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Inhaled Fluticasone Propionate

A Review of its Therapeutic Efficacy at Dosages ≤500 μg/day in Adults and Adolescents with Mild to Moderate Asthma

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Data Selection

Sources: Medical literature published in any language since 1966 on fluticasone propionate, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. 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 Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.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: AdisBase search terms were 'fluticasone' and 'asthma'. Medline and EMBASE search terms were 'fluticasone' and 'asthma'. Searches were last updated 22 March, 1999.

Selection: Studies in patients with asthma who received fluticasone propionate ≤500 μg/day. 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: Asthma, fluticasone propionate, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Fluticasone propionate is a corticosteroid with comparatively high receptor affinity and topical activity. Inhaled fluticasone propionate ≤500 μg/day provided effective corticosteroid maintenance treatment in patients with mild to moderate asthma in randomised, controlled clinical studies of 4 to 24 weeks in duration. Dosages of 50 to 250μg twice daily produced consistent improvement in spirometric measures of lung function, reduced the frequency of as-needed β_2-agonist bronchodilator use, asthma symptom scores and night-time wakenings, and prevented asthma exacerbations compared with placebo. Fluticasone propionate ≤250μg twice daily provided significantly greater improvements in lung function than nedocromil 4mg 4 times daily, theophylline (5 to 15 mg/L) or zafirlukast 20mg twice daily. Health-related quality of life improved significantly with fluticasone propionate 88μg twice daily, but not zafirlukast 20mg twice daily or placebo. In comparative trials in which fluticasone propionate was given at half the dosage of beclomethasone dipropionate, budesonide or flunisolide, fluticasone propionate ≤250μg twice daily produced equivalent or greater improvement in spirometric parameters and equivalent reductions in the use of as-needed β_2-agonists than beclomethasone dipropionate, budesonide or flunisolide. Fluticasone propionate 250μg twice daily was generally more effective than triamcinolone acetonide 200μg 4 times daily in two 24-week trials.

The combination of inhaled fluticasone propionate ≤250 plus salmeterol ≤50μg twice daily allowed for the use of lower dosages of the inhaled corticosteroid.

The incidence of adverse events in patients receiving inhaled fluticasone propionate 50 to 250μg twice daily was similar to that in beclomethasone dipropionate 168 to 500μg twice daily and budesonide 100 to 600μg twice daily recipients and greater than that in recipients of triamcinolone acetonide 200μg 4 times daily in comparative trials. The incidence of oral candidiasis was ≤8% in patients treated with fluticasone propionate ≤250μg twice daily or other agents. There was no evidence of clinically significant hypothalamo-pituitary-adrenal (HPA) axis suppression with fluticasone propionate ≤250μg twice daily in comparative trials.

Conclusions. Inhaled fluticasone propionate ≤500 μg/day is an effective anti-inflammatory therapy for mild to moderate asthma in adolescents and adults. The drug is more effective than nedocromil, theophylline or zafirlukast and is at least as effective as other inhaled corticosteroids administered at twice the fluticasone propionate dosage. The addition of inhaled salmeterol allows the use of lower maintenance dosages of fluticasone propionate. The drug is well tolerated and there is no evidence of a clinically significant effect of this dosage on HPA axis function. Hence, fluticasone propionate ≤500 μg/day is a particularly suitable agent for patients with mild to moderate asthma.

Pharmacological Properties

Fluticasone propionate ≤250μg twice daily attenuates antigen processing, suppresses recruitment and activation of inflammatory cells and reduces the thickness of the basement membrane in the airways of patients with mild asthma. At dosages ranging from 100 to 250 μg/day the drug generally reduced bronchial hyperresponsiveness, as measured by the dose of inhaled histamine, methacholine or adenosine 5′-monophosphate required to provoke a 20% decline (PD_{20}) in forced expiratory volume in 1 second (FEV_1) in patients with mild to moderate asthma. The PD_{20} for histamine was significantly greater after 2 weeks' treatment with fluticasone propionate 100μg twice daily than zafirlukast 20mg twice daily in a crossover study. Fluticasone propionate 250μg and salmeterol 50μg, each given alone or in combination, reduced bronchial hyperresponsiveness in patients with significant diurnal variation in the PD_{20} of methacholine.

In general, fluticasone propionate ≤250μg twice daily had minimal effects on hypothalamo-pituitary-adrenal (HPA) axis function in adult patients with mild to moderate asthma enrolled in placebo-controlled studies and there was no difference in HPA axis function when fluticasone propionate dosages ≤500 μg/day were compared with other inhaled corticosteroids in clinical trials.

Plasma concentrations of fluticasone propionate were below the limit of detection (<0.025 μg/L) after inhalation of 100μg twice daily for 4 weeks. Concentrations of the drug in peripheral lung tissue exceeded those in plasma by approximately 100-fold and fluticasone propionate could be detected in lung tissue and serum for 16.3 and 13.3 hours, respectively, after inhalation of a single 1000μg dose prior to pneumonectomy or lobe resection. The oral and pulmonary bioavailability of fluticasone propionate was, respectively, <1% and 14.9% in healthy volunteers. The terminal elimination half-life of fluticasone propionate was 7.6 to 14.4 hours after inhalation of a single 1000μg dose or inhalation of 1000μg twice daily for 7 days from a dry powder inhaler.

Therapeutic Efficacy

Fluticasone propionate 50 to 500 μg/day produced improvements in lung function in patients with mild to moderate persistent asthma in randomised, comparative trials of 4 to 24 weeks' duration. Improvements in morning and evening peak expiratory flow rate (PEF) and FEV_1 in patients treated with fluticasone propionate 25 to 250μg twice daily were generally significantly greater than in those treated with placebo, inhaled nedocromil 4mg 4 times daily, oral theophylline (titrated to plasma concentrations of 5 to 15 mg/L) or oral zafirlukast 20mg twice daily. In comparative trials with inhaled beclomethasone 168 to 500μg twice daily, budesonide 200 to 600μg twice daily or flunisolide 500μg twice daily, in which fluticasone propionate was given at half or less than half the microgram dosage of the other inhaled corticosteroid (i.e. fluticasone propionate 50 to 250μg twice daily), improvements in morning and/or evening PEF in fluticasone propionate recipients were generally similar to, or significantly greater than, those in patients treated with the comparator. In two 24-week trials, improvements in morning PEF and FEV_1 after 24 weeks were significantly greater in fluticasone propionate 250μg twice daily recipients than in triamcinolone acetonide 200μg 4 times daily or placebo recipients.

In concert with improvements in lung function, requirements for as-needed β_2-agonists and nocturnal awakenings generally decreased and asthma symptoms improved in patients treated with fluticasone propionate 25 to 250μg twice daily in comparative trials. The frequency of as-needed β_2-agonist use decreased significantly in fluticasone propionate 25 to 250μg twice daily recipients compared

with those receiving placebo, nedocromil 4mg 4 times daily or zafirlukast 20mg twice daily. Recipients of fluticasone propionate 100 but not 50μg twice daily used significantly less supplementary salbutamol compared with theophylline-treated patients. The frequency of as-needed β_2-agonist use decreased from baseline in comparative trials in which fluticasone propionate was administered at half or less than half the microgram dose of beclomethasone dipropionate 200 to 336μg twice daily or budesonide 200 or 400μg twice daily. Furthermore, requirements for supplementary salbutamol decreased significantly in patients treated with fluticasone propionate 250μg twice daily compared with those receiving triamcinolone acetonide 200μg 4 times daily or placebo.

The frequency of withdrawal from comparative trials because of loss of efficacy generally declined in patients treated with fluticasone propionate 25 to 250μg twice daily. More than half (52 to 71%) of the placebo-treated patients withdrew from 5 of 7 placebo controlled trials because of asthma exacerbations; however, the frequency of withdrawal was significantly lower in fluticasone propionate 25 to 250μg twice daily recipients (6 to 37%) with no statistical differences between fluticasone propionate dosage groups. Loss of efficacy was significantly less frequent in fluticasone propionate 250μg twice daily (15%) than nedocromil 4mg 4 times daily recipients (27%) in 1 trial, but not in a second. Significantly fewer fluticasone propionate 50 or 100μg twice daily recipients experienced asthma exacerbations (≤19%) compared with those receiving theophylline (38%) or placebo (52%) during a 12-week trial. Withdrawal because of loss of efficacy occurred infrequently in comparative trials involving fluticasone propionate 50 to 250μg twice daily and beclomethasone dipropionate 200 to 500μg twice daily (≤20.8%) or budesonide 100 to 600μg twice daily (≤7.8%) with no significant differences between treatment groups. Loss of efficacy was significantly less frequent in fluticasone propionate 250μg twice daily (17%) or triamcinolone acetonide 200μg 4 times daily recipients (≤33%) than placebo (≤65%) in two 24 week trials, in 1 of which there was a significant difference in the frequency of loss of efficacy between fluticasone propionate and triamcinolone acetonide groups.

Fluticasone propionate ≤250μg twice daily had a beneficial effect on health-related quality of life (QOL) in patients with mild to moderate asthma. Health status, as measured by a disease- specific instrument (Living with Asthma), sleep patterns, and scores on the physical functioning and role-physical dimensions of the Medical Outcomes Study Short Form-36 (SF-36) improved significantly in fluticasone 50, 100 and 250μg twice daily recipients compared with placebo. Those in the 2 higher dosage groups also had significantly higher SF-36 scores in health perceptions, vitality and mental health compared with placebo.

In other studies, QOL was measured with the Asthma Quality of Life Questionnaire (AQLQ). Global AQLQ scores and scores on each of the 4 domains (Activity Limitation, Asthma Symptoms, Emotional Function and Environmental Exposure) were significantly higher after 12 weeks treatment with fluticasone propionate 88μg twice daily than either zafirlukast 20mg twice daily or placebo and more patients treated with fluticasone propionate than zafirlukast or placebo experienced moderate or large improvements in Global AQLQ scores. In another study Global AQLQ scores and scores on 3 of the 4 domains on the scale (all except Environmental Exposure) were significantly higher after 24 weeks of treatment with fluticasone propionate 250μg twice daily than with either triam-

cinolone acetonide 200μg 4 times daily or placebo. Moreover, the difference in global AQLQ scores between fluticasone propionate and placebo recipients was considered to be clinically significant.

Combining inhaled salmeterol with fluticasone propionate may improve asthma control and allow for the use of a lower fluticasone propionate dosage. The combination of salmeterol 42μg plus fluticasone propionate 220μg twice daily produced significantly greater improvements in FEV_1 compared with either drug given separately. Loss of efficacy was significantly less frequent in those treated with salmeterol 50μg plus fluticasone propionate 100μg twice daily (5%) compared with either drug given alone (≤24%) or placebo (44%).

Equivalent daily dosages of fluticasone propionate ≤500 μg/day administered once or twice daily improved or maintained lung function in patients with mild to moderate asthma. However, twice daily, compared with once daily administration generally provided numerically greater improvement in morning and evening PEF.

Tolerability

The incidence of adverse effects was generally not significantly different in patients treated with inhaled fluticasone propionate ≤250μg twice daily or placebo in comparative studies. Withdrawal because of adverse events occurred in ≤4% and ≤2% of fluticasone propionate and placebo recipients, respectively. Oral candidiasis and dysphonia (hoarseness) or pharyngitis were reported by ≤6% and ≤3% of fluticasone propionate and placebo recipients, respectively.

In trials comparing fluticasone propionate ≤250μg twice daily with either beclomethasone dipropionate or budesonide, the frequency of adverse events was similar between groups. Oral candidiasis was reported by ≤6.5% of patients receiving fluticasone propionate or the other inhaled corticosteroid in these studies.

The frequency of treatment-related adverse events was significantly greater in patients treated with fluticasone propionate 250μg twice daily (20%) than either triamcinolone acetonide 200μg 4 times daily (5%) or placebo (5%) in 1 trial. In a second, similar trial, the incidence of oral candidiasis was significantly greater in fluticasone propionate 250μg twice daily recipients (8%) than either triamcinolone acetonide 200μg 4 times daily (3%) or placebo recipients (1%).

In trials comparing fluticasone propionate ≤250μg twice daily with other inhaled corticosteroids or nedocromil <10% of patients were withdrawn from any treatment group because of adverse events.

Dosage and Administration

In the UK the recommended dosage of inhaled fluticasone propionate for patients aged ≥16 years with mild asthma is 100 to 250μg twice daily and for those with moderate asthma, 250 to 500μg twice daily.

In the US, the recommended dosage in patients ≥12 years of age is 88 to 440μg twice daily by metered dose inhaler or 100 to 500μg twice daily by dry powder inhaler.

1. Introduction

Asthma is a chronic inflammatory disorder of the airways. The disease is associated with significant morbidity and impinges on the quality of life of patients. Indeed, a survey in California revealed that one-third of patients with asthma had cancelled activities and approximately half had missed at least 1 day of school or work because of asthma in the previous month.[1] Furthermore, in adult patients with asthma, lung function declines significantly over time and there is an increased risk of mortality compared with healthy individuals.[2,3] Hence, the ideal therapy for asthma would not only

	Asthma severity	Lung function		Symptom frequency	Nocturnal symptoms	Exacerbations
		PEF or FEV_1[a]	PEF variability[b]			
	Severe	≤60%	>30%	Continual	Frequent	Frequent
Persistent	Moderate	>60<80%	>30%	Daily	>1/week	Affect activity
	Mild	≥80%	20-30%	>2/week<1/day	>2/month	May affect activity
Intermittent	Mild	≥80%	<20%	≤2/week	≤2/month	Are brief

Fig. 1. The asthma classification scheme developed by the Global Initiative for Asthma.[6] The presence of ≥1 feature in a severity level is sufficient to place a patient in that level. Daily preventive therapy is recommended for all patients with persistent asthma. Severe exacerbations may affect patients at any level of severity. The focus of this review includes patients with mild to moderate persistent asthma (shaded area). **a** = predicted values based on age, gender and height. **b** = variability between morning and evening. **FEV_1** = forced expiratory volume in 1 second; **PEF** = peak expiratory flow rate.

alleviate patients' symptoms, but would arrest or reverse the underlying disease process and improve health-related quality of life (QOL) as measured by a valid instrument.

Corticosteroids are the most effective anti-inflammatory agents for asthma and, across the entire spectrum of severity for this condition, inhaled corticosteroids are recognised as the preferred preventive therapy.[4] In the last decade, guidelines for the diagnosis and management of asthma have been developed and disseminated.[5-8] Contemporary guidelines recommend early intervention with inhaled corticosteroids with the goal of minimising symptoms and maintaining normal activity levels, including exercise.[6-8]

Figure 1 depicts the classification scheme developed by the Global Initiative for Asthma (GINA).[6] The GINA and US guidelines recommend that daily preventive therapy be instituted in all patients with persistent asthma.[6,8] The British guidelines on asthma management recommend daily preventive therapy in all patients requiring as-needed β_2-agonist bronchodilators more than once per day.[7]

Inhaled fluticasone propionate is a well established corticosteroid therapy for severe asthma that has been previously reviewed in *Drugs*.[9] This review will evaluate the use of inhaled fluticasone propionate at dosages ≤500 μg/day in adults and adolescents with mild to moderate asthma. Fluticasone propionate was administered by inhalation unless specified otherwise.

2. Pharmacological Properties

Corticosteroids inhibit cytokine secretion, lymphocyte migration and produce a marked reduction in the number of eosinophils, mast cells, macrophages and T lymphocytes in bronchial epithelium and submucosa in humans. Plasma exudation, mucus secretion and goblet cell hyperplasia are also reduced. These drugs also may prevent down-regulation of β_2-receptors, thereby maintaining airway responsiveness to β_2-agonist bronchodilators.[10] Clinically, these effects result in a decline in airway hyperresponsiveness. Among the currently available inhaled corticosteroids, fluticasone propionate has the greatest topical activity, lipophilicity and affinity for the glucocorticoid receptor.[4,11]

Available evidence suggests that, in addition to the above-mentioned effects, inhaled fluticasone propionate attenuates antigen processing, suppresses recruitment and activation of inflammatory cells and reduces the thickness of the basement membrane in the airways of patients with mild asthma.[12,13] Infiltration of eosinophils and mast cells into the lamina propria was significantly attenuated, degranulation of mast cells was suppressed and the thickness of the basement membrane decreased by 23.4% in 9 patients treated with inhaled fluticasone propionate 250μg twice daily for 6 weeks (table I).[12] There were no significant changes in any of these parameters in 8 placebo recipients.[12] The percentage of cells expressing intracellular adhesion molecule-1 (ICAM-1) and

the β_2-integrin, macrophage-1 (MAC-1), and tryptase levels in bronchoalveolar lavage (BAL) fluid were significantly reduced by fluticasone propionate 250μg twice daily.[12] ICAM-1 and MAC-1 are associated with recruitment of eosinophils to sites of inflammation and are elevated in patients with asthma. Moreover, expression of heat shock protein 70 (hsp70) and HLA-DR, 2 proteins thought to be involved in antigen processing by antigen presenting cells, was significantly reduced after 6 weeks' treatment with fluticasone propionate 250μg twice daily (n = 8) compared with placebo (n = 10).[13]

2.1 Effects on Bronchial Hyperresponsiveness

Bronchial hyperresponsiveness may be assessed by provocation with inhaled allergen, histamine or an anticholinergic compound such as methacholine. In such assays the efficacy of an antiasthmatic medication is expressed as the dose of the provocative substance required to elicit a decline in some objective measure of lung function to below a predetermined threshold. Hence, the dose required to provoke a 20% decline (PD_{20}) in forced expiratory volume in 1 second (FEV_1) should increase significantly with an effective medication.

Short term treatment with fluticasone propionate 100 to 250μg twice daily generally reduced bronchial hyperresponsiveness in patients with mild to moderate asthma. Although there was no significant difference in the PD_{20} of methacholine after 8 weeks in 138 patients randomised to treatment with fluticasone propionate 50 or 100μg twice daily or placebo, the mean log PD_{20} of methacholine, expressed as the average of 4 determinations during the 8-week study, was significantly ($p < 0.05$) greater in fluticasone propionate 100μg twice daily recipients than fluticasone propionate 50μg twice daily or placebo recipients.[14]

In another placebo-controlled trial, the mean PD_{20} of methacholine increased more than 2-fold from baseline (2.45 g/L) to end-point (7.09 g/L; $p < 0.02$) in 9 patients with asthma treated with fluticasone propionate 250μg twice daily, but was unchanged in 8 placebo recipients (baseline PD_{20} = 3.36; end-point PD_{20} = 3.73 g/L) at the end of the 6-week study.[12]

Fluticasone propionate reduced bronchial hyperresponsiveness to a greater extent than the leukotriene type-1 receptor antagonist zafirlukast in a crossover study.[15] After 2 weeks, the mean PD_{20}s for histamine in 25 patients treated with fluticasone propionate 100μg or zafirlukast 20mg twice daily were 1.61 and 0.99 g/L, respectively ($p < 0.05$).[15]

Fluticasone propionate 250μg and salmeterol 50μg, each given alone or in combination, reduced bronchial hyperresponsiveness in 46 patients with significant diurnal variation in the PD_{20} of methacholine ($p < 0.05$ for PD_{20} at 4:00am *vs* 4:00pm).[16] The PD_{20} for methacholine at these times increased by 1.5 to 3.0 ($p = 0.02$ to < 0.001 *vs* baseline) doubling doses for all 3 treatments, although there was no significant difference in the degree of improvement between the 3 treatments. Furthermore, increases in the PD_{20} for inhaled adenosine 5′-monophosphate (measured in the

Table I. Anti-inflammatory effects of inhaled fluticasone propionate 250μg twice daily for 6 weeks in the lungs of adult patients with mild asthma ($FEV_1 \geq 82\%$ predicted) as measured by bronchoalveolar lavage (BAL) and bronchial biopsies in 2 randomised, double-blind, parallel-group studies[12,13]a

Bronchial biopsy[b]	Decreased number of eosinophils* and mast cells** in bronchial mucosa[12]
	Decreased percentage of degranulated mast cells in bronchial mucosa*[12]
	Down-regulation of hsp70 and HLA-DR in epithelial cells*[13]
	Decrease in basement membrane thickness*[12]
BAL fluid[b]	Decreased percentage of cells expressing ICAM-1* and MAC-1*[12]
	Decreased concentration of tryptase***[12]
	Down-regulation of hsp70*** and HLA-DR* in cells[13]

a Patients had not received inhaled corticosteroids for ≥ 6 months prior to enrolment.

b All statistical comparisons are between end of treatment and baseline in 8[13] and 9[12] fluticasone propionate recipients. There were no significant differences between baseline and end of treatment in 10[13] and 8[12] placebo recipients.

FEV_1 = forced expiratory volume in 1 second; **hsp70** = heat shock protein 70; **ICAM-1** = intracellular adhesion molecule-1; **MAC-1** = macrophage-1 (CD11b/CD18), a β_2-integrin; *p < 0.05; **p < 0.01; ***p < 0.001 *vs* baseline.

morning) of 2.9 to 5.7 doubling doses occurred in each treatment group ($p = 0.003$ to < 0.0001 *vs* baseline) with no statistically significant between-group differences.[16]

2.2 Effects on Adrenal Function

All corticosteroids have the potential to suppress hypothalamo-pituitary-adrenal (HPA) axis function as a result of negative feedback inhibition of the pituitary gland. However, fluticasone propionate undergoes considerable first-pass metabolism which minimises systemic exposure to swallowed drug and reduces the likelihood of adrenal suppression.[17]

Fluticasone propionate ≤500 μg/day generally had minimal effects on HPA axis function in patients with mild to moderate asthma. Mean plasma cortisol levels, a relatively insensitive measure of HPA axis function,[18] were not significantly different from baseline after 4 to 12 weeks treatment with fluticasone propionate ≤500 μg/day or placebo.[19-21] Similar results were obtained in studies which used more sensitive tests of HPA axis function including corticotrophin stimulation[19,21-24] and urinary free cortisol excretion.[19]

In general, there were no differences in HPA axis function when fluticasone propionate ≤500 μg/day was compared with other inhaled corticosteroids. Mean plasma cortisol values, urinary cortisol levels and/or the response to stimulation with tetracosactide (tetracosactrin) were similar in patients treated with multiple doses of fluticasone propionate ≤500 μg/day, beclomethasone dipropionate 400 μg/day,[25] budesonide 200 to 800 μg/day,[26-31] triamcinolone acetonide 600 to 1000 μg/day[32-35] or flunisolide 1000 μg/day.[33,36]

Although the clinical significance of small, short term perturbations in markers of HPA axis function are unclear, mean serum cortisol levels were significantly higher in 108 patients treated with fluticasone propionate 100μg twice daily (429 nmol/L) than in 114 patients treated with beclomethasone dipropionate 200μg twice daily (394 nmol/L; $p = 0.006$) for 4 weeks. Nonetheless, mean serum cortisol levels remained within the normal range in both groups (140 nmol/L).[37] In the same study, mean serum cortisol levels were significantly higher in 80 fluticasone propionate recipients (811 nmol/L) than in 87 beclomethasone dipropionate recipients (724 nmol/L; $p = 0.024$) in response to an injection of tetracosactide.[37]

Inhaled fluticasone propionate had a greater effect on HPA axis function than the same microgram dose of inhaled budesonide in 1 study. In a double-blind, crossover study, 12 patients received fluticasone propionate or budesonide 250, 500 or 1000μg twice daily or placebo for 4 days.[38] Mean plasma cortisol values and urinary cortisol/creatinine ratios were significantly ($p < 0.05$) lower in fluticasone propionate than budesonide or placebo recipients (plasma cortisol levels were 331, 414 and 398 nmol/L and urinary cortisol/creatinine ratios were 3.1, 5.5 and 5.2 nmol/mmol in fluticasone propionate 250μg twice daily, budesonide 250μg twice daily and placebo recipients, respectively).[38] It is difficult to interpret these results in the absence of measures of therapeutic efficacy, since a clinically meaningful comparison would have involved therapeutically equivalent dosages.

2.3 Pharmacokinetic Properties

Limited pharmacokinetic data from patients with mild to moderate asthma receiving fluticasone propionate are available. Few pharmacokinetic studies have included inhaled dosages ≤250μg twice daily. Moreover, in patients with mild to moderate asthma plasma, concentrations of fluticasone propionate were below the limit of detection (<0.025 μg/L) after inhalation of 100μg twice daily for 4 weeks (table II).[20,39] The following description of the pharmacokinetics of fluticasone propionate is a summary of data obtained in patients and volunteers receiving inhaled dosages ≥500 μg/day or oral or intravenous dosages. The pharmacokinetic properties of fluticasone propionate have also been extensively reviewed elsewhere.[40-42]

Depending on the inhalation device used, approximately 10 to 30% of an inhaled dose of an inhaled corticosteroid is deposited in the lung (reviewed by Meibohm et al.[40]) Available evidence

Table II. Mean steady-state pharmacokinetic values of inhaled fluticasone propionate (FP) in adults with mild to moderate asthma

Reference [study duration (wk)]	Treatment (no. of patients)	C_{max} (μg/L)	AUC_{12} (μg/L • h)	C_{12} (μg/L)
Falcoz et al.[39] (4)	FP 100μg bid DH (10)	BDL	BDL	BDL
	FP 500μg bid DH (10)	0.096[a]	0.491	0.037
	FP 500μg bid DH (15)	0.120[a]	0.412	0.032
	FP 500μg bid DK (13)	0.092[a]	0.474	0.040
Lawrence et al.[20] (4)	FP 100μg bid DH (6)	BDL	BDL	
	FP 500μg bid DH (9)	0.116[a]	0.629[a]	
	FP 20mg od PO (5)	0.248[a]	1.230[a]	

a Median values.

AUC_{12} = area under the plasma concentration-time curve to 12 hours post-dose; **BDL** = below the detection limit (<0.025 μg/L); **bid** = twice daily; **C_{max}** = maximum plasma concentration; **C_{12}** = plasma concentration 12 hours post-dose; **DH** = Diskhaler® dry powder inhaler; **DK** = Diskus® dry powder inhaler; **od** = once daily; **PL** = placebo; **PO** = orally.

suggests that the inhaled rather than the swallowed fraction of a dose of fluticasone propionate results in systemic exposure. Fluticasone propionate undergoes considerable first-pass metabolism; <1% of a 200μg oral dose of fluticasone propionate reaches the systemic circulation.[43] However, 14.9% of a 1000μg inhaled dose, administered as a dry powder, was absorbed from the lungs in 12 healthy volunteers.[43] Furthermore, concentrations of the drug in peripheral lung tissue exceeded those in plasma by approximately 100-fold and fluticasone propionate could be detected in lung tissue and serum for 16.3 and 13.3 hours, respectively, after inhalation of a single 1000μg dose from a dry powder inhaler prior to pneumonectomy or lobe resection.[44] The volume of distribution of fluticasone propionate was estimated to be 4.2 L/kg and 91% of the drug in circulation was bound to plasma proteins.[45] The drug is not significantly bound to transcortin in plasma.[45]

In patients with mild to moderate asthma, the area under the plasma concentration-time curve at steady state was similar after inhalation of fluticasone propionate 500μg twice daily from either the Diskhaler® (0.412 μg/L · h; n = 78) or the Diskus®/Accuhaler® (0.474 μg/L · h; n = 64) delivery devices.[46] These results suggest that the 2 devices have similar efficiency in delivering the drug to the lung.

In healthy volunteers, the bioavailability of fluticasone propionate was considerably greater (≈58% greater) than in patients with mild to moderate asthma.[46] The reason for this difference is not readily apparent and further studies are required to confirm and explain this discrepancy.

The mean terminal elimination half-life of fluticasone propionate after intravenous infusion of a single 500 or 1000μg dose was 7.8 hours,[47] 14.4 hours[43] after inhalation of a single 1000μg dose and 11.1 hours after inhalation of 1000μg twice daily for 7 days[48] from a dry powder inhaler. The longer terminal elimination half-life after inhaled administration compared with intravenous administration suggests that this parameter is governed by the slow rate of absorption of the drug from the lung (reviewed by Meibohm et al.[40]).

Fluticasone propionate is rapidly cleared from the systemic circulation. The total systemic clearance of the drug in healthy volunteers following intravenous administration was 66 L/h.[47] Fluticasone propionate undergoes oxidative metabolism via cytochrome P450 3A4 in the gut and liver and the only circulating metabolite, the 17β-carboxylic acid derivative of the parent compound, is pharmacologically inactive.[40,45] Renal clearance accounts for less than 0.02% of the total clearance of fluticasone propionate.[45]

3. Therapeutic Efficacy of Inhaled Fluticasone Propionate

Fluticasone propionate ≤500 μg/day has been compared with placebo,[14,19-22,49-51] theophylline,[52] nedocromil,[53,54] zafirlukast,[55] and other inhaled corticosteroids including beclomethasone dipropionate,[25,37,56-58] budesonide,[27-29,59-62] flunisolide[63-65] and triamcinolone acetonide[66,67] in adults and adolescents with mild to moderate

asthma. Once and twice daily dosage regimens of the drug have been compared in this patient group.[68-72] Fluticasone propionate ≤500 μg/day has also been studied in combination with salmeterol.[73-83] In this section, the results of multicentre, randomised, parallel group, comparative studies evaluating fluticasone propionate ≤500 μg/day are reviewed. Many of these trials were double-blind.[14,19-22,25,37,49,50,52,55-57,64,66-70,75-79,82] In some trials, fluticasone propionate dosages ≥500 μg/day were also studied.[19,20,25,50,79] Results for these dosage groups are beyond the scope of this review and are generally not presented.

Most trials used quantitative measures of lung function [e.g. a minimum unmedicated FEV_1 or peak expiratory flow rate (PEF), ≥15% reversibility of bronchoconstriction after inhalation of salbutamol (albuterol), diurnal variation in PEF] and/or asthma symptoms (frequency of as-needed β_2-agonist bronchodilator usage, asthma symptom scores, nocturnal awakenings) for inclusion criteria. All patients were using short-acting β_2-agonist bronchodilators on an as-needed basis and may have been receiving other asthma therapies including inhaled corticosteroids, sodium cromoglycate (cromolyn sodium), nedocromil, theophylline or inhaled long-acting β_2-agonist bronchodilators before enrolment. All trials excluded patients receiving oral corticosteroids.

Asthma severity represents a continuum rather than a collection of discrete and mutually exclusive categories. Accordingly, the inclusion criteria for most trials did not correspond to specific categories of asthma severity such as those in contemporary asthma guidelines.[6-8] Most trials used broad inclusion criteria which resulted in the recruitment of patient groups with a wide range of disease severity. Hence, in addition to including patients with mild or moderate asthma, some trials allowed for the inclusion of patients with more severe impairment of airflow (i.e. FEV_1 or PEF ≤60% of the predicted value for their age, gender and height).[20-22,27-29,49,50,52,55,59,63,66,67,76,78,83] Inclusion criteria and baseline characteristics are provided in the text and tables to assist the reader in assessing the severity of asthma of patients included in the various studies.

A 1- or 2-week run-in period, during which time baseline data were collected, was employed in all trials. In studies which recruited inhaled corticosteroid users, the regular inhaled corticosteroid was stopped before or after the run-in period. In other studies, recent use of inhaled corticosteroids was an exclusion criterion.[14,21,22,49,52,54,55,61,64,72,83]

All patients were offered inhaled salbutamol or terbutaline on an as-needed basis and some trials allowed patients to continue established steroid-sparing therapies.[19,22] The duration of active treatment ranged from 4 to 24 weeks.

Objective and subjective measures were used to evaluate the efficacy of fluticasone propionate and comparators in the various trials. Morning PEF was the most frequent objective outcome assessment; FEV_1 and other spirometric measures were reported less often. Quantitative asthma symptom scores [ranging from 0 (no symptoms) to 3 (severe symptoms that interfere with daily activities or interrupt sleep)], the frequency of as-needed β_2-agonist bronchodilator usage and nocturnal awakenings were recorded daily by patients in diary cards in many studies. Loss of efficacy was usually defined by objective criteria, with patients withdrawn from the study if they had an asthma exacerbation or if an objective measure of lung function declined below a predefined threshold (e.g. FEV_1 decreased by ≤15% from baseline).

QOL was measured with valid, disease-specific instruments [i.e. Asthma Quality of Life Questionnaire (AQLQ) or the Living With Asthma questionnaire] in several studies. The AQLQ consists of a 32 items which evaluate the degree of impairment in QOL in 4 domains (Activity Limitation, Symptoms, Emotional Function and Environmental Stimuli) over the preceding 2 weeks.[84] Lower scores indicate a greater degree of impairment in QOL. A change of 0.5 in the mean Global AQLQ score or in the mean score in any of the 4 domains is considered to be clinically significant; changes of 1 and 1.5 units represent moderate and large changes in QOL, respectively.[85]

The Living With Asthma Questionnaire is a valid disease specific instrument that was used to measure QOL in 1 study.[51] The questionnaire consists of 20 items and lower scores are correlated with greater QOL.[51]

In most studies the dosage of fluticasone propionate was reported as the total dose delivered per actuation ('actuator dose') of the delivery device (i.e. fluticasone propionate 25, 50, 100 and 250μg). However, in accord with US labelling, the dosage was reported as the portion of the dose delivered through the mouthpiece of the delivery device in several studies ('mouthpiece dose').[55,57,76,82,83] To facilitate comparisons between studies, the reader should bear in mind that fluticasone propionate 88, 110 and 220μg are mouthpiece doses which are equivalent to actuator doses of 100, 125 and 250μg; beclomethasone dipropionate 168 and 336μg (mouthpiece doses) are equivalent to beclomethasone dipropionate 200 and 400μg (actuator doses) and; salmeterol 42μg (mouthpiece dose) is equivalent to salmeterol 50μg (actuator dose).

3.1 Comparisons with Placebo

In adult patients with asthma, inhaled fluticasone propionate 25 to 250μg twice daily produced consistent improvements in lung function compared with placebo.[14,19-22,49,50] Statistically significant improvements in morning and evening PEF and FEV_1, compared with placebo, were obtained in all fluticasone propionate dosage groups in all studies, with 1 exception (morning and evening PEF in patients receiving 25μg twice daily in Sheffer et al.;[49] table III). In general, there were no significant differences between fluticasone propionate dosage groups; however, in 1 study, improvement in morning PEF was greater with fluticasone propionate 100μg twice daily than 250μg twice daily.[50] Significant increases in forced expiratory flow at midphase (FEF_{25-75}) and forced vital capacity (FVC) were obtained with fluticasone propionate 25 to 250μg twice daily in the 2 studies that reported these parameters ($p < 0.05$[21] and $p < 0.01$[19] *vs* placebo). Normal lung function, defined as ≥85% of the patient's predicted FEV_1, was achieved by 23 to 28% of patients receiving fluticasone propionate (25, 50 or 100μg twice daily) and 10% of those receiving placebo in 1 study (statistical significance not reported).[49]

In concert with improvements in lung function there was a general decrease in the frequency of as-needed β_2-agonist usage and nocturnal awakenings, and a decrease in asthma symptom scores in fluticasone propionate recipients. Indeed, the frequency of as-needed salbutamol usage declined significantly in every study[14,19-22,49,50] and the frequency of nocturnal awakenings was significantly lower with fluticasone propionate treatment than placebo in all but 1 study.[14] Improvement in nocturnal awakenings from a study in which patients had a high baseline frequency is presented in figure 2.[21] Asthma symptom scores decreased from baseline to end-point in all fluticasone propionate dosage groups in all studies (range –0.01 to –0.36),[14,19-22,49,50] and overall symptom scores were significantly lower in fluticasone propionate- than placebo-treated patients at end-point in 5 studies.[14,19,20,22,50]

Fluticasone propionate ≤250μg twice daily consistently reduced the frequency of asthma exacerbations in placebo-controlled studies. In 5 of 7 studies, more than half (52 to 71%) of the patients receiving placebo withdrew studies because of loss of efficacy; however, the frequency of withdrawal for loss of efficacy in fluticasone propionate recipients in these studies (6 to 37%) was significantly lower (table III). There were no significant differences in the frequency of withdrawal for loss of efficacy between fluticasone propionate dosage groups in any of these 5 studies,[19,20,22,49,50] or between fluticasone propionate- and placebo-treated patients in the 2 remaining studies.[14,21]

Fluticasone propionate had a beneficial effect on QOL in patients with moderate asthma (FEV_1 50 to 80% of the predicted value for their age, gender and height) in 1 study. After 12 weeks' treatment, recipients of fluticasone propionate 50 (n = 89), 100 (n = 84) or 250μg twice daily (n = 91) had significantly better health status ($p \leq 0.05$), as measured by a disease-specific instrument (Living with

Table III. Summary of multicentre, randomised, double-blind, parallel-group trials comparing inhaled fluticasone propionate (FP) ≤ 500 μg/day with placebo (PL) in adults with asthma

Reference [duration (wk)]	Dosage (delivery device) [no. of patients[a]]	Baseline characteristics (mean)		Results at end-point			
		FEV_1 (L) [% predicted]	β_2-agonist usage (puffs/day)	FEV_1 (L)[b]	PEF (am, pm; L/min)[bc]	β_2-agonist usage (puffs/day)[b]	LOE (%)
Chervinsky et al.[19] (8)[def]	FP 25μg bid (MDI) [78]	2.66 [72]		↑0.09**	↑11**, ↑7**	↓0.63**	23***
	FP 100μg bid (MDI) [80]	2.75 [72]		↑0.14**	↑15**, ↑12**	↓0.65**	13***
	PL [80]	2.53 [71]		↓0.26	↓19, ↓23	↑0.2	63
Lawrence et al.[20] (6)[def]	FP 100μg bid (DH) [63]	2.5 [67]	3.6	↑0.27**	↑15**	↓1.0**	6***
	PL [64]	2.42 [65]	4.2	↓0.19	↓15	↑0.7	52
Noonan et al.[14] (8)[egh]	FP 50μg bid (MDI 1%)	[76]	2.37	↑0.30*	↑29*, ↑16*	↓0.93*	11
	FP 100μg bid (MDI 1%)	[73]	2.77	↑0.38*	↑34*, ↑29*	↓1.39*	3
	FP 100μg bid (MDI 10%)	[74]	2.35	↑0.24*	↑28*, ↑18*	↓1.43*	3
	PL	[74]	2.95	↓0.08	0, ↑8	↑0.11	22
Pearlman et al.[22] (12)[egh]	FP 50μg bid (DH) [85]	2.41 [66]	4.1	↑0.43***	↑20***, ↑7***	↓0.9***	13***
	FP 100μg bid (DH) [81]	2.57 [66]	3.4	↑0.47***	↑16***, ↑8***	↓1.1***	13***
	FP 250μg bid (DH) [86]	2.55 [67]	3.8	↑0.44***	↑27***, ↑18***	↓1.2***	7***
	PL [75]	2.41 [67]	3.5	↓0.22	↓24, ↓23	↑1.7	65
Sheffer et al.[49] (12)[egh]	FP 25μg bid (MDI) [76]	2.43 [64]	3.99-4.73[i]	↑0.40*	↑31, ↑22	↓1.58*	37*
	FP 50μg bid (MDI) [79]	2.38 [62]		↑0.51*	↑27*, ↑21*	↓1.81*	25*
	FP 100μg bid (MDI) [79]	2.45 [63]		↑0.42*	↑45*, ↑35*	↓1.85*	33*
	PL [73]	2.36 [62]		↑0.14	↑12, ↑8	↓0.28	53
Wasserman et al.[21] (12)[egh]	FP 50μg bid (DH) [79]	2.68	3.0	↑0.59*	↑33*, ↑26*	↓1.31*	10
	FP 100μg bid (DH) [78]	2.57	3.2	↑0.54*	↑42*, ↑30*	↓1.57*	6
	FP 250μg bid (DH) [82]	2.66	3.1	↑0.58*	↑39*, ↑31*	↓1.51*	8
	PL [82]	2.6	3.3	↑0.24	↑7, ↑8	↓0.19	18
Wolfe et al.[50] (12)[defhj]	FP 100μg bid (MDI) [75]	2.38 [66]	3-4[i]	↑0.39***	↑25*[†]	↓0.91-1.43[k]**	14***
	FP 250μg bid (MDI) [68]	2.34 [66]		↑0.30***	↑16*		14***
	PL [69]	2.3 [64]		↓0.31	↓9	↑1.25	71

a Number of patients included in the efficacy analysis, except in Sheffer et al.,[49] for which the number of patients enrolled is presented.

b Mean change from baseline.

c When only 1 value is provided, it is the morning value.

d Data from a higher FP dosage group are not presented as FP dosages >500 μg/day are outside the scope of this review.

e Patients had an unmedicated FEV_1 between 60 and 90%,[19] 60 and 85%,[14] 50 and 80%[20-22,50] or 45 and 75%[49] of the predicted value for their age, gender and height.

f Patients were receiving inhaled corticosteroids at the time of enrolment (beclomethasone dipropionate 400 to 800 μg/day;[19,50] or ≥336 μg/day or triamcinolone acetonide ≥800 μg/day[20]).

g Patients had not received inhaled corticosteroids previously[14] or within 1 month of enrolment.[21,22,49]

h Adolescents aged ≥ 12 years were included.

i Mean baseline β_2-agonist usage (puffs/day) across all treatment groups.

j Use of a spacer device was prohibited.

k The range includes the value for an FP 500μg twice daily dosage group.

am = morning; **β_2-agonist usage** = use of as-needed β_2-agonist bronchodilators; **bid** = twice daily; **DH** = Diskhaler® dry powder inhaler; **FEV_1** = forced expiratory volume in 1 second; **LOE** = withdrawal for loss of efficacy/asthma exacerbation during the study; **MDI** = metered dose inhaler; **MDI 1%** = metered dose inhaler with 1% lecithin; **MDI 10%** = metered dose inhaler with 10% lecithin; **PEF** = peak expiratory flow rate; **pm** = evening; ↓ indicates decrease; ↑ indicates increase; *p < 0.05, **p < 0.01, *** p ≤ 0.001 *vs* PL; [†]p = 0.039 *vs* FP 250μg bid.

Asthma), and significantly better sleep patterns ($p \leq 0.0001$) compared with placebo (n = 78).[51] Patients in all 3 dosage groups had higher scores on the physical functioning and role-physical dimensions of a general health status questionnaire (Medical Outcomes Study Short Form-36; $p \leq 0.0001$),[51] and those in the 2 highest dosage groups had significantly higher scores on general health perceptions ($p < 0.03$), vitality ($p < 0.007$) and mental health ($p < 0.03$) compared with placebo.[51]

The results of placebo-controlled studies in patients with mild to moderate asthma show that there is little difference in the clinical response to dosages of fluticasone propionate ≤250μg twice daily. Although statistically significant increases in morning (4.3 L/min for each doubling dose; p = 0.001) and evening PEF (3 L/min for each doubling dose; p = 0.017), and the proportion of symptom-free days (2% increase per doubling dose; p = 0.048) have been demonstrated with fluticasone propionate 100 to 800 μg/day, the clinical significance of such a shallow dose-response relationship is unclear.[25] Hence, it appears that in patients with mild to moderate asthma, maximum clinical benefit may be achieved with dosages as low as 50 to 100μg twice daily.

In summary, inhaled fluticasone propionate ≤250μg twice daily produced consistent improvements in lung function, reduced the severity of symptoms, the frequency of as-needed salbutamol usage and nocturnal awakenings, prevented exacerbations and improved QOL in patients with mild to moderate asthma compared with placebo.

3.2 Comparisons with Nonsteroidal Agents with Anti-Inflammatory Properties

Inhaled corticosteroids are acknowledged to be the most effective anti-inflammatory therapy for asthma.[4] Nonetheless, current US[8] and British[7] guidelines consider inhaled sodium cromoglycate or nedocromil to be alternatives to inhaled corticosteroids in patients with mild chronic asthma. Moreover, sustained release theophylline and leukotriene antagonists (e.g. montelukast, zafirlukast, zileuton) are recognised as alternative preventive medications in patients with mild persistent asthma in the US.[8] Comparative data are available from controlled trials between fluticasone propionate and nedocromil,[53,54] theophylline[52] or zafirlukast[55] Results of these trials provide insight into the relative effectiveness of these agents in patients with mild to moderate asthma.

Inhaled fluticasone propionate was more effective than inhaled nedocromil in patients with mild to moderate persistent asthma (FEV_1 60 to 90% of the predicted value for their age, gender and height) in 1 study. Morning and evening PEF and FEV_1 improved significantly in patients treated for 8 weeks with fluticasone propionate 250μg twice daily than nedocromil 4mg 4 times daily ($p < 0.05$; table IV).[53] FEF_{25-75} also increased to a greater extent in fluticasone propionate- than nedocromil-treated patients by the end of the study (38.3 *vs* 18.5 L/sec; p = 0.02). Reductions in the use of as-needed salbutamol during day and night were both significantly greater with fluticasone propionate than nedocromil (fig. 3).[53] However, it should be noted that approximately 50% of patients enrolled in this trial were receiving beclomethasone dipropionate ≤1000 μg/day or equivalent at baseline.

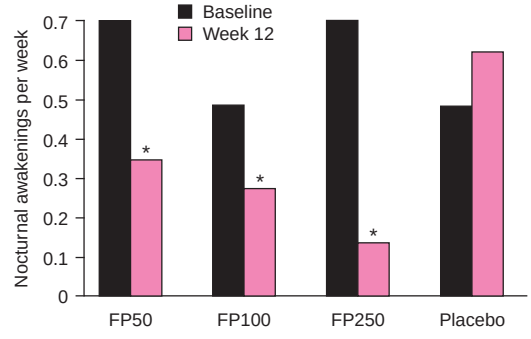

Fig. 2. Reductions in nocturnal awakenings with fluticasone propionate. Frequency of nocturnal awakenings at baseline and after 12 weeks' treatment with inhaled fluticasone propionate 50 (FP50; n = 79), 100 (FP100; n = 78) or 250μg (FP250; n = 82) or placebo (PL; n = 82) twice daily by Diskhaler® in a multicentre, randomised, double-blind study.[21] *$p < 0.05$ *vs* placebo.

Table IV. Summary of multicentre, randomised, parallel-group trials comparing inhaled fluticasone propionate (FP) ≤ 500 μg/day with non-steroidal agents with anti-inflammatory properties in adults with asthma

Reference [duration (wk)]	Dosage (delivery device) [no. of patients]	Baseline	Results at end-point		
		FEV_1 (L) or PEF (L/min) [% predicted]	FEV_1 (L)[a]	PEF (am, pm; L/min)[ab]	LOE (%)
Inhaled nedocromil (NED)					
Grison et al.[54] abstract (12)[c]	FP 250μg bid [93]	360[d]		↑42*	15*
	NED 4mg qid [85]	387[d]		↑9	27
Pauli & Aubert[53] (8)[e]	FP 250μg bid (MDI) [101]	2.35 [71.9][f]	↑18.1%*	↑60***, ↑49***	1
	NED 4mg qid (MDI) [103]	2.30 [70.4][f]	↑8.4%	↑7, ↑9	9
Theophylline (TH)					
Galant et al. [52] (12)[ghi]	FP 50μg bid (MDI) [91]	2.44 [62][f]	↑0.66**	↑54***	13**
	FP 100μg bid (MDI) [86]	2.29 [60][f]	↑0.65**	↑49***	19**
	TH bid PO[j] [89]	2.40 [62][f]	↑0.37	↑21	38
	PL [87]	2.31 [61][f]	↑0.19	↑19	52
Zafirlukast (ZAF)					
Johnson et al.[55] abstract (12)[ghk]	FP 88μg bid [214]	[67-68][fl]	↑0.5***	↑40.8***, ↑32.1***	
	ZAF 20mg bid PO [219]		↑0.32	↑16.7, ↑17.1	
	PL [229]		↑0.25	↑8.8, ↑11.5	

a Mean change from baseline.

b When only 1 value is provided, it is the morning value.

c Patients were receiving long-acting β_2-agonist bronchodilators or theophylline prior to enrolment. The delivery device (i.e. DPI or MDI) used during the study was not indicated.

d PEF at the end of a 2-week run-in period, during which patients received prednisolone 25mg daily.

e Patients had a baseline FEV_1 between 60 to 90% of the predicted value and ≥15% reversibility in FEV_1 after inhalation of salbutamol (albuterol). No patients had received inhaled NED or sodium cromoglycate within 1 month of enrolment, but ≈50% of those enrolled had been receiving beclomethasone dipropionate ≤1000 μg/day (or equivalent) prior to enrolment.

f FEV_1.

g Double-blind.

h Adolescents ≥ 12 years were included.

i Patients had a baseline FEV_1 between 45 to 75% of the predicted value, ≥15% reversibility in FEV_1 after inhalation of salbutamol and had not received inhaled corticosteroids for ≥1 month prior to enrolment.

j Theophylline dosage was titrated to achieve a trough plasma concentration of 5 to 15 mg/L.

k Pooled results from 2 studies of similar design. Patients had a baseline FEV_1 between 50 and 80% of the predicted value and were not receiving inhaled corticosteroids prior to enrolment.

l Mean baseline FEV_1 (% predicted) across all treatment groups.

am = morning; **bid** = twice daily; **FEV_1** = forced expiratory volume in 1 second; **MDI** = metered dose inhaler; **LOE** = withdrawal for loss of efficacy/asthma exacerbation during the study; **PEF** = peak expiratory flow rate; **PL** = placebo; **pm** = evening; **PO** = orally; **qid** = 4 times daily; ↑ indicates increase; *p < 0.05, **p < 0.01, ***p ≤ 0.001 FP *vs* NED, TH, ZAF and PL.

Fluticasone propionate 250μg twice daily and nedocromil 4mg 4 times daily were compared in a further study designed to evaluate the ability of these agents to maintain lung function in patients with asthma.[54] Only inhaled corticosteroid-naive patients with chronic asthma were eligible for enrolment; however, oral prednisolone 25mg was given once daily during a 2-week run-in phase.[54] After 12 weeks' treatment, morning PEF values increased to a significantly greater extent and significantly fewer patients withdrew for loss of efficacy among fluticasone propionate treated-patients ($p < 0.05$; table IV).[54] Thus, fluticasone propionate was more effective in maintaining lung function and preventing exacerbations than nedocromil.

Fluticasone propionate was generally more effective than theophylline in patients with moderate to severe persistent asthma (FEV_1 45 to 75% of the predicted value for their age, gender and height) who were not taking inhaled corticosteroids at

baseline. After 12 weeks, improvements in morning PEF and FEV_1 were significantly greater in recipients of fluticasone propionate 50 or 100µg twice daily than in recipients of theophylline or placebo (table IV).[52] Similar trends were observed for FEF_{25-75} and FVC ($p < 0.01$ for fluticasone propionate 50 or 100µg twice daily *vs* theophylline or placebo).[52] Significantly more placebo and theophylline recipients discontinued treatment because of loss of efficacy than fluticasone propionate recipients ($p < 0.01$; table IV); however, the difference in withdrawal rates between placebo and theophylline recipients was not significant. Use of as-needed salbutamol declined significantly with all active treatments compared with placebo (fig. 4).[52] Moreover, recipients of fluticasone propionate 100µg twice daily, but not 50µg twice daily, used significantly less rescue salbutamol than theophylline-treated patients. Total asthma symptom scores decreased significantly in both fluticasone propionate dosage groups compared with placebo ($p \leq 0.05$) and symptom scores in fluticasone propionate 50µg twice daily recipients were significantly ($p < 0.05$) lower than those in theophylline-treated patients; symptom scores in the theophylline group did not differ significantly from placebo.[52] There was no difference in the frequency of nocturnal awakenings between treatments after 12 weeks, although the baseline frequency was quite low (0.2 to 0.4 per week).[52]

In a pooled analysis of 2 studies, fluticasone propionate 88µg twice daily was superior to oral zafirlukast 20mg twice daily and placebo in controlling asthma in 662 patients who were not receiving inhaled corticosteroids at the time of enrolment.[55] In the US,[8] but not in Britain,[7] leukotriene antagonists (e.g. zafirlukast) are recognised as alternative preventive agents to inhaled corticosteroids in patients with mild persistent asthma.

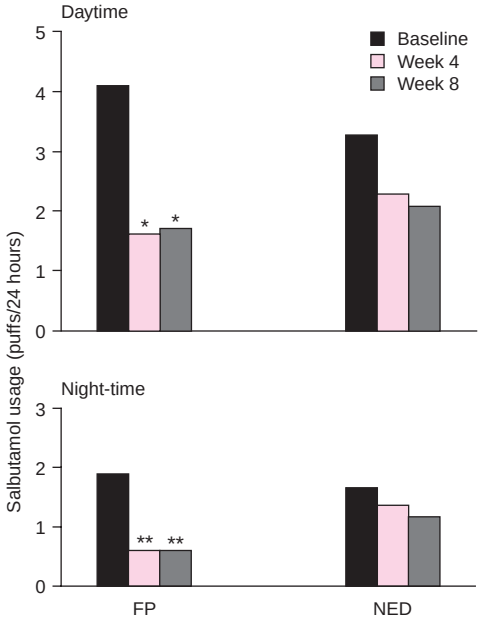

Fig. 3. Use of salbutamol (albuterol) in fluticasone propionate- or nedocromil-treated patients. Daytime and night-time use of as-needed salbutamol in patients with mild to moderate asthma (FEV_1 60 to 90% of the predicted value for their age, gender and weight) treated with inhaled fluticasone propionate 250µg twice daily (FP; n = 101) or nedocromil 4mg 4 times daily (NED; n = 103) given by metered dose inhaler during an 8-week, multicentre, randomised, nonblind parallel-group study.[53] **FEV_1** = forced expiratory volume in 1 second; *p ≤ 0.006; **p = 0.0001.

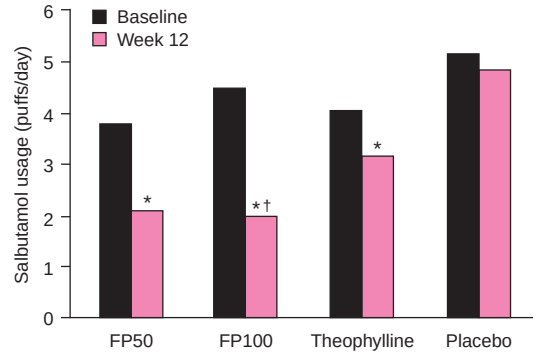

Fig. 4. Use of salbutamol (albuterol) in fluticasone propionate or theophylline recipients. Use of as-needed salbutamol in patients with asthma (FEV_1 45 to 75% of the predicted value for their age, gender and height) treated with inhaled fluticasone propionate 50µg (FP50; n = 91) or 100µg twice daily (FP100; n = 86) given by metered dose inhaler, oral theophylline titrated to achieve a trough plasma concentration of 5 to 15 mg/L (n = 89) or placebo (n = 87) for 12 weeks in a multicentre, double-blind, randomised, parallel-group study.[52] **FEV_1** = forced expiratory volume in 1 second; *p ≤ 0.05 *vs* placebo; †p < 0.05 *vs* theophylline.

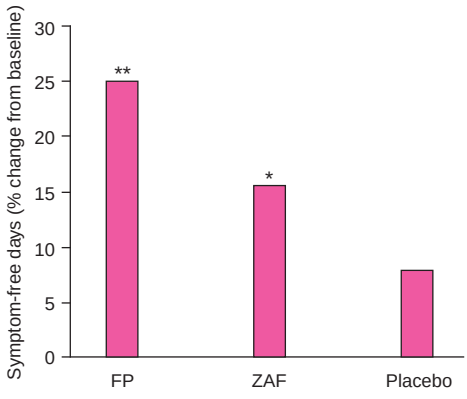

Fig. 5. Increase in symptom-free days with fluticasone propionate, zafirlukast or placebo in clinical trials. Difference between the end of 12 weeks' treatment and baseline in the number of symptom-free days in patients treated with inhaled fluticasone propionate 88μg twice daily (FP; n = 214), oral zafirlukast 20mg twice daily (ZAF; n = 219) or placebo (n = 229) in adults and adolescents with asthma during 2 multicentre, randomised, double-blind studies.[55] *$p \leq 0.05$ *vs* placebo; **$p \leq 0.01$ *vs* placebo and zafirlukast.

Improvements in lung function were significantly greater in fluticasone propionate- than zafirlukast- or placebo-treated patients after 12 weeks of treatment (table IV). The frequency of salbutamol use decreased by 2.7 ($p \leq 0.001$ *vs* zafirlukast and placebo), 2 ($p \leq 0.05$ *vs* placebo) and 1.4 puffs/day, respectively, in patients receiving fluticasone propionate, zafirlukast and placebo. Night-time awakenings in fluticasone propionate-, zafirlukast- and placebo-treated patients were reduced by 0.35 ($p \leq 0.01$ *vs* zafirlukast and placebo), 0.27 ($p \leq 0.05$ *vs* placebo) and 0.19 awakenings per night. Between baseline and the end of treatment, symptom scores decreased by 0.65 ($p \leq 0.001$ *vs* zafirlukast and placebo) in fluticasone propionate recipients, 0.39 in zafirlukast recipients and 0.47 in those receiving placebo. The proportion of symptom-free days also increased significantly between baseline and the end of treatment in the fluticasone propionate group (fig. 5).[55]

Patients treated with fluticasone propionate also experienced greater improvements in QOL, as measured by the AQLQ, than those treated with zafirlukast or placebo. Baseline AQLQ scores were significantly different between the 3 groups (not presented in the abstract); however, these differences were controlled for in the analysis. Global AQLQ scores improved to a significantly greater extent in patients treated with fluticasone propionate 88μg twice daily than those treated with either zafirlukast 20mg twice daily or placebo (32.1% *vs* 23.3 and 21%, respectively), as did improvements in the Activity Limitations (26.4% *vs* 22.9 and 18.4%), Asthma Symptoms (39.4% *vs* 26.9 and 25.2%), Emotional Function (40% *vs* 27.1 and 25.3%) and Environmental Exposure (36.5% *vs* 26.6 and 27.5%) domains of the AQLQ ($p \leq 0.045$ for fluticasone propionate *vs* zafirlukast and placebo in each instance).[86] Furthermore, a greater proportion of fluticasone propionate- than zafirlukast- or placebo-treated patients experienced moderate (1.0) and large (1.5) improvements in Global AQLQ scores, although the statistical significance of the differences was not reported (section 3).[87]

These results demonstrate that treatment with a low dosage of fluticasone propionate is superior to treatment with the recommended dosage of oral zafirlukast in patients with asthma.

In summary, the results of randomised, comparative trials demonstrate that fluticasone propionate ≤500 μg/day provides better control of persistent asthma than inhaled nedocromil or oral theophylline or zafirlukast.

3.3 Comparisons with Other Inhaled Corticosteroids

In this section the results of comparative trials between fluticasone propionate ≤250μg twice daily and other inhaled corticosteroids in patients with mild to moderate asthma are reviewed. Management guidelines for asthma recommend that fluticasone propionate be prescribed at half the microgram dosage of other inhaled corticosteroids.[7,8]

3.3.1 Beclomethasone Dipropionate

In comparative studies, inhaled fluticasone propionate and beclomethasone dipropionate consistently maintained or improved control of asthma in patients who were taking inhaled corticosteroids prior to enrolment.[25,37,56,57] In each study, there

was at least 1 patient group which received fluticasone propionate at half the dosage of beclomethasone dipropionate.

Treatment with fluticasone propionate 50 to 250μg twice daily or beclomethasone dipropionate 168 to 500μg twice daily for 4 to 12 weeks produced improvements in morning and evening PEF,[25,37,56,57] and FEV_1[37,56,57] compared with baseline (table V).

Fluticasone propionate produced significantly greater spirometric improvements than beclomethasone dipropionate in 1 trial in which patients were receiving beclomethasone dipropionate ≥336 μg/day or triamcinolone acetonide ≥800μg/day at baseline.[57] Morning PEF and FEV_1 increased significantly in recipients of fluticasone propionate 88 or 220μg twice daily compared with beclomethasone dipropionate 168μg twice daily (table V). Improvements in these parameters in the higher fluticasone propionate dosage group were significantly greater than in patients treated with beclomethasone dipropionate 336μg twice daily.[57] In

Table V. Summary of multicentre, randomised, double-blind, parallel-group trials comparing inhaled fluticasone propionate (FP) ≤ 500 μg/day with inhaled beclomethasone dipropionate (BDP) in adults with asthma

Reference [duration (wk)]	Dosage (delivery device) [no. of patients[a]]	Baseline characteristics (mean)		Results at end-point				
		Baseline FEV_1 (L) [% predicted]	β_2-agonist usage (puffs/day)	FEV_1 (L)[b]	FVC (L)[b]	PEF (am, pm; L/min)[bc]	β_2-agonist usage (puffs/day)[b]	LOE (%)
Dahl et al.[25] (4)[def]	FP 50μg bid (MDI) [137]	[75]	4.0			↑5, ↑2	↓0.2[g]	4
	FP 100μg bid (MDI) [134]	[70]	4.9			↑13, ↑7	↓0.7[g]	5
	FP 200μg bid (MDI) [137]	[73]	4.9			↑15, ↑8	↓0.6[g]	2
	BDP 200μg bid (MDI) [131]	[74]	5.1			↑11, ↑5	↓1.1[g]	2
Leblanc et al.[37] (4)[fh]	FP 100μg bid (MDI) [123]	2.34 [74]	4.6	↑0.07	↑0.04	↑17, ↑8	↓1.5	2
	BDP 200μg bid (MDI) [132]	2.21 [70]	4.5	↑0.15	↑0.10	↑17, ↑14	↓1.1	3
Lundback et al.[56] (6)[fhi]	FP 250μg bid (MDI) [193]	2.3		↑0.13	↑0.17	↑19, ↑11		3
	FP 250μg bid (DH) [198]	2.49		↑0.12	↑0.15	↑20, ↑15		3
	BDP 500μg bid (MDI) [194]	2.42		↑0.09	↑0.09	↑14, ↑14		6
Rapheal et al.[57] abstract (12)[fjk]	FP 88μg bid [99]	[65][l]		↑0.31*		↑15.8*	↓0.9*	13.1
	FP 220μg bid [104]			↑0.36*[†]		↑24.9*[†]	↓0.6*	11.5
	BDP 168μg bid [101]			↑0.18		↑0.7	0	20.8
	BDP 336μg bid [95]			↑0.21		↑7.2	↓0.2	12.6

a Number of patients included in the efficacy analysis, except in Lundback[56] for which the number of patients enrolled is presented.

b Mean change from baseline unless otherwise specified.

c When only 1 value is provided, it is the morning value.

d Data from a higher FP dosage group (400μg twice daily) are not presented as FP dosages >500 μg/day are outside the scope of this review.

e Use of a spacer device was prohibited.

f Patients were receiving inhaled corticosteroids at the time of enrolment (BDP or BUD ≤ 400 μg/day,[37] 400 to 1000 μg/day,[56] or ≤ 1000 μg/day;[25] or BDP ≥ 336μg/day or triamcinolone acetonide ≥ 800 μg/day[57]).

g Median change from baseline.

h Use of a spacer device was permitted.

i Adolescents aged ≥12 years were included.

j The delivery device (i.e. DPI or MDI) used during the study was not indicated.

k Patients had an unmedicated FEV_1 between 45 and 80% of the predicted normal value for their age, gender and height at screening.

l Mean baseline FEV_1 (% predicted for patient age, gender and height) across all treatment groups.

am = morning; **β_2-agonist usage** = use of as-needed β_2-agonist bronchodilators; **bid** = twice daily; **BUD** = budesonide; **DH** = Diskhaler® DPI; **DPI** = dry powder inhaler; **FEV_1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **LOE** = withdrawal for loss of efficacy/asthma exacerbation during the study; **MDI** = metered dose inhaler; **PEF** = peak expiratory flow rate; **pm** = evening; ↓ indicates decrease; ↑ indicates increase; *$p < 0.05$ *vs* BDP 168 bid; †$p < 0.05$ *vs* BDP 336μg bid.

other studies, no significant differences were detected in spirometric endpoints between the fluticasone propionate and beclomethasone dipropionate treatment groups.

Requirements for as-needed β_2-agonist bronchodilators generally declined in patients treated with inhaled fluticasone propionate ≤500 μg/day or beclomethasone dipropionate (table V).[25,37,57] Use of as-needed salbutamol decreased significantly after 12 weeks of fluticasone propionate 88 or 220 μg/day compared with recipients of beclomethasone dipropionate 168μg twice daily in 1 study.[57]

The frequency of symptom-free days, symptom-free nights and rescue medication-free days increased in patients treated with fluticasone propionate 100μg twice daily or beclomethasone dipropionate 200μg twice daily for 4 weeks in 1 study (fig. 6).[37] Whereas the increase in rescue medication-free days was significantly greater in patients treated with beclomethasone dipropionate than fluticasone propionate ($p < 0.05$), there was no statistical difference in the frequency of as-needed salbutamol usage between the 2 groups (table V).[37]

Withdrawal from studies because of asthma exacerbations appears to reflect the severity of asthma at baseline. Withdrawal was infrequent (≤6%) and occurred with similar frequency in fluticasone propionate and inhaled beclomethasone dipropionate recipients in 3 trials that enrolled patients with mild or moderate asthma (table V).[25,37,56] In the fourth study, patients with severe asthma (baseline FEV_1 45 to 80% of the predicted value for their age, gender and height) were included and correspondingly higher withdrawal rates for loss of efficacy were reported (11.5 to 20.8%; table V).[57] Withdrawal rates in patients treated with fluticasone propionate 88 or 220μg twice daily or beclomethasone dipropionate 336μg twice daily (11.5 to 13.1%) were considerably lower than in recipients of beclomethasone 168μg twice daily (20.8%), suggesting that the lower beclomethasone dipropionate dosage was inadequate for the severity of asthma examined in this study.[57] This is not at all surprising as patients were receiving inhaled beclomethasone dipropionate ≥336 μg/day or triamcinolone acetonide ≥800 μg/day at baseline.[57]

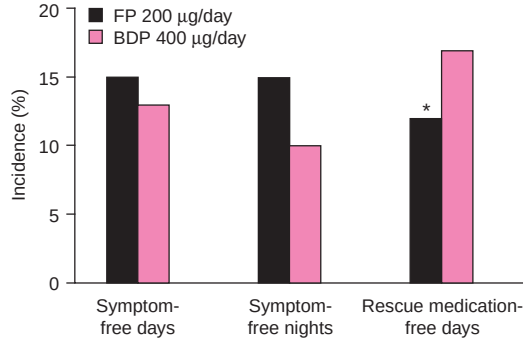

Fig. 6. Symptom improvement in patients treated with inhaled fluticasone propionate (FP) or beclomethasone dipropionate (BDP). Difference between the 4-week treatment period and the 2-week run-in period in the percentage of symptom-free days, symptom-free nights and rescue medication-free days in patients with mild to moderate asthma treated with inhaled fluticasone propionate 200 μg/day (n = 123) or inhaled beclomethasone dipropionate 400 μg/day (n = 132) by metered dose inhaler in a multicentre, randomised, double-blind, parallel-group study.[37] *$p < 0.05$ *vs* BDP.

More patients receiving fluticasone propionate 200 μg/day were rated 'improved or better' by their physicians than patients receiving beclomethasone dipropionate 400 μg/day in a Japanese study.[58] However, lung function measurements were not reported in this study.

The results of these trials suggest that fluticasone propionate at dosages ≤500 μg/day is at least as effective as beclomethasone dipropionate given at twice the microgram dosage in patients with mild to moderate asthma.

Inhaled fluticasone propionate and beclomethasone dipropionate have also been compared in studies in which a group of patients received fluticasone propionate once daily.[71,72] The results of these studies are described in section 3.5.2.

3.3.2 Budesonide

Fluticasone propionate ≤500 μg/day has been compared with budesonide 200 to 1200 μg/day in patients with mild to moderate asthma. In several trials, the daily dosage of fluticasone propionate

was less than or equal to half the daily dosage of inhaled budesonide.[27-29,60,61]

Mean improvements in morning and/or evening PEF in fluticasone propionate recipients were similar to or exceeded those in budesonide recipients in trials in which the daily dosage of inhaled fluticasone was less than half or equal to the daily dosage of budesonide, (table VI).[27-29,60,61] Moreover, improvements in morning PEF were significantly greater in fluticasone propionate than budesonide recipients in 2 studies.[28,61]

The frequency of as-needed β_2-agonist usage decreased by a similar extent in patients treated with fluticasone propionate 100 or 200μg twice daily or budesonide 200 or 400μg twice daily.[28,29]

A greater degree of symptomatic relief was obtained with fluticasone propionate 200 μg/day than budesonide 400 μg/day in 1 study.[27] After 8 weeks, the median frequency of symptom-free days increased more with fluticasone propionate than budesonide (29 to 53% *vs* no change; p = 0.05) as did symptom-free nights (29 to 58% *vs* 24 to 41%; p = 0.05), rescue medication-free days (0 to 17% *vs* no change; p = 0.01) and rescue medication-free nights (43 to 57% *vs* 29 to 31%; p = 0.02).[27]

Equal daily dosages of fluticasone propionate and budesonide were compared in 2 trials. In 1 study,[59] patients with mild persistent asthma (mean $FEV_1 \geq 80\%$ of the predicted value for their age, gender and height) receiving ongoing treatment with 400 to 800 μg/day of inhaled beclomethasone dipropionate or budesonide were randomised to receive either fluticasone propionate or budesonide at half their previous maintenance dose of inhaled corticosteroid.[59] Although the increases in morning and evening PEF from baseline and reductions in the use of as-needed β_2-agonist medication were greater in patients treated with inhaled fluticasone propionate than budesonide, the differences were not statistically significant (table VI).[59] Withdrawal rates for worsening asthma, which was not objectively defined, were similar with the 2 therapies.[59]

In another study,[62] patients with mild to moderate persistent asthma (mean FEV_1 76.2 to 77.1% of the predicted value for their age, gender and height), most of whom (≥73.5%) were inhaled corticosteroid-naive at baseline, were assigned to receive fluticasone propionate 200μg twice daily, budesonide 200μg twice daily or 400μg given in the evening (nocte).[62] After 8 weeks' treatment, mean morning and/or evening PEF had increased significantly over baseline values in all 3 groups (evening PEF measurements were not provided for budesonide 200μg twice daily recipients; table VI).[62] Improvements in asthma symptom scores and reductions in the frequency of as-needed β_2-agonist bronchodilator usage were significant compared to baseline in fluticasone propionate and budesonide nocte recipients ($p < 0.0001$ *vs* baseline); however, there was no difference between treatments.[62] Withdrawal rates for inadequate asthma control were >4 times higher in both budesonide groups than in fluticasone propionate recipients; however, the statistical significance of these differences was not reported (table VI).[62]

The results of these studies suggest that fluticasone propionate is at least as effective as budesonide when given at half the microgram dosage of budesonide in patients with mild to moderate asthma.

The effectiveness of fluticasone propionate 100μg plus salmeterol 50μg twice daily have been compared with budesonide 400μg twice daily in patients with moderate persistent asthma.[86] The results of this study are presented in section 3.4. Once daily administration of fluticasone propionate 200μg and budesonide 400μg have also been compared in a randomised study,[88] the results of which are described in section 3.5.2.

3.3.3 Flunisolide

Inhaled fluticasone propionate 250μg twice daily has been compared with inhaled flunisolide 500μg twice daily in patients with asthma in 3 comparative studies, 2 of which have been published only as abstracts.[64,65] Morning and evening PEF improved consistently in both fluticasone propionate- and flunisolide-treated patients (table

Table VI. Summary of multicentre, randomised, nonblind, parallel-group trials comparing inhaled fluticasone propionate (FP) ≤ 500 μg/day with inhaled budesonide (BUD) in adults with asthma

Reference [duration (wk)]	Dosage (delivery device) [no. of patients[a]]	Baseline characteristics (mean)		Results at end-point		
		FEV_1 (L) or PEF (L/min) [% predicted]	β_2-agonist usage (puffs/day)	PEF (am, pm; L/min)[bc]	β_2-agonist usage (puffs/day)[b]	LOE (%)
Basran[59] (8)[de]	FP 100 or 200μg bid (DH) [92]	2.8 [82][f]	3.2	↑13.9, ↑4.4	↓0.91	5.4
	BUD 100 or 200μg bid (TB) [79]	2.7 [80.4][f]	3.2	↑3.9, ↓4.5	↓0.41	7.6
Burdon et al.[60] abstract (4)	FP 250μg bid (DK) [137]			403[g]		
	BUD 600μg bid (TB) [140]			400[g]		
Connolly et al.[27] (8)[de]	FP 100μg bid (DH) [98]	380.6 [79.1][h]		↑39.7		1
	BUD 200μg bid (DPI) [91]	379.3 [79.2][h]		↑26.1		0
Langdon et al.[28] (8)[de]	FP 200μg bid (DH) [138]	381.4[h]	3[i]	↑46.1[i]**, ↑19[i]	↓1.7[i]	
	BUD 400μg bid (DPI) [131]	371.3[h]	3.6[i]	↑27.5[i], ↑12[i]	↓1.7[i]	
Langdon et al.[29] (8)[dej]	FP 100μg bid (MDI) [81]	333[h]	3.0	↑33, ↑18	↓0.89	2.5
	BUD 200μg bid (MDI) [76]	338[h]	2.92	↑25, ↑18	↓0.86	4.9
Steinmetz[61] (6)[djk]	FP 250μg bid (MDI) [235]	342[h]		↑45*		
	BUD 600μg bid (TB) [222]	338[h]		↑30		
Venables et al.[62] (8)[de]	FP 200μg bid (DH) [74]	406.1 [76.2][h]	3.4	↑32.8[††], ↑19.4[†i]	↓2.1[††i]	1.4
	BUD 200μg bid (TB) [79]	408.4 [77.1][h]		↑21.4[††]		6.3
	BUD 400μg nocte (TB) [77]	398.8 [75.3][h]	3.91	↑32.1[††], ↑22.7[††i]	↓2[††i]	7.8

a Number of patients included in the efficacy analysis, except in Venables et al.[62] for which the number of patients enrolled is presented.

b Mean change from baseline.

c When only 1 value is provided, it is the morning value.

d Patients had a baseline FEV_1 ≥40%,[59] ≥50%,[27-29] ≥60%,[62] 50-80%,[61] or 50 to 90%[60] of the predicted value for their age, gender and height.

e Patients were receiving inhaled corticosteroids at the time of enrolment (BDP, BUD or FP 0-200 μg/day;[62] BDP or BUD 0-500 μg/day[27] or 0-600 μg/day;[28] 400-800 μg/day of any inhaled corticosteroid;[59] drug and dosage not specified[29]).

f FEV_1.

g PEF at the end of the study.

h PEF.

i Estimated from graphs.

j Use of a spacer device was prohibited.

k Patients had not received inhaled corticosteroids for ≥3 weeks prior to enrolment.

am = morning; **β_2-agonist usage** = use of as-needed β_2-agonist bronchodilators; **BDP** = beclomethasone dipropionate; **bid** = twice daily; **DH** = Diskhaler® DPI; **DK** = Diskus®/Accuhaler® DPI; **DPI** = dry powder inhaler; **FEV_1** = forced expiratory volume in 1 second; **LOE** = withdrawal for loss of efficacy/asthma exacerbation during the study; **MDI** = metered dose inhaler; **nocte** = in the evening; **PEF** = peak expiratory flow rate; **pm** = evening; **TB** = Turbuhaler® DPI; ↓ indicates decrease; ↑ indicates increase; * $p < 0.01$, ** $p = 0.009$, *vs* BUD; † $p < 0.001$, †† $p < 0.0001$ *vs* baseline.

VII).[63-65] The increase in morning and evening PEF was significantly greater in fluticasone propionate recipients in 1 study, which enrolled inhaled corticosteroid-naive patients with moderate persistent asthma (FEV_1 ≤80% of the predicted value for their age, gender and height).[65] FEV_1 increased by 17.2 and 11.9%, respectively, in fluticasone propionate and flunisolide recipients in another study ($p \leq 0.04$).[64]

Greater improvements in asthma symptoms in fluticasone propionate- than flunisolide-treated patients were reported in 1 study.[63] Patients with moderate asthma (FEV_1 ≥60% of the predicted value for their age gender and height) treated with fluticasone propionate had greater improvements in cough (77 *vs* 64% rated their symptoms as better; $p = 0.03$ *vs* flunisolide) and night-time symptoms (68 *vs* 52% rated their symptoms as

better; p = 0.03 *vs* flunisolide) than flunisolide recipients.[63]

Although the evidence is limited, the results of comparative trials suggest that fluticasone propionate 250μg twice daily is at least as effective as flunisolide 500μg twice daily.

3.3.4 Triamcinolone Acetonide

Greater improvement in asthma control was achieved with fluticasone propionate 250 twice daily than triamcinolone acetonide 200μg 4 times daily after 24 weeks in 2 randomised trials of similar design.[66,67] Patients in both trials had moderate to severe persistent asthma (FEV_1 50 to 80% of the predicted value for their age, gender and height) at baseline and were receiving inhaled corticosteroids (beclomethasone dipropionate 400 to 600 μg/day or triamcinolone acetonide 800 to 1200 μg/day) prior to enrolment.

Patients treated with fluticasone propionate 250μg twice daily had significantly greater improvements in FEV_1 and morning PEF and significantly greater reductions in the frequency of as-needed β_2-agonist usage compared with recipients of triamcinolone acetonide 200μg 4 times daily or placebo (table VIII).[66,67] The frequency of nocturnal awakenings and rates of withdrawal for loss of efficacy were significantly lower in patients receiving either active treatment than placebo. Furthermore, in 1 study these parameters improved to a greater extent in fluticasone propionate than triamcinolone acetonide recipients ($p < 0.05$).[67] Overall symptom scores decreased significantly in fluticasone propionate recipients compared with placebo in both trials ($p < 0.05$).[66,67] At the end of treatment, the frequency of symptom-free days was significantly greater with either active treatment than placebo in both trials and the frequency of rescue medication-free days was significantly greater in fluticasone propionate-treated patients than triamcinolone acetonide or placebo recipients in both trials (fig. 7).

QOL was assessed during 1 trial with the AQLQ.[67] After 24 weeks, patients treated with fluticasone propionate had significantly higher global AQLQ scores compared with baseline (0.4 *vs* 0; $p < 0.001$), triamcinolone acetonide recipients (0.4 *vs* 0; p = 0.007) and placebo recipients (0.4 *vs* –0.5; $p < 0.001$).[67] Moreover, scores in 3 of the 4 domains on the scale (Activity Limitation, Asthma Symptoms and Emotional Function, but not Environmental exposure) were significantly greater in fluticasone propionate than triamcinolone acetonide ($p \leq 0.029$) or placebo recipients ($p \leq 0.008$). Global AQLQ scores were unchanged between baseline and end-point in triamcinolone acetonide recipients; nonetheless, they were significantly greater than those in placebo-treated patients ($p \leq 0.008$), in whom QOL scores decreased significantly ($p < 0.001$). The difference in AQLQ scores between fluticasone propionate and placebo recipients (0.9) at the end of treatment was clinically meaningful (defined as a difference ≥0.5).[67]

Triamcinolone acetonide 600μg twice daily has also been compared with fluticasone propionate 220μg twice daily and with fluticasone propionate

Table VII. Summary of multicentre, randomised, parallel-group trials comparing inhaled fluticasone propionate (FP) ≤ 500 μg/day with inhaled flunisolide (FLD) in adults with asthma

Reference [duration (wk)]	Dosage(delivery device) [no. of patients[a]]	Increase in PEF (am, pm; L/min)[b]
Bergmann[63] (6)[c]	FP 250μg bid (DPI) [84]	↑66, ↑48
	FLD 500μg bid (MDI[d]) [85]	↑58, ↑51
Srebro et al.[64] abstract (8)[e]	FP 250μg bid (DH) [164]	↑41
	FLD 500μg bid (MDI) [157]	↑29
Trautmann[65] abstract (6)[f]	FP 250μg bid (MDI) [169]	↑51*,↑41*
	FLD 500μg bid (MDI) [159]	↑26, ↑22

a Number of patients included in the efficacy analysis.

b Mean change from baseline to end-point (when only 1 value is provided it is the morning value).

c With the exception of 15 patients enrolled in this nonblind study, the baseline FEV_1 was ≥60% of the predicted value for the age, gender and weight of each patient. Adolescents Aged ≥ 14 years were included.

d A spacer device was used.

e Patients had not received inhaled corticosteroids for ≥ 4 weeks prior to this double-blind study.

f Patients enrolled in this nonblind study had not received prior inhaled corticosteroids and had a baseline FEV_1 of ≤80% of the predicted value for their age, gender and height.[89]

am = morning; **bid** = twice daily; **DH** = Diskhaler® DPI; **DPI** = dry powder inhaler; **FEV_1** = forced expiratory volume in 1 second; **MDI** = metered dose inhaler; **PEF** = peak expiratory flow rate; **pm** = evening; *p < 0.01; FP *vs* FLD.

88μg plus salmeterol 42μg twice daily in patients with asthma.[76] The results of this study are presented in section 3.4.

Table VIII

3.4 In Combination with Salmeterol

Combining long-acting inhaled β_2-agonist bronchodilators (e.g. salmeterol, formoterol) with inhaled corticosteroids may improve control of asthma and allow for the use of a lower inhaled corticosteroid dosage. The combination of inhaled salmeterol and inhaled fluticasone propionate has been evaluated in patients with mild to severe persistent asthma. As yet, most of these studies have been published only as abstracts.[74-79,82,83,90]

Combining the 2 drugs in the same delivery device does not alter the efficacy of fluticasone propionate plus salmeterol treatment. There were no statistically significant differences in FEV_1 or PEF, and ≥32[74] and ≥60%[90] of patients were symptom free at the end of treatment compared with ≤2[74] and ≤35%[90] at baseline in patients treated with fluticasone propionate (100[90] or 250μg[74]) plus salmeterol 50μg twice daily given in 2 separate dry powder inhalers or combined in the same dry powder inhaler (table IX).[74,90]

The results of a 4-week placebo-controlled trial suggest that fluticasone and salmeterol have additive effects.[83] After 4 weeks, FEV_1 increased by at least 2-fold in patients (FEV_1 50 to 80% of the predicted value for their age, gender and height) treated with inhaled salmeterol 42μg plus fluticasone propionate 88 or 220μg twice daily compared with recipients of salmeterol or either dosage of fluticasone propionate alone (table IX).[83] Moreover, the combination of salmeterol 42μg plus fluticasone propionate 220μg twice daily, but not salmeterol 42μg plus fluticasone propionate 88μg twice daily, produced greater improvements in FEV_1 than either drug given separately ($p < 0.05$).[83]

Fluticasone propionate 100μg plus salmeterol 50μg twice daily improved lung function, decreased asthma symptoms and prevented LOE to a greater extent than either drug given separately. The combination produced a 3-fold greater improvement in

Table VIII. Summary of multicentre, randomised, double-blind, parallel-group trials comparing inhaled fluticasone propionate (FP) ≤ 500 μg/day with inhaled triamcinolone acetonide (TAA) in patients aged ≥12 years with asthma

Reference[a] [duration (wk)]	Dosage (delivery device) [no. of patients[b]]	Baseline characteristics (mean)			Results at end-point					
		FEV_1 (L) [% predicted]	β_2-agonist usage (puffs/day)	nocturnal wakenings/ wk	FEV_1 (L)[c]	am PEF (L/min)[c]	β_2-agonist usage (puffs/day)[c]	overall symptom score[c]	nocturnal awakenings/ wk[c]	LOE (%)
Condemi et al.[66] (24)	FP 250μg bid (DH) [95]	2.37 [68]	3.0	0.09	↑0.27*†	↑21*†	↓0.9*†	↓0.3†	↓0.03†	17††
	TAA 200μg qid (MDI) [101]	2.27 [67]	3.3	0.10	↑0.07†	↓6†	↓0.2	↓0.1†	↓0.01†	27††
	PL [95]	2.25 [66]	3.2	0.08	↓0.18	↓28	↑1.6	↑0.7	↑0.27	60
Gross et al.[67] (24)	FP 250μg bid (DH) [100]	2.38 [66]	3.2	0.09	↑0.32*†	↑18*†	↓0.6*†	↓0.3†	↓0.04*†	17**††
	TAA 200μg qid (MDI) [101]	2.44 [67]	3.2	0.09	↑0.03†	↓3†	↑0.6†	↓0.1	↑0.11†	33††
	PL [103]	2.51 [68]	3.3	0.10	↓0.18	↓24	↑1.9	↑0.8	↑0.26	65

a Patients had a baseline FEV_1 of 50 to 80% predicted and had been receiving treatment with beclomethasone dipropionate 400 to 600 μg/day or TAA 800 to 1200 μg/day for ≥4 weeks prior to enrolment.

b Number of patients included in the efficacy analysis.

c Mean change from baseline.

am PEF = morning peak expiratory flow rate; **β_2-agonist usage** = use of as-needed β_2-agonist bronchodilators; **bid** = twice daily; **DH** = Diskhaler® dry powder inhaler; **FEV_1** = forced expiratory volume in 1 second; **LOE** = withdrawal for loss of efficacy/asthma exacerbation during the study; **MDI** = metered dose inhaler with spacer device; **PL** = placebo; **qid** = 4 times daily; ↓ indicates decrease; ↑ indicates increase; *p < 0.05, **p < 0.01, *vs* TAA; †p < 0.05, ††p < 0.001 *vs* PL.

PEF than fluticasone propionate 100µg given alone, and significantly decreased asthma symptom scores and the frequency of as-needed salbutamol use compared with fluticasone propionate 100µg twice daily, salmeterol 50µg twice daily or placebo ($p \leq 0.003$) in a 12-week trial.[75] In another trial, in which 44% of placebo recipients were withdrawn for loss of efficacy, the frequency of loss of efficacy was significantly lower in patients treated with fluticasone propionate 100µg plus salmeterol 50µg twice daily (5%) than in those treated with either drug alone or placebo (significance level not provided; table IX).[78]

The addition of inhaled salmeterol may be an effective alternative to increasing the dose of inhaled corticosteroid in patients with uncontrolled asthma (FEV_1 < 80% of the predicted value for their age, gender and height). In patients with mild to severe persistent asthma ($FEV_1 \geq 40\%$ of the predicted value for their age, gender and height) not controlled by inhaled fluticasone propionate 88µg twice daily during a 2- to 4-week run-in period,

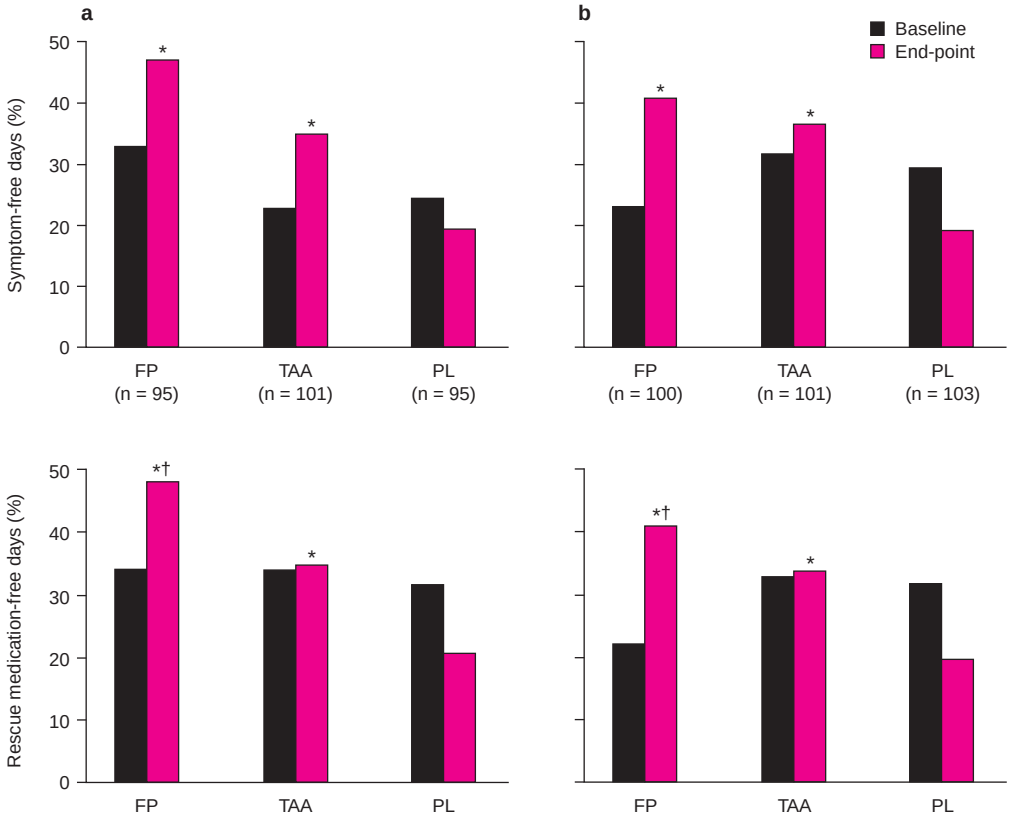

Fig. 7. Symptom-free days and rescue medication-free days in fluticasone propionate, triamcinolone acetonide or placebo recipients in 2 clinical trials. Difference between the final 3 weeks of the 24-week treatment period (end-point) and the 1-week run-in period (baseline) in the percentage of symptom-free days and rescue medication-free days in patients receiving inhaled fluticasone propionate 250µg twice daily (FP) given by Diskhaler®, inhaled triamcinolone acetonide 200µg 4 times daily (TAA) given by metered dose inhaler or placebo (PL) in 2 multicentre, randomised, double-blind, parallel-group trials [Condemi et al. (**a**)[66] and Gross et al. (**b**)[67]] Patients had mild to moderate persistent asthma ($FEV_1 \geq 60\%$ of the predicted value for their age, gender and height) and had been receiving treatment with inhaled beclomethasone dipropionate 400 to 600 µg/day or inhaled triamcinolone acetonide 800 to 1200 µg/day prior to enrolment. **FEV_1** = forced expiratory volume in 1 second; *p < 0.05 vs placebo; † p < 0.05 *vs* triamcinolone acetonide.

Table IX. Summary of multicentre, randomised, parallel-group trials comparing inhaled fluticasone propionate (FP) ≤ 500 μg/day plus inhaled salmeterol (SLM) with placebo (PL) or other therapies in patients with asthma

Reference [duration (wk)]	Dosage (delivery device) [no. of patients[a]]	Baseline	Results at end-point		
		FEV_1 (L) or PEF (L/min) [% predicted]	FEV_1 (L)[b]	amPEF (L/min)[b]	LOE (%)
FP plus SLM in separate delivery devices versus FP plus SLM combined in the same delivery device					
Bateman et al.[90] (12)[cd]	FP 100μg plus SLM 50μg bid (DK) [121]	2.42 [75][e]	↑0.20	↑47	0
	FP 100μg bid (DK) plus SLM 50μg bid (DK) [123]	2.33 [76][e]	↑0.17	↑39	0
Ringdal et al.[74] abstract (28[f])[c]	FP 250μg plus SLM 50μg bid (DK) [371]		↑0.26	↑43	
	FP 250μg bid (DK) plus SLM 50μg bid (DK)		↑0.24	↑36	
FP plus SLM versus other comparators					
Cook et al.[76] abstract (12)[cgh]	FP 220μg bid [114]		↑0.45†††	↑33.2†	
	FP 88μg plus SLM 42μg bid [118]		↑0.46†††	↑42†††	
	TAA 600μg bid [118]		↑0.20	↑4.9	
Di Lorenzo et al[77] abstract (24)[di]	FP 250μg plus SLM 50μg bid (MDI) [177]			↑30	7
	BDP 500μg plus SLM 50μg bid (MDI)			↑38	9
Edwards et al.[78] abstract (12)[cdh]	FP 100μg bid (DK) [356]	[64][ej]			12
	SLM 50μg bid (DK)				24
	FP 100μg plus SLM 50μg bid (DK)				5
	PL				44
Gross et al.[75] abstract (12)[cd]	FP 100μg bid (DK) [90]	377[k]		↑18	
	SLM 50μg bid (DK) [92]	371[k]		↑0.2	
	FP 100μg plus SLM 50μg bid (DK) [92]	400[k]		↑54**	
	PL [82]	384[k]		↓23	
Ind et al.[79] abstract (24)[dgl]	FP 250μg bid [496]	347[k]		↑22.5	
	FP 500μg bid	357.4[k]		↑21.5	
	FP 250μg plus SLM 50μg bid	346.6[k]		↑47.8‡‡‡	
Johansson et al.[86] abstract[adm]	FP 100μg plus SLM 50μg bid (DK) [349]	383[k]		↑44††	
	BUD 400μg bid	382[k]		↑31	
Kalberg et al.[82] abstract (24)[dl]	FP 220μg bid (MDI) [489]			↑30	32[n]
	FP 88μg plus SLM 42μg bid (MDI)			↑45‡‡	20[n]
Stricker et al.[83] abstract (4)[gko]	FP 88μg bid [23]	2.9 [69][e]	↑0.3*		
	FP 220μg bid [23]	2.5 [65][e]	↑0.3*		
	SLM 42μg bid [21]	2.8 [70][e]	↑0.3		
	FP 88μg plus SLM 42μg bid [25]	2.3 [67][e]	↑0.6*		
	FP 220μg plus SLM 42μg bid [21]	2.6 [69][e]	↑0.7*†‡		
	PL [23]	2.4 [68][e]	0		

a Number of patients included in the efficacy analysis except Ringdal et al.,[74] Di Lorenzo et al.,[77] Edwards et al.,[78] Ind et al.,[79] Johansson et al.[86] and Kalberg et al.[82] for which the total number of patients enrolled in the trial are presented.

the addition of inhaled salmeterol 42μg produced similar[76] or greater ($p \leq 0.004$)[82] improvements in morning PEF than increasing the dose of fluticasone propionate to 220μg twice daily (table IX). Morover, in 1 of these studies,[82] the frequency of symptom-free days increased by a significantly greater amount in patients treated with combined salmeterol 42μg plus fluticasone propionate 88μg twice daily than with fluticasone propionate 220μg twice daily (28 *vs* 11%; $p \leq 0.004$).[82]

Similar results were obtained in patients with moderate asthma not controlled (PEF < 90% of the predicted value for their age, gender and height) by 4 weeks' treatment with fluticasone propionate 250μg twice daily.[79] The addition of salmeterol 50μg twice daily produced significantly greater improvement in PEF than doubling the dose of fluticasone propionate ($p < 0.0001$; table IX). In addition to the superior improvement in lung function, a significantly greater proportion of patients treated with the combination had median symptom scores of 0 than those receiving fluticasone propionate 250 or 500μg twice daily alone.[79]

Fluticasone propionate 100μg (or 88μg) plus salmeterol 50μg (or 42μg) twice daily produced significantly greater spirometric improvements than triamcinolone acetonide 600μg twice daily or budesonide 400μg twice daily. Spirometric improvements in patients treated with salmeterol 42μg plus fluticasone propionate 88μg twice daily or inhaled fluticasone propionate 220μg twice daily were significantly greater than those in patients treated with inhaled triamcinolone acetonide 600μg twice daily (table IX).[76] Similarly, after 12 weeks fluticasone propionate 100μg plus salmeterol 50μg twice daily produced significantly greater improvements in morning ($p = 0.006$) and evening (mean difference = 14L; $p = 0.002$) PEF than budesonide 400μg twice daily in patients with moderate asthma (mean PEF = 76% of the predicted value for their age, gender and height).[86]

Improvement in morning PEF and withdrawal rates for loss of efficacy were similar after 24 weeks in patients treated with inhaled fluticasone propionate 250μg plus salmeterol 50μg twice daily

b Mean change from baseline.

c Adolescents aged ≥ 12 years were included.

d Double-blind.

e FEV_1.

f PEF results were those obtained after 12 weeks.

g The delivery device (i.e. DPI or MDI) used during the study was not indicated.

h Patients had a baseline FEV_1 of 40 to 85% predicted[76,78] plus ≥15% reversibility in FEV_1 despite inhaled corticosteroid treatment.[76]

i Patients were receiving inhaled corticosteroids (400 to 1000 μg/day BDP or flunisolide) and long-acting inhaled β_2-agonists prior to enrolment.

j Mean baseline FEV_1 across all treatment groups.

k PEF.

l Only patients who were symptomatic after receiving FP 88[82] or 250μg bid[79] for 2 to 4 weeks were eligible for enrolment.

m Patients had a baseline FEV_1 of 76% of the predicted value for their age, gender and height and were receiving inhaled corticosteroids ≤500μg prior to enrolment.

n Number of patients (not percentage) requiring oral corticosteroids for asthma exacerbations.

o Patients had a baseline FEV_1 of 50 to 80% of the predicted value for their age, gender and height plus ≥15% reversibility in FEV_1 and were not receiving inhaled corticosteroids prior to enrolment.

amPEF = morning peak expiratory flow rate; **BDP** = beclomethasone dipropionate; **bid** = twice daily; **DK** = Diskus®/Accuhaler® DPI; **DPI** = dry powder inhaler; **FEV_1** = forced expiratory volume in 1 second; **LOE** = loss of efficacy/asthma exacerbation during the study; **MDI** = metered dose inhaler; **PEF** = peak expiratory flow rate; **TAA** = triamcinolone acetonide; *p < 0.05 *vs* PL; **p < 0.001 *vs* PL and other agents; †p < 0.05 *vs* TAA 600μg bid or SLM 42μg bid; ††p = 0.006 *vs* BUD 400μg bid; ††† p < 0.001 *vs* TAA 600μg bid; ‡p < 0.04 *vs* FP 220μg bid; ‡‡p ≤ 0.004 *vs* FP 220μg bid; ‡‡‡p < 0.0001 *vs* FP 250 or 500μg bid.

Table X. Summary of multicentre, randomised, double-blind, parallel-group trials of inhaled fluticasone propionate (FP) ≤500 μg/day given in 1 or 2 daily doses in adults with asthma

Reference [duration (wk)]	Dosage regimen (delivery device) [no. of patients[a]]	PEF (am, pm; L/min)[b]
Boulet et al.[68] abstract (12)[c]	FP 100μg bid [457]	↑19*, ↑13
	FP 200μg od	↑10, ↑10
Boulet et al.[68] abstract (12)[d]	FP 250μg bid [443]	↑17**, ↑10*
	FP 500μg od	↑1, ↑5
Clifford et al.[69] abstract (12)	FP 250μg bid (DK) [85]	↑35††
	FP 500μg od (DK) [80]	↑23††
	PL [80]	↓15
Kerwin et al.[70] abstract (12)	FP 100μg od (DK) [79]	↑1
	FP 200μg od (DK) [81]	↑11†
	FP 500μg od (DK) [86]	↑28*†
	PL [84]	↓15

a Number of patients included in the efficacy analysis, except Boulet,[68] for which the total number of patients enrolled in each arm of the trial is presented.

b Mean change from baseline to end-point (when only 1 value is provided, it is the morning value).

c Patients were receiving inhaled corticosteroids (0-500 μg/day) prior to enrolment. Inhaler type (i.e. DPI or MDI) not indicated.

d Patients were receiving inhaled corticosteroids (400-1200 μg/day) prior to enrolment. Inhaler type (i.e. DPI or MDI) not indicated.

am = morning; **bid** = twice daily; **DK** = Diskus® DPI; **DPI =** dry powder inhaler; **MDI** = metered dose inhaler; **od** = once daily; **PEF** = peak expiratory flow rate; **PL** = placebo; **pm** = evening; ↓ indicates decrease; ↑ indicates increase; *p < 0.05, **p < 0.001 *vs* other FP dosage regimen(s), †p < 0.05, ††p < 0.001 *vs* placebo.

or inhaled beclomethasone dipropionate 500μg twice daily plus salmeterol 50μg twice daily (table IX).[77]

Reductions in nocturnal airway obstruction improved daytime cognitive performance in patients with asthma. Performance on psychometric tests in patients with mild persistent asthma (mean FEV_1 82.4%; n = 46) and considerable circadian variation in PEF (mean = 22.9%) were evaluated in a randomised double-blind, parallel-group study.[91] At baseline, 16 healthy volunteers completed the paced auditory serial addition test (PASAT) more quickly than patients with asthma ($p < 0.05$).[91] Moreover, patients with >20% circadian variation in PEF performed less well on the PASAT test than patients with <20% variation in PEF.[91] Treatment with inhaled fluticasone propionate 250μg twice daily (n = 16), salmeterol 50μg twice daily (n = 16), or the 2 drugs combined (n = 14) for 6 weeks reduced the variation in PEF to ≤10% in all 3 groups and improved performance on psychometric tests to levels comparable with healthy controls.[91]

QOL, as measured by the AQLQ, and sleep quality improved significantly in patients treated with fluticasone propionate 250μg plus salmeterol 50μg twice daily. After 12 weeks' treatment, clinically significant differences (≥0.5 points) were seen in mean total AQLQ scores and scores on each of the 4 domains of the AQLQ between patients receiving the combination and those treated with salmeterol 50μg twice daily alone (≥ 0.84; $p \leq 0.001$) or placebo (≥ 0.96; $p \leq 0.001$).[92] In patients receiving combined fluticasone propionate plus salmeterol, mean total AQLQ scores were greater than in patients treated with fluticasone propionate 250μg twice daily (0.45; $p \leq 0.05$); however, this difference was not clinically significant.[92] Sleep quality, as measured by a 3-item sleep scale, improved significantly in patients receiving the combination, but not in those receiving salmeterol alone or placebo ($p < 0.001$).[92]

3.5 Once Daily Administration

3.5.1 Comparisons with Placebo

Once daily administration of fluticasone propionate ≤500 μg/day improved or maintained lung function and improved QOL in patients with mild to moderate asthma (table X).[68,69] Morning PEF was significantly greater in patients with mild asthma and both morning and evening PEF were significantly greater in patients with moderate asthma after 12 weeks' treatment with fluticasone propionate 100μg or 250μg twice daily, respectively, compared with once daily administration of the same daily dosage.[68] Nevertheless, pulmonary function remained within 5% of baseline in the patients receiving once daily fluticasone propionate, many of whom had been receiving inhaled corticosteroids (≤500 μg/day) prior to the study.[68] In another study, morning PEF was significantly greater after 12 weeks' treatment with fluticasone propionate 250μg twice daily or 500μg once daily than

placebo, with no significant difference between the 2 fluticasone propionate dosages.[69] Asthma symptom scores decreased significantly (–0.32 and –0.33 with 500μg daily and 250μg twice daily, respectively, *vs* 0.16 with placebo) and global AQLQ scores increased significantly (0.81 and 0.46 *vs* –0.22; $p < 0.001$) in fluticasone propionate recipients compared with placebo recipients in the latter trial.[69,93]

Fluticasone propionate 100, 200 or 500μg once daily maintained or improved morning PEF compared with placebo in patients with moderate to severe persistent asthma (FEV_1 45 to 75%) previously treated with inhaled corticosteroid or β_2-agonist therapy (table X). After 12 weeks, morning PEF increased significantly in recipients of fluticasone propionate 200 or 500μg once daily compared with placebo.[70] Moreover, the frequency of as-needed salbutamol use and nocturnal awakenings, and asthma symptom scores decreased significantly in patients treated with fluticasone propionate 200 or 500μg once daily than placebo ($p < 0.05$).[70] The frequency of as-needed salbutamol usage was significantly lower in patients treated with fluticasone propionate 100μg once daily than placebo; however, there were no statistically significant differences between these 2 groups for any other efficacy parameters.

The results of these studies demonstrate that once daily administration of fluticasone propionate maintains or improves lung function in patients with mild to moderate asthma.

3.5.2 Comparisons with Other Inhaled Corticosteroids

In 299 inhaled corticosteroid-naive patients with asthma, fluticasone propionate 200μg once daily or 100μg twice daily or beclomethasone dipropionate 168μg twice daily (i.e. twice the daily dosage of fluticasone propionate) generally improved control of asthma.[72] PEF ($p < 0.005$) and FEV_1 ($p < 0.05$) increased and usage of as-needed β_2-agonists decreased ($p < 0.05$) significantly in patients receiving active treatment compared with placebo.[72] Significantly fewer fluticasone propionate than placebo recipients were withdrawn for loss of efficacy (7 and 5 patients from once and twice daily groups *vs* 19 from placebo; $p < 0.01$).[72] In contrast, the number of beclomethasone dipropionate recipients (not presented) withdrawn for loss of efficacy did not differ from placebo.

In another study, in which patients were receiving inhaled beclomethasone dipropionate ≥400 μg/day or triamcinolone acetonide ≥800 μg/day prior to enrolment (n = 271) greater spirometric improvements were obtained with twice daily than once daily administration of fluticasone propionate.[71] Improvements in FEV_1 were significantly greater in patients receiving either fluticasone propionate 100μg or beclomethasone 168μg twice daily than placebo ($p \leq 0.002$).[71] Lung function did not deteriorate in patients receiving fluticasone propionate 200μg once daily (mean FEV_1 increased by 0.11L), but there was no significant difference in the FEV_1 in patients in this group and the placebo group at end-point ($p = 0.055$). Nonetheless, asthma symptom scores ($p < 0.04$), rescue salbutamol usage ($p \leq 0.003$) and withdrawal rates for loss of efficacy ($p < 0.05$) were significantly lower in patients receiving all active treatments compared with placebo.[71]

In a further comparative trial, once daily administration of fluticasone propionate 200μg or budesonide 400μg for 12 weeks provided similar improvements in morning PEF in patients with mild to moderate asthma (n = 219).[88]

These trials provide further evidence that once daily administration of fluticasone propionate is effective in maintaining or improving lung function in patients with mild to moderate asthma.

3.6 Device Preference

Fluticasone propionate is currently available in a pressurised metered dose inhaler (MDI) and 2 different breath activated dry powder inhalers (DPI), the Diskhaler® and the Diskus®/Accuhaler®. There were no differences in any outcome measures (morning and evening PEF, the frequency of symptom-free days or nights and requirements for as-needed salbutamol) when equivalent dosages of fluticasone propionate were administered with

the MDI or Diskhaler® DPI (100μg twice daily) in 296 adult patients (use of a spacer device was permitted with the MDI),[94] or when the Diskhaler® DPI and the Diskus®/Accuhaler® DPI (250μg twice daily) were compared in 364 patients with mild to moderate asthma.[95]

The 2 DPI devices have a high rate of patient acceptance,[95-97] although most patients enrolled in randomised, double-blind, double dummy trials preferred the Diskus®/Accuhaler® to the Diskhaler® (61.4 *vs* 25.4%[96]; 65 *vs* 25%[95]) and more patients preferred the MDI to the Diskhaler® in a further study (40 *vs* 33%).[56]

The Diskus®/Accuhaler® received higher preference ratings than the Turbuhaler® from patients with asthma.[98,99] When interviewed in their own homes, significantly more patients (n = 159) preferred the Diskus®/Accuhaler® (65%; $p < 0.001$ *vs* the Turbuhaler®) and perceived it to be easier to use than the Turbuhaler® ($p = 0.002$).[98] In a nonblind, parallel-group study, more patients (n = 277) assigned to the Diskus®/Accuhaler® used the device correctly the first time (81 *vs* 61%) and found it very easy to use (65 *vs* 47%) compared with the Turbuhaler®.[99] In another nonblind, study in which fluticasone propionate was compared with budesonide (see table VI[62]), more patients preferred the Turbuhaler® than the Diskhaler® (59 *vs* 41%; $p = 0.015$) during a 4 week crossover phase.[62]

3.7 Pharmacoeconomic Studies

The cost effectiveness of fluticasone propionate has been compared with that of budesonide[100-102] and flunisolide[103,104] in adult patients with mild to moderate asthma.

Inhaled fluticasone propionate was more cost effective than budesonide when given at doses that were less than half of or equal to the dose of budesonide (table XI).[100,101] When the costs of medications, physician visits and hospitalisations incurred during a clinical trial (see table VI[61])

Table XI. Cost-effectiveness comparisons of inhaled fluticasone propionate (FP) ≤500 μg/day and other inhaled corticosteroids in adults with asthma

Reference (country and year)	Dosage	Successful treatment (% of patients)[a]	Symptom-free days (%)	Cost of successful treatment (per patient)	Cost per symptom-free day
Comparisons with budesonide (BUD)					
Booth et al.[100] (UK 1995)[b]	FP 200μg bid (DH)	57		£11.18/week	
	BUD 400μg bid (TB)	46		£11.98/week	
Steinmetz et al.[101] (Germany 1997)[c]	FP 250μg bid (MDI)	47	40	DM9.00/day	DM10.58
	BUD 600μg bid (MDI)	42	34	DM12.36/day	DM15.26
Venables et al.[102] (UK 1996)[b]	FP 200μg bid (DH)	48	48	£2.08/day	£2.08
	BUD 200μg bid (TB)	39	39	£1.44/day	£1.44
	BUD 400μg nocte (TB)	45	43	£1.20/day	£1.26
Comparisons with flunisolide (FLD)					
Volmer et al.[103] abstract (Germany)[d]	FP 250μg bid (DH)	55.3	14.4	DM338.8	DM13.13
	FLD 500μg bid (MDI)	44.5	11.2	DM369.1	DM14.78
Volmer et al.[104] abstract (Germany)[d]	FP 250μg bid (DH)	56.8	15.3	DM314.46/patient	DM11.79
	FLD 500μg bid (MDI)	39.6	12	DM375.32/patient	DM12.50

a Defined as an increase of 5%[100,102] or 10%[101,103,104] in predicted peak expiratory flow rate.

b Costs accounted for included study medication, other asthma medications and medication required to manage adverse events.

c Costs accounted for included study medication, other asthma medications, medications required to manage adverse events, physician office visits and hospitalisations.

d The nature of the costs and the year in which they were incurred was not provided.

bid = twice daily; **DH** = Diskhaler® dry powder inhaler; **DM** = Deutschmark; **MDI** = metered dose inhaler; **nocte** = in the evening; **TB** = Turbuhaler® dry powder inhaler; **£** = pounds sterling.

were collated, fluticasone propionate 250μg twice daily was more cost effective than budesonide 600μg twice daily from a German third-party payer perspective.[101] Fluticasone propionate was cost effective when total treatment costs were changed by ±20%, PEF values were varied by ±10% or the cost per puff of budesonide was reduced by 30% in univariate sensitivity analyses. In a similar economic analysis of a UK study (see table VI[28]),[100] the cost of successful treatment with fluticasone propionate 200μg twice daily was lower than budesonide 400μg twice daily and remained lower when the minimum improvement in PEF varied from 1 to 10% in a sensitivity analysis (table XI).[100] Only medication costs were accounted for in this analysis.

In a further comparison, in which only medication costs were accounted for, budesonide 200μg twice daily or 400μg nocte was more cost effective than fluticasone propionate 200μg twice daily.[102] However, the same dosage of fluticasone propionate and budesonide were used in this study (see table VI[62]), which does not reflect the recommendations for 2-fold dosage differences in contemporary asthma treatment guidelines.[7,8]

Two analyses have shown fluticasone propionate 250μg twice daily to be more cost effective than flunisolide 500μg twice daily (table XI).[103,104] These studies are available only as abstracts, in which the nature of the costs included and excluded were not disclosed and no sensitivity analyses were presented.

These cost-effectiveness studies suggest that inhaled fluticasone propionate is more cost effective than budesonide and possibly flunisolide when the dosage of fluticasone propionate is less than half the dose of budesonide or flunisolide. However, only a portion of the direct costs associated with asthma care were considered in these trials and the often substantial indirect costs associated with asthma (absence from school or work, loss of wages, lost productivity) were not considered.

4. Tolerability

The incidence of adverse events in clinical trials was generally not significantly different in patients treated with fluticasone propionate ≤250μg twice daily compared with placebo.[19-22,49,50] The overall incidence of adverse events ranged from 4 to 11% in placebo recipients and 10 to 19% in fluticasone propionate recipients in comparative studies.[14,21,22,49,50] In only 1 trial did more fluticasone propionate than placebo recipients experience more adverse events ($p = 0.05$ for fluticasone propionate 50 or 100μg twice daily *vs* placebo).[49] Withdrawal from a study because of an adverse event was rare, occurring in ≤4 and ≤2% of fluticasone propionate and placebo recipients, respectively.[14,20-22,49,50] Oral candidiasis, dysphonia (hoarseness) or pharyngitis were reported by ≤6% and ≤3% of fluticasone propionate and placebo recipients, respectively.[19-22,49,50]

In trials comparing fluticasone propionate 50 to 250μg twice daily with either beclomethasone dipropionate 168 to 500μg twice daily or budesonide 100 to 600μg twice daily, the frequency of adverse events was similar. Oral candidiasis was reported in ≤6.5% of fluticasone propionate recipients and in ≤5.4% of patients receiving either inhaled beclomethasone dipropionate or budesonide in these trials.[25,27-29,37,56,61,62]

A higher frequency of adverse events was reported in trials comparing fluticasone propionate 250μg/day and triamcinolone acetonide 200μg 4 times daily. The frequency of treatment-related adverse events was significantly ($p < 0.001$) greater in patients treated with fluticasone propionate 250μg twice daily (20%) than either triamcinolone acetonide 200μg 4 times daily (5%) or placebo (5%) in 1 trial.[67] In another study, which employed the same design, the frequency of adverse events in fluticasone propionate, triamcinolone acetonide and placebo recipients was 15, 8 and 13%, respectively.[66] There were no differences in the incidence of individual adverse events with the exception of oral candidiasis, which was reported by 8% of fluticasone propionate recipients, 3% of triamcinolone acetonide recipients and 1% of placebo-

treated patients (p = 0.035 for fluticasone propionate *vs* triamcinolone acetonide or placebo).[66]

In trials comparing fluticasone propionate ≤250μg twice daily with other inhaled corticosteroids or nedocromil, <10% of patients were withdrawn from any treatment group because of adverse events.[25,27,28,37,53,59,61,62,66,67] No unexpected adverse events have been associated with fluticasone propionate in patients with mild to moderate asthma.

5. Dosage and Administration

Ideally the initial dosage of inhaled corticosteroid should be sufficient to promptly establish disease control and abolish symptoms in patients with persistent asthma.[7,8] Once control is established, particular attention should be paid to establishing the lowest effective maintenance dosage for any given patient as, although systemic adverse effects are unusual with the dosages used for mild to moderate asthma, the lowest effective dosage is desired in any patient treated with inhaled corticosteroids.[7,8] A step-wise dosage reduction should be considered once control of asthma is achieved. The British guidelines recommend reducing the daily dosage of inhaled corticosteroid by 25 to 50% at 1- to 3-month intervals while carefully monitoring the patient.[7]

In the UK, the manufacturer recommends using inhaled fluticasone propionate for the prophylactic management of mild asthma when patients require intermittent symptomatic bronchodilator medication on a regular basis. In patients aged ≥16 years, the initial dosage of fluticasone propionate for mild asthma is 100 to 250μg twice daily. For moderate asthma, defined as unstable or worsening symptoms despite prophylactic therapy or bronchodilator medication, the recommended initial dosage is 250 to 500μg twice daily. The recommended dosage range for patients ≥16 years of age is 100 to 1000μg twice daily. In patients <16 years of age the recommended dosage is 50 to 100μg twice daily. Fluticasone propionate is available as a dry powder (in the Accuhaler® and Diskhaler® inhalation devices) and as a metered dose inhaler in the UK.[105]

In the US, in patients aged ≥12 years who are either corticosteroid-naive or have previously used other inhaled corticosteroids for asthma, the recommended dosage range is 88 to 440μg twice daily when administered by metered dose inhaler[1] and 100 to 500μg twice daily when administered as a dry powder in the Rotadisk® inhalation device.[45]

The maximum recommended dosage in the UK and US is, respectively, 1000 and 880μg twice daily.[45,105] Dosage adjustments are not required in elderly patients.[45]

Patients should be instructed to rinse their mouth after inhalation to reduce the incidence of hoarseness and/or oral candidiasis.[45,105]

6. Place of Inhaled Fluticasone Propionate in the Management of Mild to Moderate Asthma

Inflammation of the airways is the fundamental characteristic of asthma. In patients with mild asthma not previously treated with inhaled corticosteroids, including newly diagnosed patients, there is evidence of airway mucosal inflammation, with epithelial changes and increased numbers of eosinophils, lymphocytes, macrophages and mast cells present in lung tissue.[106,107] Moreover, in patients with mild asthma, there is a correlation between the quantity of inflammatory cells in BAL fluid, the magnitude of bronchial hyperresponsiveness and the degree of impairment of FEV_1.[108] Anti-inflammatory therapy is essential to control the disease process in patients, including those with mild asthma.

Anti-inflammatory therapy produces significant improvement in patients with mild asthma. The thickness of the basement membrane was significantly reduced in patients with mild asthma after treatment with inhaled corticosteroids.[12,109] Inhaled corticosteroids reduced bronchial hyperresponsiveness, improved lung function and amel-

1 Different dosage recommendations reflect differences in labelling requirements in the UK, where the total dose delivered per actuation (e.g. 50, 100, 250μg) is used, and in the US, where the portion of the dose delivered through the mouthpiece (e.g. 88, 220μg) is used.

iorated symptoms to a significant extent compared with β_2-agonist bronchodilator therapy alone in patients with mild asthma.[110-112] Furthermore, when inhaled corticosteroids were introduced shortly (i.e. ≤6 months) after diagnosis of mild or moderate asthma, the improvement in lung function was significantly greater compared with later (i.e. ≥2 years) intervention, independent of patient age.[113] More impressively, these improvements were maintained over a period of at least 2 years.[110,113,114]

There is evidence that early intervention with inhaled corticosteroids may prevent admissions to hospital because of asthma exacerbations. A case-control study revealed that initiation of inhaled corticosteroids within 12 months of the diagnosis of asthma reduced the risk of hospitalisation for asthma, relative to patients receiving theophylline, by up to 80% during the following year.[115]

These findings support the recommendation that inhaled corticosteroids be introduced early in the management of asthma.[6-8] For example, the GINA guidelines recommend the introduction of inhaled corticosteroids when asthma symptoms occur more than once weekly or when night-time symptoms occur more than twice monthly.[8]

In spite of the evidence that patients with mild asthma benefit from inhaled corticosteroids, and the availability of treatment guidelines that advocate the use of these drugs, there are indications that inhaled corticosteroids are underused. Among asthma patients enrolled in a California health maintenance organisation, fewer than 40% of those with mild to moderate asthma had obtained an inhaled corticosteroid in the previous 6 months.[116] Moreover, of those who had a corticosteroid inhaler at home, ≤42.5% of patients had used it daily during the preceding month.[1] In Britain, more than one-third of adolescents aged 12 to 14 years whose sleep was disturbed by asthma on more than 1 occasion per week were not receiving inhaled corticosteroids.[117] Similarly, a survey in France revealed that, of those in whom anti-inflammatory therapy was mandated by guidelines, 62 and 84% of patients in Montpellier and Paris, respectively, were not receiving inhaled corticosteroids.[118] Other studies provide further evidence of the underuse of inhaled corticosteroids[119-121] or link underuse of inhaled corticosteroids with adverse outcomes.[122-124]

In patients with mild to moderate asthma, fluticasone propionate ≤250μg twice daily provides consistent control of asthma. In placebo-controlled trials, the drug produced significant improvements in objective and subjective measures of lung function, reduced the frequency of exacerbations and improved QOL. In comparative trials, fluticasone propionate was superior to nedocromil, theophylline or zafirlukast. The drug was at least as effective as inhaled beclomethasone dipropionate, budesonide or flunisolide when given at half the dosage of the comparator. Moreover, fluticasone propionate 250μg twice daily was generally more effective than triamcinolone acetonide 200μg 4 times daily. The drug is also effective when given once daily, which may be preferred by some patients.

Corticosteroid sparing therapies, such as inhaled long acting β_2-agonists (e.g. salmeterol, formoterol) may be used to minimise the maintenance dosage of inhaled corticosteroids. In comparative studies in patients with mild to moderate asthma, the addition of an inhaled long acting β_2-agonist bronchodilator, salmeterol, to fluticasone propionate 88 to 250μg twice daily was as effective as doubling the dosage of fluticasone propionate. Furthermore, the frequency of asthma exacerbations was significantly lower in patients receiving combined salmeterol 50μg plus fluticasone propionate 100μg twice daily than in patients treated with either drug alone.[78]

Inhaled fluticasone propionate ≤500 μg/day was well tolerated in patients with mild to moderate asthma. Oropharyngeal adverse effects occurred with low frequency and there was no evidence of clinically significant impairment of HPA axis function.

In conclusion, fluticasone propionate ≤500 μg/day is an effective anti-inflammatory therapy for mild to moderate asthma in adolescents and adults. The drug is more effective than nedocromil,

theophylline or zafirlukast in these patients and is at least as effective as other inhaled corticosteroids when given at half the microgram dosage of the other agent. The addition of inhaled salmeterol allows for the use of low maintenance dosages of fluticasone propionate. The drug is well tolerated and there is no evidence of a clinically significant effect of these dosages on HPA axis function. Hence, fluticasone propionate ≤500 μg/day is a particularly suitable agent for use in patients with mild to moderate asthma.

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