twice daily (bid) via a Diskus® dry powder inhaler and patients continued to receive short-acting β_2-adrenoceptor agonists as required

Study [trial duration (wk)]	Regimen (μg bid) [no. of pts]	Mean increase from baseline			
		morning PEF (L/min)[b]	evening PEF (L/min)	FEV_1 (L)	symptom-free days (%)[c]
Adults and adolescents					
Aubier et al.[64]	S/FP 50/500 [167]	35[d]	29*[d]	0.25[e]	
(28)	SAL 50 + FP 500 [171]	33[d]	23[d]	0.15[e]	
	FP 500 [165]	15[d]	9[d]	0.18[e]	
Bateman et al.[66]	S/FP 50/100 [121]	42	36	0.20	
(12)	SAL 50 + FP 100 [123]	33	30	0.17	
Chapman et al.[65]	S/FP 50/250 [180]	43[d]	35†[d]	0.26[d]	34[d]
(28)	SAL 50 + FP 100 [191]	36[d]	25[d]	0.24[d]	30[d]
Children					
Van den Berg et al.[32]	S/FP 50/100 [125]	33	25	0.31	37
(12)	SAL 50 + FP 100 [132]	28	29	0.13	39

a Mean baseline FEV_1 values were approximately 73%,[64] 75%,[66] 76%[65] and 85%[32] of predicted values.

b Mean morning PEF baseline measures were ≈352,[64] ≈366,[66] ≈395[65] and 242 L/min.[32]

c Median value.

d 12-wk data reported.

e Estimated from a graph.

FEV_1 = forced expiratory volume in 1 second; * $p < 0.001$ vs FP; † $p < 0.01$ vs SAL + FP.

recommended dosage of formoterol/budesonide (9 μg/320 μg twice daily).[26,27,72,73,75,78] However, one study also included a treatment arm that received a lower dosage of formoterol/budesonide.[72]

In two large (n >2250), double-blind, 6-month studies,[71,72] and one large (n = 2143), open-label, 12-month study[75] in adults and adolescents comparing twice-daily salmeterol/fluticasone propionate plus terbutaline or salbutamol as needed with twice-daily formoterol/budesonide maintenance and reliever therapy, the time to first severe asthma exacerbation (primary endpoint) was not significantly different between treatment groups in one study (patients received high-dose salmeterol/fluticasone propionate 50 μg/500 μg),[71] but was shorter ($p < 0.01$) with salmeterol/fluticasone propionate plus terbutaline or salbutamol in the other two studies[72,75] (table IV). In these trials, the severe exacerbation rate per 100 patient-years (31 vs 25 [$p < 0.05$];[71] 19 vs 12 [$p < 0.001$];[72] and 31 vs 24 [$p < 0.01$][75]) and the hospital/emergency department visit rate per 100 patient-years in two trials (13 vs 9 [$p < 0.05$];[71] and 8 vs 5 [$p < 0.01$][72]) was significantly higher in the groups receiving fixed-dose salmeterol/fluticasone propionate plus terbutaline than in the groups receiving maintenance and reliever therapy with formoterol/budesonide.

Results from studies using SABAs as relief therapy in addition to study medication were somewhat different to those already described, in which formoterol/budesonide was used for maintenance and relief. The adjusted annual mean exacerbation rate was significantly lower with fixed-dose twice-daily salmeterol/fluticasone propionate than with adjustable maintenance dosages of twice-daily formoterol/budesonide in the double-blind CONCEPT (CONtrol CEntered Patients Treatment) study (0.18 vs 0.33; $p < 0.01$; relative risk reduction of 47%).[26] The primary efficacy analysis in this study demonstrated that patients receiving fixed dosages of twice-daily salmeterol/fluticasone propionate had significantly more symptom-free days (24-hour period

Table IV. Efficacy of salmeterol/fluticasone propionate (S/FP) compared with formoterol/budesonide (F/BUD) in patients (pts) with symptomatic asthma.[a] Results are intent-to-treat analyses from randomized, multicentre trials of 24 weeks to 1 year in adults[26,27] or adults and adolescents[71-74,78] previously treated with inhaled corticosteroids. S/FP was administered via a Diskus® dry powder inhaler and where F/BUD was not given for relief therapy,[71,72,75] pts continued to receive short-acting β_2-adrenoceptor agonists as required (prn)

Study (trial duration)	Regimen (μg)	No. of pts	Asthma exacerbations[b] (% of pts)	Increase from baseline (mean value unless stated otherwise)				
				morning PEF (L/min)	evening PEF (L/min)	rescue-free days (%)	symptom-free days (%)	nights with no awakenings (%)
Double-blind studies								
Bousquet	S/FP 50/500 bid + TER prn	1145	11.3[c]	30	24	49	37	19
et al.[71] (6 mo)	F/BUD 4.5/160 2 inhal bid + prn	1144	9.4[c]	29	26	48	37	20
Dahl et al.[27]	S/FP 50/250 bid	694	10[c]	42		82	63	
(24 wk)	F/BUD 4.5/160 2 inhal bid	697	11[c]	41		81	60	
Fitzgerald	S/FP 50/250 bid	344	11.3	38**		91**	59*[c]	
et al.[26] (12 mo)	F/BUD 4.5/160 2 inhal bid for	344	17.7	28		86	52[c]	
[CONCEPT study]	4 wk then AMD[d]							
Kuna et al.[72]	S/FP 25/125 2 inhal	1123	12[c]	29	23	50	37	18
(24 wk)	bid + TER prn							
	F/BUD 4.5/160 1 inhal bid + prn	1107	9†‡[c]	26	22	47	35	20
	F/BUD 9/320 1 inhal bid + TER prn	1105	11[c]	27	22	49	36	18
Open-label studies								
Aalbers et al.[73]	S/FP 50/250 bid	224	22	35				
(6 mo)[e]	F/BUD 4.5/160 2 inhal bid for 4 wk then AMD[f]	219	16	27				
	F/BUD 4.5/160 2 inhal bid	215	27	34				
Busse et al.[78]	S/FP 50/250 bid	404	9.2[c]	34		39	25	8
(6 mo)[g]	F/BUD 4.5/160 2 inhal bid for 4 wk then AMD[h]	389	8[c]	35		42	27	10
	F/BUD 4.5/160 2 inhal bid	422	8.8[c]	31		41	26	10
Vogelmeier et al.[75]	S/FP 50/250 bid + SAB prn	1076	19[c]					
(12 mo)	F/BUD 4.5/160 2 inhal bid + prn	1067	15[c]					

a Mean baseline FEV_1 measurements were approximately 71%,[71] 78%,[27] 81%,[26] 73%,[72] 85%,[73] 79%[78] and 73%[75] of predicted values.

b Generally includes moderate to severe exacerbations. In three studies, the primary endpoint was the time to first severe exacerbation, which was not significantly different between treatment groups in one,[71] and significantly shorter with S/FP plus TER,[72] or S/FP plus SAB,[75] than with F/BUD for maintenance and relief in the other two ($p < 0.01$ for all).

c Primary endpoint.

d If asthma control was achieved after the first 4 wk, pts reduced F/BUD dosage to 1 inhal bid then 1 inhal/day, and if asthma worsened, pts reverted to 1 inhal bid.

e Before commencing the 6-mo open-label phase, pts received double-blind treatment with fixed dosages of S/FP or F/BUD for 1 mo.

f If asthma control was achieved after the first 4 wks, pts reduced F/BUD dosage to 1 inhal bid, and if asthma worsened, pts could increase up to 4 inhals bid for 7–14 d.

g Pts received fixed dosages of S/FP or F/BUD for 1 mo, after which, those receiving F/BUD were randomized to fixed or AMD of F/BUD for 6 mo.

h If asthma control was achieved after the first 4 wk, pts reduced F/BUD dosage to 2 inhal od, and if asthma worsened, pts could increase up to 4 inhals bid for 7–14 d.

AMD = adjusted maintenance dosage; **bid** = twice daily; **CONCEPT** = CONtrol CEntered Patients Treatment study; **inhal** = inhalations; **od** = once daily; **PEF** = peak expiratory volume; **SAB** = salbutamol; **TER** = terbutaline; * $p < 0.05$, ** $p < 0.01$ vs F/BUD AMD; † $p < 0.001$ vs S/FP + TER; ‡ $p < 0.05$ vs F/BUD + TER.

with a symptom score of 0) in 1 year than patients receiving adjustable maintenance dosages of twice-daily formoterol/budesonide (table IV) [both groups had no symptom-free days at baseline].[26] Interestingly, during the initial 4-week period in which both treatment groups received fixed dosages, the percentage of symptom-free days was not significantly different between groups, but from week 5 to 52, when dosage adjustment of formoterol/budesonide was allowed, the percentage of symptom-free days was significantly higher in the salmeterol/fluticasone propionate group (74% vs 65%; $p < 0.05$).[26]

The mean rate of exacerbations (primary endpoint) in two 6-month studies (one double-blind[27] and one open-label[78]) was not significantly different between groups receiving fixed-dose twice-daily salmeterol/fluticasone propionate or fixed-dose twice-daily formoterol/budesonide (2.69 vs 2.79; includes mild exacerbations),[27] or between fixed-dose twice-daily salmeterol/fluticasone propionate or fixed- or adjustable dosages of twice-daily formoterol/budesonide (0.189 vs 0.24 and 0.196).[78] Furthermore, in another open-label, 6-month study, the odds of achieving a well controlled asthma week (primary endpoint) were not significantly different between fixed dosages of salmeterol/fluticasone propionate and adjustable dosages of formoterol/budesonide, but were significantly higher with adjustable than with fixed maintenance dosages of formoterol/budesonide ($p < 0.05$) [all drugs administered twice daily].[73]

In a well designed 12-week, noninferiority study in adults and adolescents ($n = 428$) comparing twice-daily salmeterol/fluticasone propionate 50 μg/250 μg with twice-daily concurrent formoterol 12 μg plus budesonide 800 μg, the mean increase from baseline in morning PEF in the per-protocol population (primary endpoint) was not significantly different between treatment groups (43 vs 41 L/min; treatment difference −3.2 L/min [95% CI −15.0,8.6]).[74] Thus, salmeterol/fluticasone propionate 50 μg/250 μg was noninferior to relatively higher dosages of formoterol 12 μg plus budesonide 800 μg, based on the lower limit of the confidence interval being greater than or equal to −15 L/min.[74]

4.4 Compared with Montelukast with or without Fluticasone Propionate

4.4.1 Adults and Adolescents

Salmeterol/fluticasone propionate 50 μg/100 μg twice daily was significantly more effective than monotherapy with oral montelukast 10 mg once daily in symptomatic patients previously treated with SABAs,[56,57] and significantly more effective than concomitant therapy with oral montelukast 10 mg once daily plus fluticasone propionate 100 μg twice daily in symptomatic patients previously treated with ICS,[67,68] in randomized, double-blind, 12-week studies (table V). For all endpoints summarized in table V, the treatment difference significantly favoured twice-daily salmeterol/fluticasone propionate ($p < 0.05$).

The incidence of asthma exacerbations (generally defined as a requirement for asthma medication other than that permitted by the protocol) was also lower in patients receiving salmeterol/fluticasone propionate 50 μg/100 μg twice daily than in patients receiving montelukast 10 mg once daily plus fluticasone propionate 100 μg twice daily (2% vs 6% of patients experienced an asthma exacerbation in one study[68] and 10% vs 15% of patients had at least one exacerbation in the second study;[67] $p < 0.05$ for both).

The results of individual studies are supported by those of a meta-analysis (reported in an abstract)[50] of the four studies[56,57,67,68] discussed in this section. Treatment with salmeterol/fluticasone propionate ($n = 1053$) was associated with a significantly lower incidence of asthma attacks than treatment with oral montelukast alone ($n = 428$) or with fluticasone propionate ($n = 626$) [$p \leq 0.01$ for both].[50]

Results from a 12-month observational study of asthmatics aged ≥15 years ($n = 1414$) who commenced therapy with twice-daily salmeterol/fluticasone propionate or once-daily oral montelukast suggested that treatment with salmeterol/fluticasone propionate was more likely to improve asthma symptoms, as assessed by several outcome measures, and HR-QOL measures, and reduce the need for emergency care or hospitalization.[88]

Table V. Efficacy of salmeterol/fluticasone propionate (S/FP) compared with oral montelukast (MON) with or without fluticasone propionate (FP), or sustained-release theophylline (SR-T) plus FP in patients (pts) with asthma.[a] Results are from randomized, double-blind, multicentre trials of 12 weeks' duration (except for one trial of 8 weeks[28]) in adults,[28] adults and adolescents,[56,57,67,68] or children.[33] Pts had previously been treated with short-acting β_2-adrenoceptor agonists (SABAs),[33,56,57] inhaled corticosteroids (ICS)[67,68] or oral SR-T.[28] The primary endpoint was the mean improvement from baseline in mean morning peak expiratory flow (PEF) [four studies[28,33,67,68]] or forced expiratory volume in 1 second (FEV_1) [two studies[56,57]], and analyses were in the intent-to-treat (ITT) population. S/FP was administered via a Diskus® dry powder inhaler and pts continued to receive SABAs as required

Study	Regimen [no. of pts]	Increase from baseline (mean value unless stated otherwise)				
		morning PEF (L/min)[b]	evening PEF (L/min)	FEV_1 (L)[c]	symptom-free days (%)	SABA-free days (%)
Compared with monotherapy with oral MON						
Calhoun et al.[56]	S/FP 50/100 μg bid [211]	90**	70**	0.54**	49**	53**
	MON 10 mg od [212]	34	31	0.27	22	26
Pearlman et al.[57]	S/FP 50/100 μg bid [216]	81**	65**	0.61**	40**	53**
	MON 10 mg od [216]	42	39	0.32	27	27
Children aged 6–14 years						
Maspero et al.[33]	S/FP 50/100 μg bid [281]	46**	46**	0.47**	9*	9**
[PEACE study]	MON 5 mg od [267]	29	29	0.30	4	6
Compared with oral MON plus FP						
Nelson et al.[68]	S/FP 50/100 μg bid [222]	25**	19**	0.34**		26*
	MON 10 mg od + FP 100 μg bid [225]	13	10	0.20		19
Ringdal et al.[67]	S/FP 50/100 μg bid [356]	36*	29*	0.26*	50*[d]	71*[d]
	MON 10 mg od + FP 100 μg bid [369]	19	14	0.17	39[d]	67[d]
Compared with oral SR-T plus FP						
Adachi et al.[28]	S/FP 50/250 μg bid [194]	30**[e]	24*	0.17*		
	SR-T 200 mg + FP 250 μg bid [188]	16[e]	14	0.05		

a Mean baseline FEV_1 measurements were approximately 67%,[56,57,68] 73%,[33] 75%[67] and 66%[28] of predicted values.

b In studies evaluating PEF as the primary endpoint, baseline measures were 218,[33] ≈396,[68] ≈368[67] and ≈325[28] L/min.

c In studies evaluating FEV_1 as the primary endpoint, mean morning baseline measures were ≈2.43[56] and ≈2.40[57] L.

d Median value.

e Treatment difference in ITT population (results for the ITT and per-protocol populations were similar, so only results for the ITT population were reported) was 13.4 L/min (95% CI 6.00, 20.86; $p < 0.001$), thereby demonstrating superiority of S/FP based on predefined lower limit of the 95% CI >0 L/min.

bid = twice daily; **od** = once daily; * $p < 0.05$, ** $p \leq 0.001$ vs comparator.

4.4.2 Children

Two randomized, double-blind, double-dummy studies in children aged 6–14 years with persistent asthma reported better asthma control with salmeterol/fluticasone propionate than with oral montelukast.[33,89] In the 12-week PEACE (PEdiatric Asthma Control Evaluation) study, the adjusted mean increase from baseline in morning PEF (primary endpoint) was significantly greater with salmeterol/fluticasone propionate 50 μg/100 μg than with oral montelukast 5 mg once daily (46 vs 29 L/min; $p < 0.001$).[33] Similarly, the treatment difference for all other endpoints significantly favoured salmeterol/fluticasone propionate ($p < 0.05$) [table V].[33]

The 48-week PACT (Pediatric Asthma Controller Trial) compared three treatment regimens: salmeterol/fluticasone propionate 50 μg/100 μg in the morning plus salmeterol 50 μg in the evening (PACT combination group; n = 94), oral montelukast 5 mg in the evening (n = 95), or fluticasone propionate 100 μg morning and evening (n = 96).[89] The percentage of days with asthma control (generally defined as no requirement for asthma medication other than that permitted by the protocol, no symptoms or night-time

awakenings, and no unscheduled hospital visits) was greater in the the twice-daily fluticasone propionate group than in the montelukast group (64% vs 53%; $p < 0.01$); the percentage of asthma-control days in the PACT combination group, which received fluticasone propionate only once daily in the morning, was 60% (nonsignificant difference with other treatment groups).[89]

4.5 Compared with Other Agents

Compared with twice-daily oral sustained-release theophylline 200 mg plus fluticasone propionate 250 μg, twice-daily salmeterol/fluticasone propionate 50 μg/250 μg was significantly more effective in a randomized, double-blind, double-dummy, multicentre, 8-week study in adult asthmatics in Japan (table V).[28] The significant difference between treatment groups in favour of salmeterol/fluticasone propionate was evident from day 1.

Twice-daily beclomethasone/formoterol 100 μg/6 μg was noninferior to salmeterol/fluticasone propionate 25 μg/125 μg in a randomized, double-blind, multicentre, 12-week noninferiority study in adult asthmatics (n = 225; per-protocol population).[29] The improvement in mean morning PEF (from baseline measures of 330 and 333 L/min, respectively) in the final 2 weeks of treatment was not significantly different between groups (49 vs 53 L/min, respectively; treatment difference −3.32 [95% CI −17.92, 11.28]). Thus the noninferiority of beclomethasone/formoterol compared with salmeterol/fluticasone propionate was demonstrated based on the predefined lower limit of the 95% confidence interval being greater than −20 L/min.[29]

4.6 Step-Down Therapy

In patients with asthma well controlled with twice-daily salmeterol/fluticasone propionate 50 μg/250 μg, stepping-down therapy to twice-daily salmeterol/fluticasone propionate 50 μg/100 μg was more effective than switching to fluticasone propionate 250 μg alone in two well designed, noninferiority trials (table VI).[25,79] Based on mean morning PEF measurements, twice-daily fluticasone propionate 250 μg did not demonstrate noninferiority to twice-daily salmeterol/fluticasone propionate 50 μg/250 μg[25] or 50 μg/100 μg,[79] and twice-daily salmeterol/fluticasone propionate 50 μg/100 μg demonstrated noninferiority to twice-daily salmeterol/fluticasone propionate 50 μg/250 μg.[25] Furthermore, based on predefined criteria to claim superiority, twice-daily salmeterol/fluticasone propionate 50 μg/100 μg was significantly more effective than twice-daily fluticasone/propionate 250 in patients who were well controlled with twice-daily salmeterol/fluticasone propionate 50 μg/250 μg (table VI).[79]

Similar results were observed with secondary endpoints. For example, after switching from salmeterol/fluticasone propionate 50 μg/250 μg, the mean change in daytime asthma symptom score after 12 weeks' treatment with salmeterol/fluticasone propionate 50 μg/100 μg or fluticasone propionate 250 μg was 0.03 versus 0.09 ($p < 0.05$).[79]

Asthma control worsened when patients who were well controlled on twice-daily salmeterol/fluticasone propionate 50 μg/100 μg were stepped down to monotherapy with twice-daily fluticasone propionate 100 μg, salmeterol 50 μg or montelukast 10 mg orally (table VI).[80]

In a randomized, double-blind, 16-week study of patients aged >6 years with mild asthma that was well controlled with twice-daily fluticasone propionate 100 μg, asthma control was maintained with a switch to once-daily salmeterol/fluticasone propionate 50 μg/100 μg but not with a switch to once-daily oral montelukast 5 or 10 mg.[34] The treatment failure rate (primary endpoint; generally defined as a need for hospitalization or therapy other than that defined in the protocol) in the groups receiving once-daily (at night) salmeterol/fluticasone propionate 50 μg/100 μg, twice-daily fluticasone propionate 100 μg or once-daily oral montelukast 5 μg (children aged 6–14 years) or 10 mg was 20.4%, 20.2% and 30.3% ($p < 0.05$ for both comparisons with montelukast).[34]

4.7 Health-Related Quality of Life

Twice-daily salmeterol/fluticasone propionate achieved clinically meaningful improvements from baseline in HR-QOL based on overall AQLQ scores. In the GOAL study (section 4.1.2), AQLQ

Table VI. Efficacy of stepping-down therapy with salmeterol/fluticasone propionate (S/FP) in patients (pts) with well controlled asthma.[a] Adults[25] or adults and adolescents[79,80] with well controlled asthma during an open-label run-in period were randomized to step-down therapy in a double-blind manner in multicentre trials. The primary endpoint was the mean improvement from baseline in morning peak expiratory flow (PEF). Results shown are for the intent-to-treat (ITT) population unless stated otherwise. S/FP was administered twice daily (bid) via a Diskus® dry powder inhaler and pts continued to receive short-acting β_2-adrenoceptor agonists as required

Study [trial duration (wk)]	Regimen prior to randomization (μg bid)	Regimen (μg bid unless stated otherwise)	No. of pts in ITT [PP] population	Mean change from baseline		
				morning PEF (L/min)[b]	symptom-free days (%)	rescue-free days (%)
Bateman et al.[79]	S/FP 50/250	S/FP 50/100	246 [208]	−0.3**[c]		
[12]		FP 250	238 [188]	−13.2[c]		
Godard et al.[25]	S/FP 50/250	S/FP 50/250	159 [117]	1.76***[d]	−0.8*[e]	−0.6*[e]
[24]		S/FP 50/100	157 [129]	−3.1[d]	−1.6[e]	−2.2[e]
		FP 250	159 [113]	−16.5[d]	−5.5[e]	−5.4[e]
Koenig et al.[80]	S/FP 50/100	S/FP 50/100	172	4**†‡[f]	5.7	5.7
[16]		FP 100	159	−17[f]	−0.5	−9.6
		SAL 50	152	−26[f]	−5.1	−15.5
		MON 10 mg orally od	164	−32[f]	−10.0	−20.7

a Definition of asthma control based on that used in GOAL study (section 4.1.2)[25,79] or satisfying several criteria including FEV_1 ≥95% of pts best.[80]

b Mean morning PEF baseline measures were ≈414,[79] ≈465[25] and ≈396[80] L/min.

c Treatment difference in PP population (actual data not reported) was 16.0 L/min (95% CI 10.8, 21.2; $p < 0.001$), thereby not demonstrating noninferiority of FP 250 to S/FP 50/100 based on predefined limit for noninferiority of a lower 95% CI limit of greater than −15 L/min. Treatment difference in ITT population was 12.9 L/min (95% CI 8.1, 17.6; $p < 0.001$), thereby demonstrating superiority of S/FP 50/100 over FP 250 based on predefined limit for superiority of a lower 95% CI limit >0.

d Primary endpoint in PP population at 12 wk. Mean difference between S/FP 50/250 and S/FP 50/100 was −4.83 L/min (97.5% CI −12.39, 2.72), thereby demonstrating noninferiority of S/FP 50/100 to S/FP 50/250. Mean difference between S/FP 50/250 and FP 250 was −18.27 L/min (97.5% CI −26.05, −10.49; $p < 0.0001$), thereby not demonstrating noninferiority of FP 250 to S/FP 50/250. Predefined limit for noninferiority was a lower CI limit greater than −15 L/min.

e Results are at 12 wk.

f Data are estimated from a figure.

FEV_1 = forced expiratory volume in 1 second; **FP** = fluticasone propionate; **MON** = montelukast; **od** = once daily; **PP** = per protocol; **SAL** = salmeterol; * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ vs FP; † $p < 0.001$ vs SAL; ‡ $p < 0.001$ vs MON.

scores improved in both the salmeterol/fluticasone propionate group and the fluticasone propionate group throughout the 1-year study, and in strata 2 and 3, the difference between treatment groups was significant in favour of combination salmeterol/fluticasone propionate treatment ($p < 0.005$).[55] After 52 weeks' treatment, the proportion of patients with near maximum mean overall AQLQ scores (i.e. a score of ≥6) had increased in the salmeterol/fluticasone propionate and fluticasone propionate groups from 6–10% at baseline to 63% versus 62% in stratum 1, 64% versus 53% in stratum 2 and 57% versus 45% in stratum 3. Furthermore, mean AQLQ scores were significantly higher in patients achieving total control than in those classified as well controlled ($p < 0.001$), and between those with well controlled or not well controlled asthma ($p < 0.001$).[85]

The mean change in overall AQLQ score was not significantly different between groups receiving fixed dosages of salmeterol/fluticasone propionate or adjustable maintenance dosages of formoterol/budesonide in the 1-year CONCEPT trial[26] (section 4.3) in symptomatic patients previously receiving ICS with or without LABAs.[86] However, a *post hoc* analysis showed that significantly more patients in the salmeterol/fluticasone propionate group experienced a minimally important difference (i.e. an improvement of ≥0.5) in AQLQ overall score than those in the formoterol/budesonide group at 28 weeks (68% vs 60%; $p < 0.05$), but not at 52 weeks (71% vs 65%).[86]

In contrast, adjustable or fixed dosages of formoterol/budesonide were associated with significantly greater patient mean satisfaction scores than fixed dosages of salmeterol/fluticasone propionate for the ATSM items of onset of action (51.3 [$p < 0.01$] and 52.9 [$p < 0.05$] vs 47.7 points) and sensation that medication is working (40.1 [$p < 0.01$] and 36.6 [$p < 0.05$] vs 32.8 points) in patients ($n = 832$) aged ≥18 years previously receiving ICS (reported in an abstract and poster).[87]

Compared with once-daily oral montelukast 10 mg, twice-daily salmeterol/fluticasone propionate 50 μg/100 μg achieved significantly greater improvements in AQLQ scores ($p < 0.001$) in symptomatic patients previously treated with as required SABAs alone (section 4.4.1).[57]

5. Tolerability

Tolerability data for salmeterol/fluticasone propionate are derived from clinical studies (see section 4 for trial design and dosage details), and from the manufacturer's prescribing information.[20] The drug is generally well tolerated in adults, adolescents and children and, overall, the most frequent treatment-related adverse effects associated with treatment include upper respiratory tract infection, pharyngitis, headaches and throat irritation/cough.[20]

In clinical trials, the incidence of treatment-related effects was generally similar to that of comparator agents. For example, in the GOAL study, the most common (occurring in ≥5% of either treatment group) adverse events were nasopharyngitis (13% in the salmeterol/fluticasone propionate group vs 14% in the fluticasone propionate group), upper respiratory tract infection (13% vs 13%), headache (5% vs 7%), sinusitis (5% vs 4%) and influenza (5% vs 4%).[55] Similarly, drug-related adverse events occurred in 6.3% of salmeterol/fluticasone propionate recipients and 5.9% of formoterol/budesonide recipients in the CONCEPT trial.[26] Nine (2.5%) serious adverse events occurred in each group, two and three of these, respectively, led to asthma exacerbations and hospitalization.[26] In a 12-week study comparing salmeterol/fluticasone propionate with oral montelukast, the incidence of drug-related adverse effects was 8% versus 11%, and the most common events were headache (2% vs 1%), dry mouth (<1% vs 1%) and hoarseness (3% vs <1%).[57] The incidence of adverse events in treatment groups receiving salmeterol/fluticasone propionate or oral sustained-release theophylline plus fluticasone propionate were also not significantly different.[28] Salmeterol/fluticasone propionate has not been associated with clinically relevant laboratory test abnormalities.[20] The tolerability profile of twice-daily salmeterol/fluticasone propionate 50 μg/100 μg, 50 μg/250 μg and 50 μg/500 μg administered via a hydrofluoroalkane MDI for 1 year was not different to that of the Diskus® inhaler.[90]

In children, frequent adverse events not generally reported in adults include throat irritation and ear, nose and throat infections.[20] In a well designed 12-week safety study in asthmatic children aged 4–11 years ($n = 203$) previously receiving ICS who were randomized to twice-daily salmeterol/fluticasone propionate 50 μg/100 μg or fluticasone propionate 100 μg, the overall incidence of adverse events (all cause) was 59% versus 57%.[91] The percentage of children experiencing asthma exacerbations was 3% versus 8%, and 2% versus 5% were withdrawn from the study because of asthma exacerbations.[91] The most commonly reported adverse event in children aged 6–14 years receiving salmeterol/fluticasone propionate or oral montelukast (section 4.4.2) was headache (all causalities, 23% vs 27%).[33] The incidence of treatment-related adverse effects was 2% in each treatment group, with serious events reported in zero and three patients, respectively.[33]

Although systemic effects associated with ICS are less likely than with oral corticosteroids, possible adverse effects, particularly with high ICS dosages, include Cushing's syndrome, adrenal suppression and growth retardation in children and adolescents.[20] After 2 years of treatment, the difference in height increase from baseline in children (aged 6–14 years) randomized to salmeterol/fluticasone propionate 50 μg/100 μg in the morning plus salmeterol 50 μg in the evening, fluticasone propionate 100 μg morning and evening, or oral montelukast 5 mg in the evening did not reach significance (5.3, 5.3 and 5.7 cm, respectively).[89] Furthermore, 24-hour urinary cortisol excretion

remained within normal limits after 12 weeks of treatment with salmeterol/fluticasone propionate 50 μg/100 μg in children aged 4–11 years.[91]

Excessive use of local corticosteroids, such as fluticasone propionate, are associated with a localized infection of the mouth and pharynx with *Candida albicans*.[20] In adult and adolescent asthmatics receiving twice-daily salmeterol/fluticasone propionate 50 μg/100 μg or 50 μg/250 μg in placebo-controlled trials, the incidence of oral candidiasis was 1% and 4%, and the incidence of hoarseness/dysphonia was 5% and 2%.[20] Monotherapy with LABAs, such as salmeterol, may increase the risk of asthma-related death,[92] and a warning to this effect is included in the manufacturer's prescribing information.[20] As a result, treatment guidelines state that LABAs should only be used in combination with an ICS.[3,93]

6. Pharmacoeconomic Considerations

Pharmacoeconomic analyses on the use of salmeterol/fluticasone propionate in the management of asthma have been reviewed previously.[4,94] This section summarizes recent (i.e. those with a year of costing of 2003 or later) analyses[95-100] based on well designed studies[55,57,75] (see section 4 for study details). Cost-effectiveness analyses were performed from the perspective of a healthcare payer[95-100] (i.e. included direct medical costs) and/or society (i.e. included total [direct and indirect] costs).[97,98]

Salmeterol/fluticasone propionate was cost effective relative to monotherapy with fluticasone propionate[95,99,100] or oral montelukast (or other leukotriene modifiers)[96,99] with regard to the incremental cost per quality-adjusted life-years (QALY) gained, per symptom- or rescue-free day, or cost per 12% improvement in FEV_1, but results of studies comparing salmeterol/fluticasone propionate with formoterol/budesonide were mixed (table VII).[97,98,100]

In the cost-utility analysis[95] based on the GOAL study,[55] the improved asthma control (section 4.1.1) associated with salmeterol/fluticasone propionate relative to fluticasone propionate alone led to direct costs per QALY gained of ≤£13 700 (table VII),[95] which are likely to be considered cost effective based on National Institute of Clinical Excellence (NICE) value judgments.[101] Furthermore, a decision-analysis model that estimated US costs and health outcomes over 1 year, based on various clinical data, reported an incremental cost-effectiveness ratio of $US9.55 per symptom-free day with salmeterol/fluticasone propionate versus fluticasone propionate alone.[99]

In two analyses[97,98] that were based on the clinical trial by Vogelmeier et al.,[75] in which the maximum recommended dosage of formoterol/budesonide administered for maintenance and relief achieved greater efficacy than relatively lower dosages of salmeterol/fluticasone propionate plus salbutamol for relief (section 4.3), formoterol/budesonide was considered more cost effective relative to salmeterol/fluticasone propionate with regard to the direct or total cost per severe exacerbation avoided (table VII).[97,98] However, a further modelled analysis of direct costs based on 2006 prices (UK) and using various clinical data in adults, adolescents and children with uncontrolled asthma found that salmeterol/fluticasone propionate, with regard to QALYs gained, was a cost effective alternative to formoterol/budesonide, and was cost effective relative to increasing the dose of either fluticasone propionate or beclomethasone dipropionate.[100]

Where reported, sensitivity analyses demonstrated that results were robust to changes in key parameters.[96,99,100]

Pharmacoeconomic analyses of salmeterol/fluticasone propionate, as with all such modelled analyses, are subject to a number of limitations, with the potential for input data to differ from real-life situations. However, modelled cost-effectiveness analyses with salmeterol/fluticasone propionate were generally well conducted, included appropriate parameters, and model designs were justified. As is common for pharmacoeconomic studies, analyses were sponsored by the pharmaceutical industry.[95-100]

7. Dosage and Administration

In the EU, salmeterol/fluticasone propionate is indicated for long-term maintenance treatment of adults, adolescents and children aged ≥4 years, who

Table VII. Pharmacoeconomic studies of twice-daily salmeterol/fluticasone propionate (S/FP). Analyses were based on clinical trials of S/FP vs fluticasone propionate (FP) or formoterol/budesonide (F/BUD), oral montelukast (MON), or other leukotriene modifiers (LEU) in adults and adolescents,[95-99] or in adults, adolescents and children[100] with asthma. Analyses included direct costs and were conducted from the perspective of a healthcare payer; two studies also estimated total costs (direct plus indirect costs) from a societal perspective.[97,98] The time horizon was 1 year in all analyses, except for one of 12 weeks[96]

Study	Country (year of costing)	Base study	Comparators[a]	ICERs[b]
Briggs et al.[95][c]	UK (2003–4)	GOAL[55] stratum 1	S/FP vs FP	£13 700 per QALY gained
		stratum 2		£11 000 per QALY gained
		stratum 3		£7600 per QALY gained
Borker et al.[96]	US (2003)	Pearlman et al.[57]	S/FP vs MON	$US 2.87 per symptom-free day $US1.79 per FEV_1 improvement of ≥12%
Doull et al.[100]	UK (2006)	Several studies	S/FP vs FP	£6852 per QALY gained in adults £15 739 per QALY gained in children
			S/FP vs F/BUD	S/FP dominant[d] per symptom-free day
Johansson et al.[97]	Italy, France, Germany, UK (2003)	Vogelmeier et al.[75]	F/BUD vs S/FP	Direct cost: F/BUD €100 (Italy), €267 (France) or dominant[d] (Germany and UK) per severe exacerbation avoided Total cost: F/BUD dominant[d] per severe exacerbation avoided (all countries)
Miller et al.[98]	Canada (2005)	Vogelmeier et al.[75]	F/BUD vs S/FP	Direct and total costs: F/BUD dominant[d] per severe exacerbation avoided
Shih et al.[99]	USA (2005)	Several studies	S/FP vs FP	$US9.55 per symptom-free day $US8.93 per rescue-free day
			S/FP vs LEU	S/FP dominant[d] per symptom-free day S/FP dominant[d] per rescue-free day

a Study treatments were given via inhalation twice daily, except for MON/LEU, which was given orally once daily. Generally, dosages of comparator agents were equipotent (refer to section 4 for further details).

b Direct costs unless stated otherwise.

c Patients were stratified according to corticosteroid use at randomization: stratum 1 (no inhaled corticosteroid); stratum 2 (≤500 μg/day beclomethasone dipropionate or equivalent); and stratum 3 (501–1000 μg/day).

d The drug was more effective and less costly.

FEV_1 = forced expiratory volume in 1 second; **ICER** = incremental cost-effectiveness ratio; **QALY** = quality-adjusted life-year.

are not adequately controlled with ICS and as required SABAs, or who are adequately controlled on LABAs plus ICS.[21] In the US, salmeterol/fluticasone propionate is indicated for maintenance treatment in asthmatics aged ≥4 years, not including those whose asthma can be managed by ICS with occasional use of SABAs, or those requiring relief of acute bronchospasm.[20] The maintenance dosage in patients aged ≥12 years is salmeterol/fluticasone propionate 50 μg/100 μg, 50 μg/250 μg or 50 μg/500 μg twice daily. The starting dosage should be based on asthma severity. In children aged 4–11 years, the dosage is salmeterol/fluticasone propionate 50 μg/100 μg twice daily.[20,21]

It is recommended that the salmeterol/fluticasone propionate dosage be titrated to the lowest effective dose, but therapy should only be stepped down under physician supervision.[20,21] It is also important to note that the fluticasone propionate dose should be lower than that of other ICS, with fluticasone propionate 100 μg being approximately equivalent to beclomethasone dipropionate 200 μg.[21]

The dosage of salmeterol/fluticasone propionate does not need to be adjusted in the elderly or those with renal impairment.[21] Patients with hepatic impairment should be monitored for signs of increased drug exposure (section 3).[20,21] Local prescribing information should be consulted for more details regarding precautions, contraindications and warnings.

8. Place of Salmeterol/Fluticasone Propionate in the Management of Asthma

As there is no cure for asthma, the primary goal of management is to achieve and maintain clinical control.[3,102] This includes controlling symptoms, enabling maintenance of normal activities, including exercise, maintaining normal or near-normal lung function, preventing exacerbations, avoiding treatment-related adverse effects, and preventing asthma mortality. In the majority of patients, asthma control can be achieved and maintained with a pharmacological intervention strategy developed in partnership between the patient/family and the doctor.[3,102] Unfortunately, data suggest that many patients settle for a lower level of asthma control than could be achieved with guideline-based treatment.[103-105]

A stepwise approach to pharmacological treatment is recommended in current guidelines.[3,93,102] The first step is reliever medication, and for the majority of patients this will be a SABA, administered on an as-needed basis. Low-dose ICS are first-line controller medications and should be combined with as-required SABAs in patients not adequately controlled with SABAs alone. Other controller medications for use if ICS are not appropriate include leukotriene modifiers (e.g. montelukast), sustained-release theophylline or cromones (e.g. nedocromil sodium). At the next step, the preferred option in adults and adolescents is to combine ICS with a LABA, and because of the additive effect of this combination (section 2), a low-dose ICS is usually sufficient, as was demonstrated in clinical trials with salmeterol/fluticasone propionate (section 4.1.1). In children, particularly those aged ≤5 years, increasing the dose of ICS is usually preferred before initiating LABAs.[3,102] When asthma control is not adequate, the dosage of the ICS component of the combination should be increased. However, increasing from a medium- to high-dose ICS provides relatively minimal additional benefit with an increased risk of systemic corticosteroid effects. For patients with persistent severe asthma, other controller medications, such as oral corticosteroids, can be added to medium- or high-dose ICS plus a LABA. Once asthma control has been achieved, patients should be monitored by their doctor on an ongoing basis, stepping treatment up or down as required to maintain optimum control with the lowest possible dosages.[3,102] In most patients, an assessment of asthma severity based on clinical measures will adequately predict the need for additional therapy.[106]

Primary results of clinical trials have demonstrated the efficacy of salmeterol/fluticasone propionate in the treatment of asthma in adults, adolescents and children aged 4–11 years (section 4). This fixed combination therapy demonstrated greater efficacy, as measured by lung function tests and symptom control (and following exercise challenge), than fluticasone propionate alone (section 4.1.1). It should be noted that the greater improvement with the combination agent versus fluticasone propionate alone included assessment using a comprehensive composite guideline-based control measure and persisted for up to 1 year in the well designed GOAL study (section 4.1.2). Furthermore, the combination agent had a corticosteroid-sparing effect, achieving asthma control with lower dosages of fluticasone propionate than those required to achieve control when this agent was used alone (section 4.1.1).

Compared with other agents in well designed trials, the efficacy of salmeterol/fluticasone propionate was greater than that of montelukast in adults, adolescents and children, greater than that of montelukast combined with fluticasone propionate in adults and adolescents (section 4.4), and greater than that of oral sustained-release theophylline plus fluticasone propionate in adults (section 4.5). However, results of comparative trials with formoterol/budesonide in adults and adolescents are equivocal (section 4.3). Indeed, in a recent Cochrane Review of randomized trials comparing fixed-dose salmeterol/fluticasone propionate with fixed-dose formoterol/budesonide, there were no significant differences between treatments in respect to the odds of experiencing an asthma exacerbation requiring oral corticosteroids or hospital admission.[107]

In clinical studies, salmeterol/fluticasone propionate or formoterol/budesonide achieved similar efficacy, according to the primary endpoint, when

SABAs were used by both groups as reliever medication (section 4.3).[27,78] Three studies[26,73,78] comparing salmeterol/fluticasone propionate and formoterol/budesonide used adjustable maintenance dosages of formoterol/budesonide, which allowed dosage adjustment based on symptoms following an initial fixed-dose period. This approach is designed to minimize dosage levels. Primary efficacy, as measured by the number of symptom-free days, was greater with fixed-dose salmeterol/fluticasone propionate than with adjustable maintenance dosages of formoterol/budesonide in the double-blind CONCEPT trial,[26] but according to the primary endpoint in two open-label studies (asthma exacerbations and the odds of having a well controlled week),[73,78] efficacy was similar (section 4.3). While the use of the adjustable-dosage strategy resulted in a reduction in dosages compared with fixed-dose treatment, results of the CONCEPT trial suggest that a minimum maintenance dosage of formoterol/budesonide may need to be established to ensure optimum control.[26]

In two studies[72,75] in which one treatment arm used formoterol/budesonide as controller and reliever medication, as opposed to SABAs for relief, the time to first severe asthma exacerbation was shorter with salmeterol/fluticasone propionate plus SABAs as required than with formoterol/budesonide, although in another study comparing the same regimens, but with higher salmeterol/fluticasone propionate dosages, efficacy (as measured by this endpoint) was similar (section 4.3).[71] This treatment approach of using formoterol/budesonide as maintenance and reliever medication, eliminating the need for SABAs, was also associated with reduced dosages of ICS over time compared with patients receiving fixed dosages of salmeterol/fluticasone propionate or formoterol/budesonide plus SABAs,[72] suggesting that ICS administered at the time of worsening inflammation may provide greater efficacy than when administered as controller medication alone.[108] The single inhaler approach to therapy is also simple for patients to use and is likely to improve compliance. The mechanism of action of combination LABA and ICS agents given as relief therapy is not fully understood.[108]

Asthma treatment guidelines recommend that once asthma control has been achieved and maintained, treatment should be stepped down to avoid over treatment and the associated risk of adverse effects.[3,102] Limited data are available to assist in determining the optimal timing or sequence of treatment reductions; however, generally asthma control should have been maintained for 3–6 months. In fact, data suggest that maintaining optimum control for a minimum of 3 months will help ensure beneficial effects on symptom control, airway inflammation, lung function and remodelling.[109] In well designed studies in well controlled asthmatics, better asthma control was maintained when twice-daily salmeterol/fluticasone propionate 50 μg/250 μg was stepped down to twice-daily dosages of 50 μg/100 μg rather than switching to fluticasone propionate 250 μg alone (section 4.6). Thus, lowering the ICS dosage component of salmeterol/fluticasone propionate appears preferable to continuing ICS alone as a first step down in well controlled patients.

The patient's perception of HR-QOL is recognized as an important endpoint alongside therapeutic goals, and evidence suggests that patient-perceived control is strongly associated with improvements in health status.[110] Salmeterol/fluticasone propionate is associated with clinically meaningful improvements in HR-QOL, and in the GOAL study, about two-thirds of patients in the salmeterol/fluticasone propionate group achieved near maximum AQLQ scores at 1 year (section 4.7). This study also demonstrated that AQLQ scores reflect the level of control achieved, even between those who were well or totally controlled, suggesting that total control is a realistic goal with corresponding benefits for the patient's HR-QOL. As shown in efficacy analyses, results of studies comparing HR-QOL associated with salmeterol/fluticasone propionate or formoterol/budesonide were mixed.

The economic burden of asthma in most countries is well recognized, but cost should not present a barrier to achieving asthma control. Exacerbation-related costs account for between 35–50% of direct costs associated with the disease; therefore, eliminating or reducing exacerbations with effective treatment will impact resource use.[3] A recent

retrospective evaluation of health insurance claims supports this view, with lower asthma care costs incurred when symptomatic patients were switched from ICS to salmeterol/fluticasone propionate rather than adding salmeterol via a separate inhaler or oral montelukast.[111] In cost-utility studies, salmeterol/fluticasone propionate was cost effective compared with monotherapy with fluticasone propionate, or oral montelukast, with regard to the cost per QALY gained, per symptom- or rescue-free day, or per 12% improvement in FEV_1, but results of studies comparing salmeterol/fluticasone propionate with formoterol/budesonide were mixed (section 6). The similar efficacy achieved with these two combination agents is likely to lead to similar resource use, and consideration of local costs may provide a better basis for treatment choice.

Salmeterol/fluticasone propionate is generally well tolerated in adults, adolescents and children and, in clinical trials, the incidence of adverse effects was not significantly different to that reported with comparator agents, including fluticasone propionate alone, formoterol/budesonide or oral montelukast (section 5). Importantly, the use of salmeterol combined with fluticasone propionate appears to eliminate the small but significant risk of asthma-related death that was observed with LABAs alone. In a large meta-analysis of 66 clinical trials in >20 000 patients, salmeterol plus ICS effectively controlled asthma symptoms and did not appear to alter the risk for asthma-related hospitalizations or deaths compared with ICS alone.[48] Further research into why LABAs are associated with this small risk of asthma-related deaths is probably warranted, particularly as other longer-acting LABAs are being developed. While salmeterol/fluticasone propionate was as effective as the same dosages of salmeterol plus fluticasone propionate administered concurrently using separate inhalers (section 4.2), the fixed combination agent provides added protection against patients inadvertently using LABAs alone. Furthermore, using one controller inhaler as opposed to two is likely to improve patient adherence, with subsequent improvement in asthma control.

In conclusion, twice-daily salmeterol/fluticasone propionate maintenance therapy improves lung function and asthma symptoms to a greater extent than monotherapy with ICS, such as fluticasone propionate, oral montelukast with or without fluticasone propionate, or sustained-release theophylline plus fluticasone propionate in patients with symptomatic asthma. The greater efficacy achieved with the combination agent versus fluticasone propionate alone was sustained for one year in a well designed trial. Salmeterol/fluticasone propionate is also associated with a corticosteroid-sparing effect. Results of studies comparing fixed dosages of salmeterol/fluticasone propionate with formoterol/budesonide in adults and adolescents are equivocal. Twice-daily salmeterol/fluticasone propionate is associated with clinically meaningful improvements from baseline in HR-QOL, and improvements were greater than those reported with fluticasone propionate alone. Salmeterol/fluticasone propionate is generally well tolerated in adults adolescents and children aged 4–11 years, and the fixed-combination inhaler ensures the appropriate use of a LABA in combination with an ICS. In cost-utility analyses in patients with uncontrolled asthma, salmeterol/-fluticasone propionate compares favourably with fluticasone propionate alone or oral montelukast. Thus, salmeterol/fluticasone propionate provides an effective, well tolerated and cost-effective option for maintenance treatment in patients with asthma.

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