ADIS DRUG EVALUATION

Drugs 2004; 64 (17): 1975-1996
0012-6667/04/0017-1975/$34.00/0

Inhaled Salmeterol/ Fluticasone Propionate

A Review of its Use in Chronic Obstructive Pulmonary Disease

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Data Selection

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 Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'salmeterol/fluticasone' and 'chronic obstructive pulmonary disease' or 'COPD'. EMBASE search terms were 'salmeterol fluticasone' and 'chronic obstructive lung disease' or 'COPD'. AdisBase search terms were 'salmeterol fluticasone' and 'chronic obstructive pulmonary disease' or 'COPD'. Searches were last updated 9 August 2004.

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

Index terms: Chronic obstructive pulmonary disease, salmeterol, fluticasone propionate, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

The salmeterol/fluticasone propionate dry powder inhaler (DPI) [Advair Diskus®, Seretide™ Accuhaler®] contains the long-acting β_2-adrenoceptor agonist salmeterol and the inhaled corticosteroid fluticasone propionate. In the US, twice-daily salmeterol/fluticasone propionate 50/250μg is approved for use in adults with chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis, and in the EU, the twice-daily 50/500μg dosage is approved for use in patients with severe COPD, repeat exacerbations and significant symptoms despite bronchodilator therapy.

In patients with moderate-to-severe COPD, twice-daily inhaled salmeterol/fluticasone propionate 50/250 or 50/500μg for 24–52 weeks improves predose forced expiratory volume in 1 second (FEV_1) significantly more than salmeterol monotherapy, improves postdose or postbronchodilator FEV_1 significantly more than fluticasone propionate monotherapy and results in clinically significant improvements in health-related quality of life. Salmeterol/fluticasone propionate 50/500μg significantly reduced annual COPD exacerbations, especially in severe COPD. Some corticosteroid-related adverse events were increased in recipients of fluticasone propionate with or without salmeterol versus salmeterol monotherapy or placebo; withdrawal from fluticasone propionate, including combination therapy, needs careful management to minimise COPD exacerbations. The DPI combining a corticosteroid and long-acting β_2-agonist provides benefits over monotherapy and may encourage patient compliance in COPD.

Pharmacological Properties

Salmeterol, a long-acting β_2-adrenoceptor agonist, and fluticasone propionate, an inhaled corticosteroid with anti-inflammatory properties, demonstrated individual and synergistic pharmacodynamic benefits in COPD. Salmeterol increases cyclic adenosine monophosphate (cAMP) concentrations when it catalyses the conversion of adenosine triphosphate to cAMP in bronchial smooth muscle, causing it to relax.

Salmeterol and fluticasone, alone or together, significantly improved ciliary function *in vitro* and in healthy volunteers, reduced fibroblast proliferation *in vitro*, reduced thrombin-stimulated fibroblast mitosis, and displayed anti-inflammatory activity *in vitro* (salmeterol) and in patients with COPD (fluticasone propionate). At some concentrations, salmeterol and fluticasone propionate were synergistic. FEV_1 improved significantly from baseline in patients with moderate-to-severe COPD after a single dose of salmeterol/fluticasone propionate 50/250μg or formoterol/budesonide 12/400μg, both via DPI.

The systemic response to salbutamol (albuterol) with twice-daily salmeterol 100μg was similar with salmeterol monotherapy or salmeterol/fluticasone propionate in healthy volunteers treated for 11 days via the Diskus® DPI, and significantly different than with placebo. In this study, mean 24-hour urinary cortisol excretion decreased with twice-daily fluticasone propionate 500μg with or without salmeterol 100μg. In patients with severe COPD, fluticasone propionate 1000μg twice daily via a metered dose inhaler (supratherapeutic dosage) for 2 weeks decreased serum osteocalcin and overnight urinary cortisol excretion.

Inhaled salmeterol and fluticasone propionate both act locally and, thus, plasma concentrations are low. No systemic pharmacokinetic interactions between salmeterol and fluticasone propionate after administration of the combination via DPI were apparent in a study in healthy volunteers. At steady state, twice-daily fluticasone propionate 500μg reached a mean maximum plasma concentration (C_{max}) of ≈112 pg/mL, time to C_{max} (t_{max}) of ≈1 hour, plasma exposure of ≈720 pg • h/mL, and median elimination half-life ($t_{½}\beta$) of ≈8 hours. Values for twice-daily salmeterol 100μg were a C_{max} of ≈0.202 ng/mL (vs 0.155 ng/mL after a single dose) and a t_{max} of 5 minutes; plasma exposure and $t_{½}\beta$ could not be determined. Bioavailability of fluticasone propionate via the Diskus® averaged ≈13% in patients with COPD versus 21% in healthy volunteers. Plasma binding is 91%.

Fluticasone propionate metabolism occurs mostly in the liver, via the cytochrome P450 (CYP) 3A4 enzyme. Accumulation may occur in patients with hepatic impairment and significant increases in fluticasone propionate concentrations have been demonstrated after coadministration of other CYP 3A4 inhibitors.

Therapeutic Efficacy

Twice-daily salmeterol/fluticasone propionate 50/500μg and 50/250μg significantly improved pre- and postdose/post-bronchodilator FEV_1 versus placebo in three large, randomised, 24- to 52-week trials in patients with moderate-to-severe COPD. After 24 weeks, predose FEV_1 improved significantly more with combined therapy than with salmeterol 50μg and 2-hour postdose or post-bronchodilator FEV_1 significantly more than with fluticasone propionate 250 or 500μg (all twice daily via Diskus®); over 52 weeks, combined therapy was significantly better than both monotherapies. Improvements in FEV_1 in combined-therapy recipients occurred within 2 weeks and significant increases in peak expiratory flow (PEF) within 1 day.

Clinically significant improvements versus placebo in health status and, in some trials dyspnoea, were seen with twice-daily salmeterol/fluticasone propionate; the improvements in dyspnoea also occurred within 1 week. Use of supplementary salbutamol also decreased significantly. Over 1 year, significantly fewer exacerbations (mean ≈1 vs 1.3 per patient-year) occurred with any active treatment versus placebo, particularly exacerbations requiring oral corticosteroids in patients with an FEV_1 <50% predicted. In combined therapy recipients with FEV_1 <50% predicted, annual exacerbations decreased by 30% versus placebo and those requiring oral corticosteroids by 42%.

Recipients of twice-daily inhaled salmeterol/fluticasone propionate 50/250μg for 8 weeks achieved significantly greater improvements in predose FEV_1, PEF and most symptomatic endpoints than recipients of four-times-daily salbutamol/ipratropium bromide 206/36μg. Over 4 months, salmeterol/fluticasone propionate

50/500μg and fluticasone propionate plus oral titrated theophylline both improved FEV_1, but dyspnoea and rescue salbutamol use improved significantly more with salmeterol/fluticasone propionate.

Although absolute differences were small, FEV_1, FEV_1/forced vital capacity and dyspnoea deteriorated significantly more in patients who changed treatment from inhaled salmeterol/fluticasone propionate to salmeterol, than in patients who did not. Similarly, fluticasone propionate withdrawal resulted in an increase in first and second exacerbations in COPD patients after a 4-month run-in with four-times-daily ipratropium bromide plus twice-daily fluticasone propionate, particularly in those with FEV_1 <50% predicted.

Tolerability

Drug-related adverse events in recipients of salmeterol/fluticasone propionate in placebo-controlled trials reflected those that occur with the respective monotherapies. The incidence was 16% and 20% with salmeterol/fluticasone 50/500 or 50/250μg, 19% and 15% with fluticasone propionate 500 or 250μg, 12% and 11% with salmeterol 50μg and 14% and 9% with placebo (all twice daily via Diskus®). Oropharyngeal candidiasis, throat infection or hoarseness, COPD exacerbation, oral inflammation, nausea or vomiting, headaches, tremor and vertigo affected ≤6% of salmeterol/fluticasone propionate recipients.

After 24 weeks in a 1-year trial, recipients of twice-daily fluticasone propionate 500μg with or without salmeterol 50μg, had significantly lower mean serum cortisol levels than placebo recipients. At 52 weeks, only the fluticasone propionate monotherapy group was significantly different to the placebo group. In a nested case-control study, the odds ratio for fracture incidence in patients receiving inhaled corticosteroids within the last 30 days was 1.42 (vs non-recipients). However, the incidence of fractures in a pooled analysis was 15 per 1000 patient-years with twice-daily fluticasone propionate 500μg (with or without salmeterol) for up to 3 years, versus 23 with placebo.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a multi-component disease that includes airway inflammation, airway structural changes and mucociliary dysfunction, which all contribute to a complex of lung function changes, symptoms and exacerbations.[1,2] Recently, COPD has also been associated with systemic effects, such as systemic inflammation, weight loss, decreased bone density and muscle weakness.[3] The disease is characterised by airway obstruction that is not fully reversible; this, plus a history of symptoms and/or exposure to risk factors, defines COPD.[2]

Spirometry in patients with COPD reveals a forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) of <70%.[2] Chronic cough and sputum production tend to precede other symptoms, such as progressive dyspnoea.[2] The revised Global Initiative for Chronic Lung Disease (GOLD) staging of COPD reflects the severity of symptoms and spirometry: from 0 (at risk) where symptoms are present but spirometry is normal, to IV (very severe) where symptoms are present and FEV_1 is either <30% predicted or <50% predicted in patients with chronic respiratory failure.[2] Body mass index (BMI) and dyspnoea are also helpful in predicting survival.[1]

COPD is mostly caused by cigarette smoking (≈85% of COPD in Western countries), occupational exposure to hazardous airborne substances[4] or air pollution, probably superimposed on an underlying genetic disposition.[2] Epidemiological data are approximate, as COPD definitions vary and most data are sourced from medical databases or death

certificates of patients with multiple diagnoses or causes of death.[2,5] Death in COPD is usually catalysed by another event, such as pneumonia.[4,5]

In the US in 2001, 12.1 million adults had a diagnosis of COPD and about twice this number had evidence of impaired lung function.[6] COPD was the fourth ranked cause of death, with more female than male deaths in 2000, but a higher age-adjusted death rate in males.[6] The estimated cost of COPD in the US in 2002 was $US32 billion; exacerbations account for much of this cost.[1,6] Mortality in Europe varies from <10 to >70 per 100 000 population aged 35–74 years, including <5 to ≈40 per 100 000 women.[5] In 2000, COPD affected ≈60 million people worldwide and resulted in ≈30 million (2% of the estimated total) disability-adjusted life-years, one-sixth in men aged 45–59 years.[7]

Pharmacological treatment can improve symptoms and reduce complications in COPD.[2] Indeed, recent guidelines emphasise the treatable nature of COPD.[1] Inhaled therapy is considered most effective, including bronchodilators such as long-acting β_2-adrenoceptor agonists. In patients with severe COPD and frequent exacerbations, inhaled corticosteroids may be appropriate.[2] Salmeterol/fluticasone propionate 50/500 or 50/250μg, delivered via a dry powder inhaler (DPI) [Advair Diskus® or Seretide™ Accuhaler®][1] combines these two drug classes in one inhaler.[8,9] The use of inhaled salmeterol/fluticasone propionate in COPD has been briefly reviewed previously.[10]

2. Pharmacodynamic Properties

This section overviews the pharmacodynamic effects of salmeterol and fluticasone propionate in COPD, with emphasis on the effects of these drugs when used in combination.

Salmeterol is a long-acting β_2-adrenoceptor agonist that catalyses the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP).[8] Increased concentrations of cAMP result in relaxation of bronchial smooth muscle.[10] Salmeterol also possesses some anti-inflammatory activity (section 2.2). Fluticasone propionate is an inhaled corticosteroid with anti-inflammatory properties.[9] Moreover, salmeterol and fluticasone propionate have demonstrated additive and synergistic effects when used in combination (sections 2.1.1 and 2.2). The mechanism of this synergistic effect may be β_2-adrenoceptor mediated,[11] as the protective effect of corticosteroids (e.g. dexamethasone) on the β_2-adrenoceptor down-regulation caused by β_2-adrenoceptor agonists (e.g. isoprenaline [isoproterenol]) has been well documented in a series of *in vitro* and *in vivo* studies.[12-14] Furthermore, some of the anti-inflammatory activity of salmeterol may result from its ligand-independent activation of the glucocorticoid receptor.[15]

A number of studies were reported as abstracts.[16-21]

2.1 Pulmonary Effects

2.1.1 Effects on Airways

Chronic airway inflammation is associated with epithelial goblet cell metaplasia, increased mucus-secreting glands, damage to cilia and airway wall remodelling.[2] Loss of cartilage occurs, and inflammatory infiltrate, increased smooth muscle and fibrosis thicken small airway walls and narrow airways (especially smaller airways), increasing airway resistance.[22] Decreased ciliary function reduces normal ciliary clearance and may increase the likelihood or severity of bacterial lung infections.[23,24]

In experimental studies, pretreatment of rats with intranasal fluticasone propionate reduced ozone-induced goblet cell metaplasia, as evidenced by a more than 80% reduction in nasal epithelium mucous cell density and intraepithelial stored mucosubstances ($p < 0.05$ vs controls)[25] Moreover, salmeterol[16,20,21,23,24,26] and fluticasone[23] improved ciliary function *in vitro* and in randomised, double-blind studies in healthy volunteers; lipophilic properties or a direct effect on ciliary beat activity were suggested mechanisms. For example, ciliary beat frequency was significantly increased in nasal ciliated

1 The use of trade names is for product identification purposes only and does not imply endorsement.

epithelium from patients with COPD after exposure to salmeterol 10^{-7} mol/L ($p < 0.001$ vs baseline).[16] This increase in ciliary beat frequency may increase mucociliary clearance. Indeed, two randomised, double-blind studies in healthy volunteers have shown that nasally administered salmeterol 50mg via a metered dose inhaler (MDI) increased mucociliary transport by 21% compared with a placebo aerosol spray ($p = 0.0001$)[21] and by 37.6% and 60.5% compared with untreated controls ($p = 0.001$) or MDI placebo ($p = 0.02$).[20]

Salmeterol 1–4 × 10^{-7} mol/L also attenuated the loss of ciliated cells and mucosal damage in human adenoid tissue infected with *Haemophilus influenzae*[26] and, in nasal cells from healthy volunteers, prevented ciliary dyskinesia[24] and reduced the pyocyanin-induced slowing of ciliary beating and falls in cAMP and ATP levels, probably via a β_2-adrenoceptor-mediated effect.[24]

When used in combination, salmeterol plus fluticasone propionate (both at 10^{-7} mol/L) demonstrated a synergistic effect in significantly reducing the loss of ciliated cells caused by *Pseudomonas aeruginosa* infection in human nasal turbinate tissue ($p = 0.05$ vs individual drugs and untreated controls); neither individual drug was effective at this concentration.[23] At higher concentrations, salmeterol (4 × 10^{-7} mol/L) and fluticasone propionate (10^{-6} mol/L) were effective at reducing mucosal damage ($p = 0.05$ vs controls), although synergy was not observed when used in combination.[23]

In vitro, salmeterol/fluticasone propionate, salmeterol and fluticasone propionate (all at 100 nmol/L) significantly inhibited transforming growth factor-β_1-induced proliferation of primary human airway fibroblasts (by 62.5%, 37.5% and 52.6%; all $p < 0.05$ vs controls).[18] Similarly, in cultured airway fibroblasts from healthy volunteers and patients with asthma, salmeterol 30 nmol/L plus fluticasone propionate 0.1 nmol/L inhibited thrombin-stimulated mitosis by 76%, versus ≈50% with either monotherapy alone.[17]

2.1.2 Effects on Lung Function

Improvements in FEV_1 with salmeterol/fluticasone propionate or salmeterol versus formoterol/budesonide or formoterol were assessed in two single-dose, single-blind, randomised, crossover, patient studies.[27,28]

In 16 patients with moderate-to-severe, stable COPD, FEV_1 improved significantly from baseline ($p < 0.001$) with both salmeterol/fluticasone propionate 50/250μg and formoterol/budesonide 12/400μg (both via combination DPIs).[27] The mean maximum increase in FEV_1 occurred at 2 hours with formoterol/budesonide (0.29L, 95% CI 0.21, 0.37) and at 5 hours with salmeterol/fluticasone propionate (0.32L; 95% CI 0.23, 0.41). Between-group differences were significant ($p < 0.05$) in favour of formoterol/budesonide at 2 hours and salmeterol/fluticasone propionate at 6 hours. FEV_1 increases over 12 hours and 12-hour area under the curve (AUC_{12}) values of changes in FEV_1 were otherwise similar.[27]

Mean peak bronchodilation with clinically recommended dosages of salmeterol 50μg (at 2 hours) and formoterol 12 and 24μg (at 1 hour), both via an MDI and holding chamber with mouthpiece, was also similar in a dose-response study in 12 men with severe COPD with reversibility of 20–43%.[28] However, the longer duration of action of salmeterol 50μg resulted in a significantly greater FEV_1 AUC_{12} (2.9 L • h; $p < 0.05$) compared with that of formoterol 12 and 24μg (2.3 and 2.2 L • h) or placebo ($p < 0.01$ vs all active treatments) [figures estimated from a graph].[28]

In a randomised, double-blind, single-dose, pilot study, the addition of fluticasone 500μg to salmeterol 50μg in 20 patients with COPD did not significantly affect the onset of action of salmeterol.[29] After 150 minutes, FEV_1 increased by 0.232L (95% CI 0.176, 0.288) after salmeterol/fluticasone propionate 50/500μg versus 0.200L (95% CI 0.137, 0.263) after salmeterol 50μg, with a corresponding FEV_1 AUC_3 of 39.10 (95% CI 29.61, 48.59) versus 30.98 (95% CI 22.90, 39.06).[29]

2.2 Anti-inflammatory Effects

In COPD, neutrophils, macrophages and CD8+ lymphocytes are the predominant inflammatory cells, with eosinophils more evident during exacer-

bations.[2] The main inflammatory mediators are leukotriene B4, interleukin-8 (IL-8) and tumour necrosis factor (TNF)-α, although prostaglandin (PG) $F_{2\alpha}$ and other arachidonic metabolites, known to be bronchoconstrictors, may also be implicated.[30] The anti-inflammatory effects of inhaled fluticasone propionate were assessed in placebo-controlled studies in patients with COPD,[30-34] but those of salmeterol[35-38] and salmeterol plus fluticasone propionate[11,19] were assessed mostly *in vitro*, with results varying between different models.

Three months' treatment with inhaled fluticasone propionate 500μg twice daily in patients with COPD had no effect on macrophages, eosinophils, plasma cells or fibroblasts, but the CD8 : CD4 lymphocyte ratio decreased from baseline ($p = 0.03$).[32,33] Neutrophil levels were unchanged from baseline, but increased compared with levels in placebo recipients.[33] However, higher dosages of inhaled fluticasone propionate (500μg three times daily[34] or 750μg twice daily[31]) for 8 weeks decreased neutrophil numbers from baseline ($p < 0.05$) [the decrease was not sustained after a 6-week washout period][34] and significantly decreased neutrophil elastase and chemotactic activity versus baseline and placebo (both $p < 0.05$).[31] Similarly, a longer 6-month course of treatment with inhaled fluticasone propionate 500μg twice daily significantly reduced ($p < 0.05$ vs baseline) arachidonic acid metabolites ($6kPGF_{1\alpha}$, $PGF_{2\alpha}$ and PGE_2) probably produced by alveolar macrophages in patients with COPD and bronchial hyper-responsiveness.[30]

The *in vitro* anti-inflammatory effects of salmeterol that are apparently mediated through β-adrenoceptors, such as the inhibition of TNFα in human monocytes,[36] were generally longer-lasting than effects mediated through other mechanisms, such as the dose-dependent inhibition of the O_2^--producing respiratory burst of neutrophils.[35,38] In guinea-pig lung, nebulised salmeterol at bronchodilator doses significantly reduced granulocytes and eosinophils (both $p < 0.05$ vs baseline), while formoterol reduced some mediators only at above-bronchodilator concentrations.[37] The difference may be due to the longer duration of action of salmeterol, or to different mechanisms of action.[37] Some of the anti-inflammatory activity of salmeterol (like salbutamol), as a β_2-adrenoceptor agonist, may result from ligand-independent activation of the glucocorticoid receptor.[15]

Salmeterol 10^{-15} to 10^{-5} mol/L caused a dose-independent inhibition of IL-8 and TNFα (from alveolar macrophages of COPD patients) that was greater than that with fluticasone 10^{-12} to 10^{-7} or the combination ($p < 0.0001$).[19] The reduction in both mediators was greater ($p = 0.006$ for TNFα, not stated for IL-8) with salmeterol plus fluticasone than with fluticasone alone.[19]

Conversely, in a study in human tracheal smooth muscle cells from previously healthy donors, salmeterol 0.1–1 nmol/L (via cAMP stimulation) significantly increased IL-8 accumulation after 8 hours ($p < 0.001$ vs control), although the increase was significantly lower than that stimulated by TNFα.[11] However, synergy was also apparent in this study. Fluticasone propionate 0.01–1 nmol/L significantly inhibited ($p < 0.001$) TNFα-stimulated IL-8 release and the addition of salmeterol 0.1 or 1.0 nmol/L caused a further significant decrease ($p < 0.01$ and $p < 0.001$ vs fluticasone propionate alone). The significant reversal that occurred ($p < 0.01$) when cells were pre-treated with a β_2-adrenoceptor selective antagonist suggested β_2-adrenoceptor mediation.[11]

2.3 Other Effects

The response to ≤3200μg inhaled salbutamol (administered via MDI over 1.5 hours on day 12) was similar in recipients of 11 days' treatment with twice-daily salmeterol 100μg or salmeterol/fluticasone 100/500μg via the Diskus® DPI in a randomised, double-blind, crossover study completed by 22 healthy volunteers.[39] Post-salbutamol changes in pulse rate, fasting serum glucose levels and serum potassium levels were significantly smaller with salmeterol with or without fluticasone propionate than with placebo, and the increase in the corrected QT interval was significantly smaller with salmeterol/fluticasone propionate than with placebo. The responses to salbutamol in recipients of fluti-

Table I. Pharmacokinetics of salmeterol/fluticasone propionate (SAL/FLU) 100/500μg. Healthy volunteers in a randomised, double-blind, crossover study received 11 days' treatment with twice-daily SAL 100μg, FLU 500μg or SAL/FLU 100/500μg via dry powder inhaler. Geometric mean values (unless otherwise stated) at day 11[39]

Parameter	Pharmacokinetics of SAL (n = 22)		Pharmacokinetics of FLU (n = 11)	
	SAL/FLU	SAL	SAL/FLU	FLU
C_{max} (pg/mL)	229	220	111.9	107.1
t_{max} (h)	0.083	0.083	1.0	0.75
AUC_t (pg • h/mL)			722.7	668.4
$t_{½β}$ (h)			7.56[a]	6.91[a]

a Median.

AUC_t = area under the plasma concentration-time curve within a dosing interval; **C_{max}** = maximum plasma concentration; **t_{max}** = time to C_{max}; **$t_{½β}$** = terminal elimination half-life.

casone propionate 500μg monotherapy and placebo were similar.[39]

In the same study,[39] twice-daily fluticasone propionate 500μg and salmeterol/fluticasone propionate 100/500μg both significantly reduced 24-hour geometric mean urinary cortisol excretion versus placebo (22.4 and 23.2 vs 48.6μg, $p < 0.001$ for both vs placebo), although mean morning plasma cortisol levels were similar in all treatment groups. Overnight 10-hour urinary excretion of cortisol corrected for creatinine (OUCC), and serum osteocalcin levels decreased significantly in 20 patients with severe COPD receiving 2 weeks' treatment with a supratherapeutic dose of fluticasone propionate 1000μg twice daily via an MDI and spacer.[40] In patients with or without emphysema, serum osteocalcin levels decreased from 6.92 to 5.72 nmol/L ($p = 0.03$) and from 7.24 to 6.34 nmol/L ($p = 0.04$), and OUCC decreased from 7.13 to 4.27 nmol/mmol ($p = 0.006$) and 7.86 to 4.64 nmol/mmol ($p = 0.03$), respectively.[40]

The effect of salmeterol/fluticasone propionate on plasma cortisol levels is discussed in section 5.1.

3. Pharmacokinetic Properties

The pharmacokinetic properties of salmeterol/fluticasone propionate are discussed briefly in the following section; inhaled salmeterol and fluticasone propionate exert their effects locally and plasma concentrations are therefore low. The pharmacokinetics of the individual drug components[41-43] and the combination product[44,45] were reviewed previously in more detail; some studies were primarily in patients with asthma.[41,42,44]

A randomised, double-blind, crossover study in 22 healthy volunteers found the pharmacokinetics of twice-daily inhaled salmeterol 100μg or fluticasone propionate 500μg administered via DPI over 11 days were not affected by coadministration of the other inhaled drug (table I), indicating there is no systemic pharmacodynamic or pharmacokinetic interaction (see also section 2.3).[39]

In 11 volunteers for whom the salmeterol mean maximum plasma concentration (C_{max}) values were available on days 1 and 11, the value was significantly higher after multiple versus single-dose administration (0.202 vs 0.155 ng/mL, $p = 0.0001$), although when salmeterol was administered for the second and third times, C_{max} decreased significantly compared with the first treatment ($p = 0.0032$). Time to C_{max} (t_{max}) was 0.083h (5 minutes) with multiple and single-dose administration. Salmeterol plasma concentrations were not measurable beyond 30 minutes and the terminal elimination half-life ($t_{½β}$) and area under the plasma concentration-time curve (AUC) could not be determined.[39]

Systemic absorption of fluticasone propionate, initially rapid but then prolonged, occurs mainly through the lungs. In healthy subjects, the absolute bioavailability of inhaled fluticasone propionate is 10–30%,[9] averaging 18% when administered via the Diskus®.[8]

Absorption and other pharmacokinetic parameters after 7 days of inhaled fluticasone propionate 1000 μg/day differed between ten patients with COPD and 13 matched healthy volunteers in a study

reported in an abstract.[46] Least-squares mean C_{max} was 235 versus 418 pg/mL (p = 0.03), AUC 1961 versus 2984 pg • h/mL and bioavailability 13.3% versus 21.0% (p-values not stated); individual AUC and bioavailability varied widely.[46] After inhaled fluticasone propionate 250μg twice daily via the Diskus®, mean steady-state C_{max} was 53 pg/mL (range 19–159) in 30 patients with COPD.[8] Emphysema status in patients with COPD did not affect systemic absorption of fluticasone propionate.[40] Combined data from eight studies indicated that sex, age, FEV_1 as a percentage of predicted, and height did not affect the pharmacokinetics of inhaled fluticasone propionate, although they confirmed that having asthma or COPD did (study available as an abstract).[47]

Plasma protein binding of fluticasone propionate is 91%, plasma clearance is ≈1100 mL/min and $t_{1/2}$ ≈8 hours.[9] The estimated elimination rate constants for fluticasone propionate 250 and 500μg doses via Diskus® in COPD or asthma were 0.090 and 0.167 per hour.[47] Patient weight affected the apparent volume of distribution, estimated at 4.89 L/kg in a 70kg person with COPD or asthma, and 4.54 L/kg in healthy volunteers.[47]

Most systemically absorbed fluticasone propionate is metabolised by the cytochrome P450 (CYP) enzyme CYP3A4 to an inactive 17β-carboxylic acid metabolite.[9] Unchanged fluticasone propionate and metabolites are excreted mostly in the faeces, with <5% (mainly as metabolites) excreted in the urine.[9] The mainly hepatic metabolism means patients with hepatic impairment should be closely monitored for plasma accumulation of fluticasone propionate.[8]

Significant drug interactions occurred, and others can be anticipated, between fluticasone propionate and other drugs metabolised by CYP enzymes. The plasma concentration of intranasal fluticasone propionate 200μg once daily increased several hundred-fold in a 7-day interaction study in healthy volunteers exposed to ritonavir 100mg twice daily (ritonavir is a potent inhibitor of CYP3A4); a similar interaction is expected with inhaled fluticasone propionate.[9] The increases in fluticasone propionate plasma concentrations resulted in an 86% reduction in plasma cortisol exposure, compared with the exposure after fluticasone propionate alone. Ketoconazole also increased the plasma exposure from a single inhalation of fluticasone propionate (by 150%).[9] However, there were no significant pharmacokinetic interactions when twice-daily inhaled fluticasone propionate 500μg and erythromycin 333mg three times daily were administered together.[8]

4. Therapeutic Efficacy

Twice-daily salmeterol/fluticasone propionate 50/500μg[48,49] or 50/250μg[50] in patients with moderate-to-severe COPD was compared with monotherapy and placebo in three large, randomised, double-blind studies over 24[49,50] and 52[48] weeks (the TRISTAN [TRial of Inhaled STeroids ANd long-acting β_2 agonists] trial) [section 4.1]. Two 8-week, randomised, double-blind studies compared salmeterol/fluticasone propionate 50/250μg twice daily with salbutamol/ipratropium bromide 36/206μg four times daily administered by MDI (section 4.2).[51,52] A nonblind study randomised 80 patients to twice-daily salmeterol/fluticasone propionate 50/500μg or inhaled fluticasone propionate plus oral theophylline for 4 months (section 4.2).[53] Two studies assessed the effect of withdrawal of fluticasone propionate in patients with COPD (section 4.3).[54,55]

Unless stated otherwise, salmeterol/fluticasone propionate was administered via Diskus® in all studies.

Patients had a diagnosis of COPD (FEV_1/FVC ≤70%[48-51] or chronic bronchitis and/or emphysema[51]) that was stable,[53] symptomatic[51] or met American Thoracic Society (ATS)[4] criteria,[50] and had a baseline FEV_1 of 25–70%,[48] 40–70%,[51] or <65%[49,50] of predicted, but >700mL[49-51] (or ≤700mL but ≥40% of predicted).[50,51] The TRISTAN study specified a history of exacerbations and <10% reversibility after salbutamol 400μg.[48]

Primary efficacy outcomes included predose FEV_1 at study endpoint[48-52] (one study specified FEV_1 after 6 hours without bronchodilators and 12 hours without study medication),[48] 2-hour postdose

Table II. Effect of inhaled salmeterol/fluticasone propionate (SAL/FLU) on lung function in chronic obstructive pulmonary disease (COPD). Patients (pts) with COPD (forced expiratory volume in 1 second [FEV_1]/forced vital capacity ≤70%) were included in randomised, double-blind, parallel-group, multicentre studies. Primary efficacy outcomes were predose[48-50] and 2-hour postdose[49,50] FEV_1 at study endpoint. Two studies assessed the contribution of the individual components.[49,50] For predose FEV_1, these studies assessed the contribution of fluticasone propionate by reporting the difference between combined therapy and salmeterol, and between fluticasone propionate and placebo. For 2-hour postdose FEV_1, they assessed the contribution of salmeterol by reporting the difference between combined therapy and fluticasone propionate and between salmeterol and placebo. They therefore did not report the statistical significance of SAL/FLU versus FLU for predose FEV_1 or SAL/FLU vs SAL for postdose FEV_1.[49,50] Results are adjusted mean change from baseline (BL) unless otherwise stated

Study	Treatment regimen (μg bid)	Duration (wk)	No. of pts (ITT)	BL reversibility (% predicted FEV_1)	Predose FEV_1 (mL)	2h postdose FEV_1 (mL)	PEF (L/min)
Calverley et al.[48]a	SAL/FLU 50/500	52	358	4.0	1396****††††‡‡‡[b]		274****††††‡‡‡[b]
	SAL 50	52	372	3.7	1323****[b]		257****[b]
	FLU 500	52	374	3.7	1302****[b]		255****[b]
	PL	52	361	4.0	1264[b]		242[b]
Hanania et al.[50]c	SAL/FLU 50/250	24	178		+165***†	+281***‡‡	+31**†††[d]
	SAL 50	24	177		+91	+200***	+15***[d]
	FLU 250	24	183		+109***	+147	+11***[d]
	PL	24	185		+1	+58	+1[d]
Mahler et al.[49]	SAL/FLU 50/500	24	169[e]	20.6	+156***†	+261***‡‡	+32***†††‡‡
	SAL 50	24	164[e]	21.2	+107	+233*	+17***
	FLU 500	24	173[e]	19.2	+109***	+138	+13***
	PL	24	185[e]	19.3	−4	+28	0[d]

a In SAL/FLU, SAL, FLU and PL recipients, BL predose FEV_1 values were 1308, 1245, 1260 and 1266mL, respectively, and BL PEF values were 247, 235, 246 and 243 L/min.

b Adjusted mean values at endpoint are reported rather than the change from baseline.

c In SAL/FLU, SAL, FLU and PL recipients, BL FEV_1 values were 1252, 1245, 1313 and 1289, respectively, and BL PEF values were 206, 210, 220 and 220 L/min.

d Value estimated from a graph.

e No. of pts randomised. 645 pts were evaluable.

bid = twice daily; **ITT** = intent-to-treat; **PEF** = peak expiratory flow; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ vs PL; † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$, †††† $p < 0.0001$ vs SAL; ‡ $p < 0.01$, ‡‡ $p < 0.001$, ‡‡‡ $p < 0.0001$ vs FLU.

FEV_1 at endpoint,[49,50] exacerbations[54] and health status.[54] Two studies did not analyse the statistical significance of all differences between active treatment groups or between monotherapy and placebo.[49,50] For predose FEV_1, these studies assessed the contribution of fluticasone propionate by reporting the difference between combined therapy and salmeterol, and between fluticasone propionate and placebo. For 2-hour postdose FEV_1, they assessed the contribution of salmeterol by reporting the difference between combined therapy and fluticasone propionate and between salmeterol and placebo (table II).[49,50]

Secondary endpoints included exacerbations[48-50] (one study recorded exacerbations within safety assessments[51]), supplementary salbutamol use,[48-50,52,53] post-bronchodilator FEV_1 and/or FVC,[48,52] FEV_1 AUC_6,[51] morning peak expiratory flow (PEF),[48-52] daily symptoms,[48-52] dyspnoea,[49-52] symptom-free nights[51,52] or night-time awakenings[48,51] and health status.[48-50]

Symptoms were assessed using various scales. One study graded cough and sputum production from 0 (none) to 3 (severe) and breathlessness and sputum colour from 0 (none) to 4 (breathlessness at rest/dark yellow or green sputum).[48] The Baseline Dyspnoea Index (BDI) total score ranges from 0 (worst) to 12 (best) and the Transition Dyspnoea Index (TDI) assesses the change from baseline in dyspnoea, with total scores ranging from −9 (major deterioration) to +9 (major improvement); a 1-unit change is considered clinically relevant.[51] Health

status was assessed using the St George's Respiratory Questionnaire (SGRQ) or the Chronic Respiratory Disease Questionnaire (CRDQ). SGRQ total scores range from 0–100% (no impairment to complete impairment) and a ≥4-unit change is considered clinically relevant. The CRDQ total scores range from 20–140 (worst to best) with a change of ≥10 regarded as clinically significant.

Patients underwent a 2-week (or 8–14 day[51]) run-in period during which, except for regular theophylline,[48-50] anticholinergics[48] or mucolytics,[48] salbutamol as required,[48-51] or placebo via the Diskus®,[49,50] all other COPD treatments (including inhaled[48] corticosteroids,[49,50] long-acting β_2-agonists[48] and other bronchodilators)[49-51] were stopped.

Baseline patient characteristics (see also table II) were a mean age of 61.9–65 years,[48-51] and a 42–62 pack-years[48,50,51] smoking history; 58–75% were male.[48-51] Inhaled corticosteroids had been used by 18–31% (US trials)[49,50] and ≈50% (TRISTAN trial)[48] of participants and long-acting β_2-agonists by 38–42% (TRISTAN trial).[48]

Some of the smaller studies discussed in this section were reported in abstracts,[52,53,55] as were a number of post-hoc analyses.[56-60]

4.1 Comparisons with Monotherapy and Placebo

4.1.1 Lung Function

Inhaled salmeterol/fluticasone propionate 50/500 and 50/250μg twice daily resulted in significantly greater pre- and postdose FEV_1 values or improvements from baseline than placebo in patients with COPD (table II).[48-50] In addition, predose FEV_1 improved more with salmeterol/fluticasone propionate than with salmeterol alone,[48-50] and (for the 50/500μg dosage) more than with fluticasone propionate 500μg in the trial in which the comparison was a primary efficacy outcome[48] (table II).

Two-hour postdose FEV_1 improved significantly more with salmeterol/fluticasone propionate 50/500 or 50/250μg than with placebo or fluticasone propionate in 24-week trials (table II).[49,50] After 12 months, the adjusted mean post-bronchodilator FEV_1 with salmeterol/fluticasone propionate (1484mL) was significantly better than that with salmeterol 50μg (1436mL, $p = 0.0014$), fluticasone propionate (1454mL, $p = 0.039$) or placebo (1408mL, $p = 0.002$) [respective baseline values were 1419, 1346, 1363 and 1379mL].[48] The difference between fluticasone propionate 500μg and placebo was also significant ($p < 0.01$).[48]

Additional analysis[56] revealed that both women and men receiving combined therapy achieved significant FEV_1 improvements of 152 and 127mL versus placebo in the TRISTAN trial.[48] Predose FEV_1 also improved significantly versus placebo and both monotherapies ($p < 0.001$) in patients with baseline FEV_1 <50% predicted (110mL) and ≥50% predicted (176mL).[59] In recipients of active treatment, improvements in predose FEV_1 in patients who demonstrated poor reversibility of airway obstruction were 26–126mL, versus 123–196mL in patients who demonstrated ≥12% reversibility (no statistical analysis reported).[49,50]

The significantly greater improvements in FEV_1 with combined therapy versus salmeterol (predose) and combined therapy versus fluticasone propionate (postdose) were evident within 2 weeks ($p < 0.05$)[48-50] and, where measured, within 1 week of therapy.[49,50] In one study,[48] the combined therapy group at trial end showed the least difference between pre- and postdose FEV_1; the sustained bronchodilatory effect of salmeterol may have affected the predose FEV_1 in this group 12 hours later.

PEF improved significantly more[49,50,58] with salmeterol/fluticasone propionate 50/500 or 50/250μg than with corresponding monotherapies or placebo (table II). As with FEV_1, the effect occurred early in treatment. By day 1 in the TRISTAN study, the mean improvement in PEF versus placebo was 16.1 L/min with combined therapy ($p < 0.001$ vs placebo and monotherapies), greater than the sum of the 8.9 L/min improvement with salmeterol ($p < 0.01$ vs placebo) and the 4.2 L/min improvement with fluticasone propionate.[58] At every assessment point in the two 24-week trials, the increase in PEF from baseline with salmeterol/fluticasone propionate was significantly greater than with either

monotherapy or placebo ($p \leq 0.002$), although the increases with the monotherapies were significantly greater than with placebo ($p < 0.001$).[49,50] At trial endpoint, the increases in PEF with combined therapy exceeded the sum of the monotherapy increases (table II) indicating synergistic benefits.[49,50]

4.1.2 Symptoms and Salbutamol Use

Dyspnoea, assessed by the change from a 5.7–6.2 BDI score,[49,50] improved significantly more over 24 weeks ($p < 0.05$) with combination therapy than with placebo, with clinically significant mean TDI scores of 2.1 versus 0.4 ($p < 0.001$)[49] and 1.7 versus 1.0 ($p = 0.023$).[50] In one trial, significant TDI improvements (not quantitatively reported) were evident within one week. Results versus monotherapy varied: in one trial, the mean 2.1 TDI score in salmeterol/fluticasone propionate recipients was greater than those in recipients of salmeterol (0.9, $p < 0.001$) and fluticasone (1.3, $p = 0.033$), although the score with fluticasone was significant versus placebo ($p = 0.002$).[49] In the other trial, mean TDI scores with monotherapy (1.7 and 1.6) were similar to the 1.7 score in combined therapy recipients, and the score with salmeterol was significantly better ($p = 0.043$) than with placebo.[50]

The 1-year study found patients experienced significantly less breathlessness with salmeterol/fluticasone propionate 50/500μg than with corresponding monotherapies (mean scores 1.47 vs 1.58 and 1.59 points for fluticasone propionate and salmeterol, $p \leq 0.01$ for both) and placebo (1.66, $p = 0.0001$).[48] Breathlessness improved significantly ($p \leq 0.004$) in patients with FEV_1 <50% and ≥50% of predicted.[59] Neither monotherapy was better than placebo.[48] Cough was decreased with combined therapy versus placebo (1.35 vs 1.44 points, $p = 0.018$); decreases with combined and monotherapy were similar.[48]

Over 24 weeks, the use of supplementary salbutamol decreased more from baseline in recipients of salmeterol/fluticasone propionate 50/500 or 50/250μg than in placebo or fluticasone propionate recipients ($p < 0.05$).[48-50] Mean daily actuations decreased by 1.2 with salmeterol/fluticasone propionate 500/50μg, 0.9 with salmeterol and 0.4 with fluticasone propionate, versus an increase of 0.5 with placebo ($p \leq 0.045$ vs all active treatments).[49] The adjusted mean decrease with salmeterol/fluticasone propionate 250/50μg was 1.0 actuation per day, significantly more than with fluticasone propionate (−0.2 actuations per day, $p = 0.030$) and placebo (+0.1, $p = 0.002$), but not salmeterol (−0.7).[50]

In the TRISTAN trial, median daily use of relief medications at week 52 was once daily (range 0–10 daily) in recipients of salmeterol/fluticasone propionate 50/500μg, significantly less ($p \leq 0.0003$ for all) than the twice-daily use in all other treatment groups.[48] However, use in placebo recipients ranged from 0–32 per day, versus 0–14 per day with salmeterol and 0–11 with fluticasone propionate ($p \leq 0.028$ for both vs placebo).[48]

4.1.3 Exacerbations of Chronic Obstructive Pulmonary Disease (COPD)

There were significantly fewer annual exacerbations in recipients of salmeterol/fluticasone propionate 50/500μg twice daily and corresponding monotherapies than placebo in a large 1-year study (figure 1),[48] although a 24-week trial found no statistically significant between-group differences in the number of COPD exacerbations.[50] However,

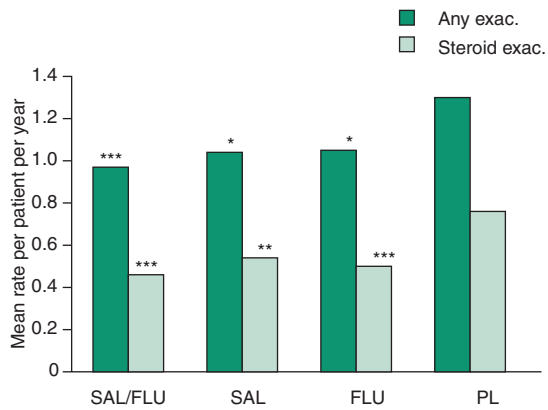

Fig. 1. Exacerbations (exac.) of chronic obstructive pulmonary disease (COPD). Patients with COPD received twice-daily salmeterol (SAL)/fluticasone propionate (FLU) 50/500μg (SAL/FLU), SAL 50μg, FLU 500μg or placebo (PL) via dry powder inhaler in a 1-year randomised, double-blind, PL-controlled trial.[48] Mean total exac. (Any exac.) or exac. requiring treatment with oral corticosteroids (Steroid exac.). * $p = 0.003$, ** $p = 0.0003$, *** $p \leq 0.0001$ vs PL.

neither 24-week study was designed to assess exacerbations. Compared with placebo recipients, exacerbations in the TRISTAN study decreased in both male (by 23%, p = 0.003) and female (by 31%, p = 0.009) recipients of combined therapy.[56]

Exacerbations affected 60% of patients with a baseline FEV_1 <50% predicted (vs 44% with FEV_1 ≥50% predicted) but decreased by 30% versus placebo with salmeterol/fluticasone propionate 50/500μg in these patients (vs 10% for FEV_1 ≥50% predicted).[48] Exacerbations requiring oral corticosteroids decreased with all active treatments (figure 1),[48] but with combined therapy, the decrease was most marked (42%, p < 0.001 vs placebo) in patients with FEV_1 <50% predicted (vs 24% [not significant vs placebo] for the smaller subgroup of patients with FEV_1 ≥50%).[59]

The annual rate of exacerbations requiring oral corticosteroids in patients with FEV_1 <50% predicted was not significantly different between active treatments, at 0.47 with salmeterol/fluticasone propionate 50/500μg, 0.52 with fluticasone propionate 500μg, 0.58 with salmeterol 50μg and 0.81 with placebo (p < 0.002 with all active treatments) [figures estimated from a graph].[59]

The effect of salmeterol/fluticasone propionate on hospitalisations and mortality were not specific endpoints in these trials.[48-50]

4.1.4 Health-Related Quality of Life

Health-related quality-of-life (HR-QOL) scores generally improved more with salmeterol/fluticasone propionate and salmeterol monotherapy than with fluticasone propionate or placebo, although some statistically significant differences were numerically small.[48-50]

There was a clinically significant improvement of 4.3 points in the raw mean SGRQ with salmeterol/fluticasone propionate 50/500μg, seen early in treatment (week 8, estimated from a graph) and at 52 weeks.[48] Mean improvements of 2–3 points occurred in other patient groups. The adjusted mean 52-week SGRQ total score was 44.1 with salmeterol/fluticasone propionate 50/500μg, significantly better than with placebo (46.3, p = 0.0003) and fluticasone propionate (45.5, p = 0.021), but not salmeterol (45.2) [baseline scores were 47.1–49.8].[48] Mean CRDQ scores in 24-week trials increased significantly from baseline scores of 84.1–88.5 with salmeterol/fluticasone propionate 50/250 or 50/500μg (p < 0.01); mean increases versus placebo are shown in figure 2.[49,50]

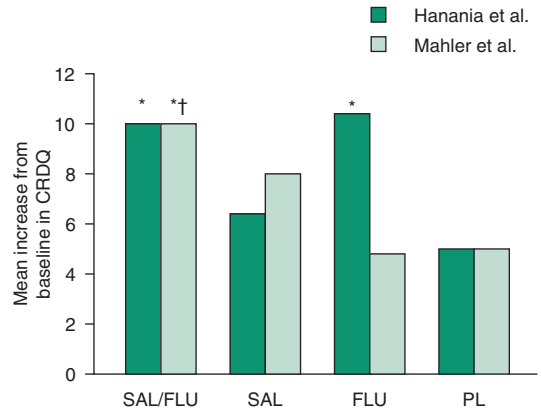

Fig. 2. Change in health status in chronic obstructive pulmonary disease with salmeterol/fluticasone propionate (SAL/FLU). Patients in two randomised, placebo (PL)-controlled trials received twice-daily SAL/FLU 50/250 (Hanania et al.[50]) or 50/500μg (Mahler et al.[49]), SAL 50μg, FLU 250μg or 500μg or PL for 24 weeks. Health status was measured by the Chronic Respiratory Disease Questionnaire (CRDQ); a change of 10 points is considered clinically significant.[49,50] * p < 0.01 vs PL; † p = 0.017 vs FLU.

4.2 Comparisons with Other Therapies

A pooled analysis (n = 2630) reviewed eight 8- to 24-week trials comparing salmeterol/fluticasone propionate 50/250μg twice daily with ipratropium bromide 36μg four times daily, salmeterol 42μg (via MDI) or 50μg (via Diskus®) twice daily or placebo.[57] More patients recorded an increase of ≥1 in TDI score with salmeterol/fluticasone propionate (63% vs 46% with ipratropium bromide, 47% with salmeterol and 38% with placebo) and fewer showed no change (29% vs 38%, 38% and 44%, respectively) [p < 0.001 for salmeterol/fluticasone propionate vs all comparators].[57]

4.2.1 Salbutamol/Ipratropium Bromide

Results of two randomised 8-week studies in patients with COPD included significantly greater improvements in predose FEV_1 and other endpoints in recipients of twice-daily salmeterol/fluticasone

Table III. Efficacy of salmeterol/fluticasone propionate (SAL/FLU) 50/250μg twice daily via Diskus® dry powder inhaler vs salbutamol/ipratropium bromide (SAB/IPR) 206/36μg four times daily via metered dose inhaler in patients (pts) with chronic obstructive pulmonary disease. Results of two 8-week, randomised, double-blind studies (n = 361[52] and 365[51]). Values are mean change from baseline (BL) at endpoint

Outcome	Donohue et al.[51]		Make et al.[52]	
	SAL/FLU	SAB/IPR	SAL/FLU	SAB/IPR
Predose FEV_1 (mL)	111***	−4	124***	−3
FEV_1 AUC_6 (L • h)	+1.39***[a]	−0.90[a]	+1.39**[a]	0.98[a]
Morning PEF (mL)	37***	7	35.9***	3.8
TDI score	2.7***	1.2	2.7**	1.5
Daytime symptom score (%)	−24*	−15	−46.7*	−28.1
Symptom-free nights (%)	28.4***	7.7	19**	8
Night-time awakenings (per night)	−0.58**	−0.20	−11.9**	−4.7
Sleep symptom score	−11.8**	−4.5	−0.46**	−0.17
SAB-free nights (%)	22.4**	8.7	34.7*	26.7
SAB-free days (%)	37.6	27.7	19***	7.3

a Primary endpoint.

FEV_1 = forced expiratory volume in 1 second; **FEV_1 AUC_6** = 6-hour area under the curve for changes in FEV_1; **PEF** = peak expiratory flow; **TDI** = transition dyspnoea index; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs SAB/IPR.

propionate 50/250μg than in recipients of salbutamol/ipratropium bromide 206/36μg four times daily (table III).[51,52]

In a pooled analysis (n = 693), predose FEV_1 and PEF improved significantly more after 8 weeks' treatment with salmeterol/fluticasone propionate 50/250μg twice daily than with salbutamol/ipratropium bromide 206/36μg four times daily, whether or not patients displayed responsiveness to salbutamol (figure 3).[60] The analysis also found a significantly greater TDI score (2.8 vs 1.3 in salmeterol/fluticasone propionate vs salbutamol/ipratropium bromide recipients responsive to salbutamol; 2.5 vs 1.3 in patients classified as non-responsive, both $p < 0.05$); change from baseline in daytime symptom scores (−51 vs −37 and −49 vs −31, both $p < 0.05$) and the percentage of symptom-free nights (22% vs 14% and 27% vs 4%, $p < 0.05$). The daytime symptom score is a scale from 0 (best) to 100 (worst).[60]

4.2.2 Fluticasone Propionate plus Theophylline

A 4-month study found twice-daily salmeterol/fluticasone propionate 50/500μg (n = 37) and fluticasone propionate 500μg plus titrated oral theophylline (n = 29) both improved FEV_1 (by a maximum of 172 and 155mL), but salmeterol/fluticasone propionate reduced dyspnoea and the use of rescue salbutamol to a significantly greater extent ($p < 0.05$, quantitative data not reported).[53]

4.3 Fluticasone Propionate Withdrawal

Discontinuing fluticasone propionate resulted in small, but statistically significant declines in lung function and symptoms in patients with COPD who had been receiving salmeterol/fluticasone propionate (n = 373).[55] Patients received 3 months' treatment with salmeterol/fluticasone propionate followed by 12 months' treatment with salmeterol, or continued combination therapy.[55] Recipients of continued combined therapy experienced a −0.1mL decrease in FEV_1 (vs −4.4mL with salmeterol, $p < 0.001$), no change in FEV_1/FVC (vs decrease of 3.7, $p = 0.002$), a 0.17 better mean dyspnoea score (on a 0–4 scale, $p < 0.001$), 6% fewer disturbed nights ($p < 0.001$ for both comparisons) and more (unspecified) days without rescue medication ($p < 0.05$). The statistically significant differences may not be clinically significant.[55]

Fluticasone propionate withdrawal was associated with more COPD exacerbations (primary outcome), particularly in patients with an FEV_1 <50% predicted, in a randomised, double-blind trial in 244 patients with COPD, all of whom received fluticasone propionate 500μg twice daily and ipratropi-

um bromide 40μg four times daily for a 4-month run-in period.[54] During the 6-month study, 57.0% of placebo recipients and 47.2% of fluticasone propionate 500μg recipients developed exacerbations, with a mean time to first exacerbation of 34.6 and 75.2 days, respectively (mean difference 34.6 days [95% CI 15.4, 53.8]). The hazard ratio with placebo versus fluticasone propionate for a first exacerbation was 1.5 (95% CI 1.05, 2.1), and for a second, after adjustment for smoking, 2.4 (95% CI 1.5, 3.9). A mean 1.3 (median 1.0) exacerbations per patient had occurred in the year before the study.[54]

For those with an FEV_1 <50% predicted, the hazard ratio for a first exacerbation with placebo versus fluticasone propionate was 2.1; it was 1.2 for those with an FEV_1 ≥50% predicted.[54] Over 21% of placebo recipients (vs 5% receiving fluticasone propionate) experienced rapid, recurrent exacerbations and were prescribed open treatment with fluticasone propionate (hazard ratio 4.4, 95% CI 1.9, 10.3). Subsequently 38% of these placebo recipients, but five of the six fluticasone propionate patients, experienced more exacerbations.[54]

5. Tolerability

Tolerability data for salmeterol/ fluticasone propionate 50/250 or 50/500 are available from the large clinical trials detailed in section 4.1[48-50] and additional studies available as abstracts.[61,62]

Drug-related adverse events reported with salmeterol/fluticasone propionate reflected those that occur with the monotherapy components, with no new adverse events reported as a result of combining the two drugs. In trials comparing salmeterol/fluticasone propionate with corresponding monotherapy and placebo, drug-related adverse events occurred in 16%[48] and 20%[50] of twice-daily salmeterol/fluticasone propionate 50/500[48] or 50/250μg[50] recipients, 19%[48] and 15%[50] of twice-daily fluticasone propionate 500[48] or 250μg[50] recipients, 12%[48] and 11%[50] of twice-daily salmeterol 50μg recipients and 14%[48] and 9%[50] of placebo recipients.

Commonly reported (incidence ≤6%) drug-related adverse events in salmeterol/fluticasone propionate recipients included oropharyngeal candidiasis, throat infection or hoarseness, COPD exacerbation, oral inflammation or nausea or vomiting, and headaches, tremor and vertigo (figure 4).[48]

Corticosteroid-related adverse events are discussed in more detail in section 5.1. Serious adverse events occurred in 4% of twice-daily salmeterol/fluticasone propionate 50/250μg recipients, 5% of

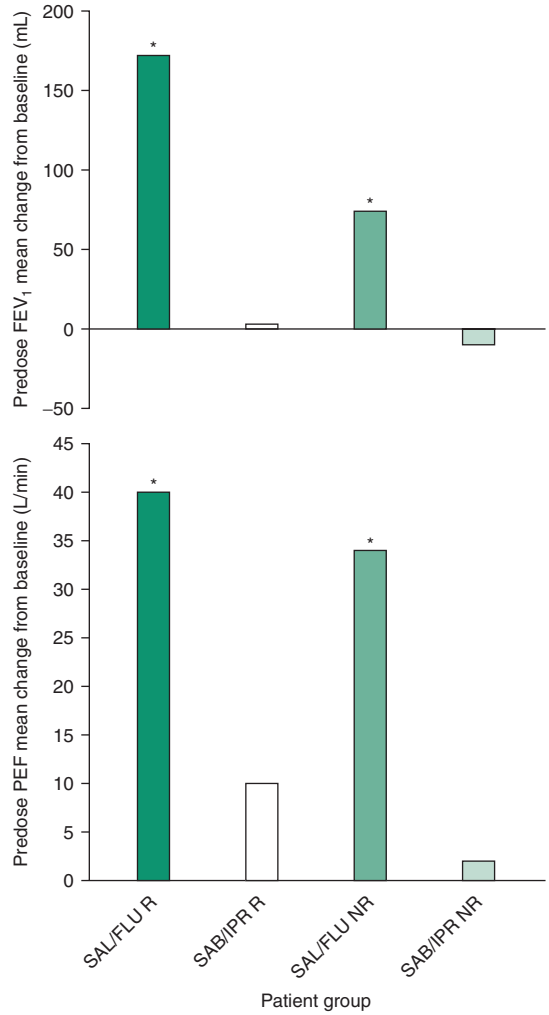

Fig. 3. Salmeterol/fluticasone propionate (SAL/FLU) 50/250μg in chronic obstructive pulmonary disease (COPD).[60] Pooled analysis (n = 693) of lung function data from two randomised, double-blind trials in patients with COPD who were responsive (R) or not responsive (NR) to salbutamol. Patients received 8 weeks' treatment with twice-daily SAL/FLU or four-times-daily salbutamol/ipratropium bromide 206/36μg (SAB/IPR). **FEV_1** = forced expiratory volume in 1 second; **PEF** = peak expiratory flow; * $p < 0.05$ vs SAB/IPR.

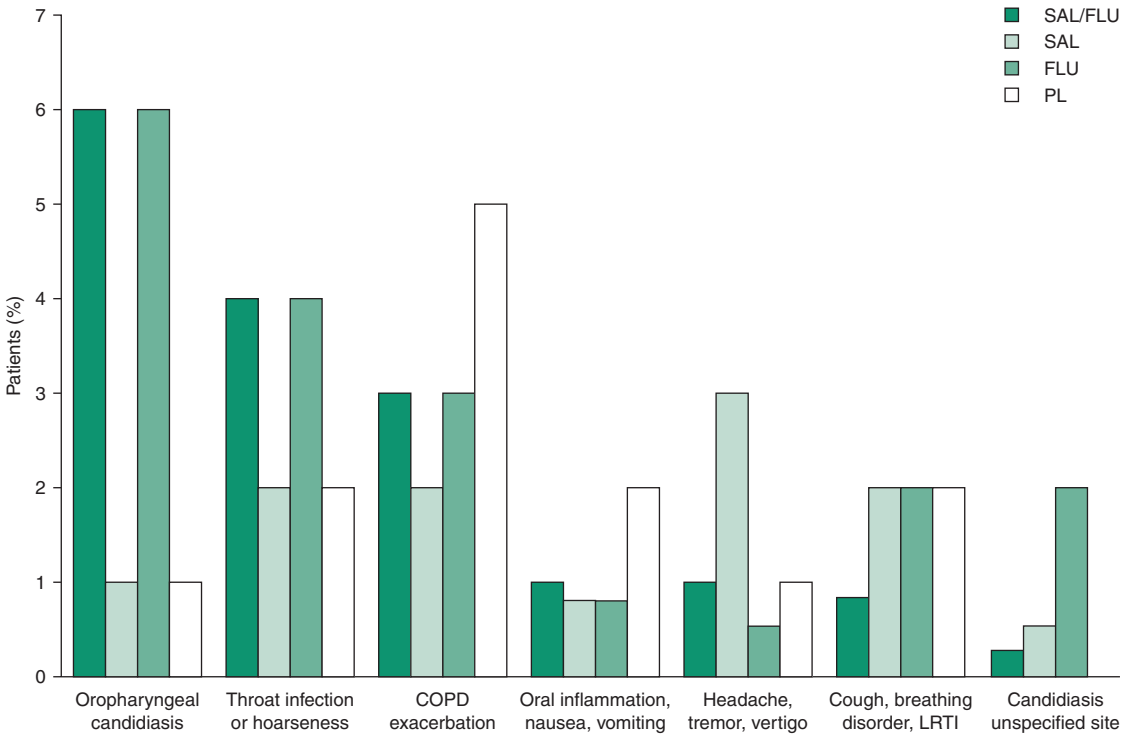

Fig. 4. Tolerability of salmeterol/fluticasone propionate (SAL/FLU) 50/500μg in chronic obstructive pulmonary disease (COPD). Patients in a large, randomised, placebo-controlled, multicentre, 52-week trial were randomised to twice-daily SAL/FLU, SAL 50μg, FLU 500μg or placebo (PL) via Diskus®. **LRTI** = lower respiratory tract infection.

twice-daily fluticasone propionate 250μg recipients, 3% of salmeterol 50μg recipients and 6% of placebo recipients in one trial.[50] Across trials, clinically significant ECG abnormalities were reported in 0–3 salmeterol/fluticasone propionate recipients, 0–4 fluticasone propionate recipients, 0–2 salmeterol recipients and 0–4 placebo recipients.[48-50]

5.1 Corticosteroid-Related Adverse Events

As expected, oropharyngeal candidiasis occurred numerically more often in recipients of salmeterol/fluticasone propionate or fluticasone propionate (6–10%) than in recipients of salmeterol or placebo (<1–3%).[48-50] Bruising affected 6–8% of patients across all treatment groups.[48]

The response to tetracosactide (cosyntropin) was abnormal at 24 weeks in 3 out of 691 patients in one trial[49] and 15 of 723 in another,[50] with no significant differences between patients receiving fluticasone propionate (as combined or monotherapy), and those not receiving fluticasone propionate.

Decreases from normal to below-normal cortisol levels in the TRISTAN trial occurred in 4% of combined therapy or placebo recipients, 5% of salmeterol recipients and 6% of fluticasone propionate recipients.[48] By 52 weeks, mean serum cortisol levels had fallen in recipients of fluticasone propionate (by 1%) and combination therapy (by 3%), but had increased by 6% with salmeterol and 4% with placebo. Differences versus placebo were significant at 24 weeks ($p < 0.05$) in recipients of fluticasone propionate and combination therapy, but at 52 weeks, significant ($p = 0.007$) only with fluticasone propionate.[48]

A nested case-control study (n = 11 261) found fracture risk was increased with use of inhaled corticosteroids within the prior 30 days (odds ratio [OR] 1.42 vs no use in past year, 95% CI 1.23, 1.65).[61]

While current use of any corticosteroid was associated with fracture, (OR 1.46, 95% CI 1.26, 1.69) use of fluticasone propionate specifically was not (OR 0.78, 95% CI 0.55, 1.09).[61] The incidence of fractures per 1000 patient-years in recipients of up to 3 years' treatment with twice-daily fluticasone propionate 500μg (n = 1594) with or without salmeterol 50μg twice daily was 15 versus 23 with placebo in a pooled analysis of four large clinical trials.[62] No fractures were considered treatment related.[62]

6. Dosage and Administration

One inhalation twice daily of salmeterol/fluticasone propionate 50/500μg via the Diskus® DPI is indicated in the EU in adults with severe COPD (FEV_1 <50%).[9] Patients must have experienced repeated exacerbations and have significant symptoms despite regular therapy with bronchodilators.[9] In the US, salmeterol/fluticasone propionate 50/250μg twice daily via the Diskus® DPI, re-evaluated every 6 months, is approved for adults with COPD associated with chronic bronchitis; the 50/500μg dosage is not recommended.[8] No dosage adjustment in elderly patients is recommended.[8,9] Salmeterol is a long-acting bronchodilator and should not be used for rescue medication. Local prescribing information should be consulted for other warnings, precautions and information concerning possible drug interactions.

7. Place of Salmeterol/Fluticasone Propionate in the Management of COPD

Recent global initiatives recognise the significance of COPD and emphasise the benefits of treatment.[2] The seven GOLD treatment aims are the prevention of disease progression, relief of symptoms, improvement of exercise tolerance and of health status, the prevention and treatment of complications and exacerbations and the reduction of mortality.[2] Disease severity and treatment effectiveness can be assessed by lung function (using spirometry), symptomatic change (especially dyspnoea), the number and severity of exacerbations, patients' assessment of their HR-QOL, and mortality. FEV_1, particularly assessed over the long term, is important, objective and (unlike, for example, exacerbations) universally defined, but the other outcome measures mentioned above are also useful in assessing disease and predicting outcomes.[1]

The recommended management of COPD includes initial and ongoing assessment, including spirometry, with supportive therapy to reduce risk factors such as smoking.[2] Pharmacological treatment should be initiated in concert with nonpharmacological/pulmonary rehabilitation programmes including nutrition counselling and exercise, both aimed at improving skeletal muscle strength (linked to dyspnoea),[63] and patient education. Patient education can improve compliance and early recognition of exacerbations. Exacerbations are common (up to 2.7 per annum when all exacerbations are reported) and are associated with decreased quality of life, incomplete recovery of lung function, particularly in severe COPD,[64-66] and increased mortality.[2] Preventing and treating exacerbations is a key treatment goal.[2]

Bronchodilators, including β_2-agonists, anticholinergics, theophylline or combinations of these are the recommended first-line pharmacological treatment in COPD.[2] Little comparative data is available between long-acting β_2-agonists or other bronchodilators. Long-acting β_2-agonists resulted in better improvements than placebo in health status (possibly more than ipratropium), symptoms, use of rescue medication and the time between exacerbations.[1] Tiotropium bromide (a long-acting anticholinergic) reduced exacerbations and improved health status versus placebo and ipratropium, and in two 6-month studies, was at least as effective as salmeterol (via MDI) in improving bronchodilation, dyspnoea and HR-QOL.[67]

In the light of recent trial reports, the addition of inhaled corticosteroids is now recommended for patients with severe or very severe (GOLD groups III and IV) COPD who experience frequent exacerbations[2] (>3 exacerbations in the last 2 years is a risk factor for further exacerbations).[1] Many patients who cannot correctly use an MDI can use a DPI and corticosteroids inhaled via a DPI may result

in fewer local adverse events from oropharyngeal drug deposition than with an MDI.[1]

It is generally held that while pharmacological therapy in COPD improves symptom control, exacerbations, health status and exercise tolerance, it does not modify the long-term decline in lung function, which is characteristic of the disease.[2] Several studies have shown no reduction in the rate of lung function decline with inhaled corticosteroids.[2]

However, a recent meta-analysis demonstrated that inhaled corticosteroid therapy for at least 2 years was associated with a small but significant slowing in the rate of lung function decline in patients with COPD, particularly in patients receiving high-dose corticosteroids.[68] The inclusion of only long-term trials and the relatively small reduction in lung function decline may explain why the meta-analysis showed a significant benefit from treatment when individual trials did not. Well designed trials examining monotherapy with fluticasone propionate in COPD demonstrated improved lung function, a decrease in exacerbations and/or improved HR-QOL.[69-71]

A combination of a corticosteroid and a long-acting β_2-agonist is a convenient COPD treatment.[1] As well as simplifying drug administration, combining a long-acting β_2-agonist and a corticosteroid may provide some synergistic benefits relative to respective monotherapies.[1] Two inhaler formulations, each combining a long-acting β_2-agonist and a corticosteroid in a DPI, are approved in the EU for the symptomatic treatment of severe COPD with repeated exacerbations and symptoms despite regular bronchodilator therapy: twice-daily salmeterol/fluticasone propionate 50/500μg[9] and twice-daily formoterol/budesonide 160/4.5μg (two inhalations) or 320/9μg (one inhalation).[72] However, only salmeterol/fluticasone propionate 50/250μg twice daily is approved for the treatment of COPD in the US (section 6). Treatment with combination salmeterol/fluticasone propionate in one inhaler appears to provide some benefits over the same components in separate inhalers, perhaps because of increased compliance or promotion of synergistic benefits of the two drugs.[73]

Significant benefits from treatment with salmeterol/fluticasone propionate were demonstrated in large, well designed studies in COPD, which generally reported adjusted means. No studies compared twice-daily salmeterol/fluticasone propionate 50/500μg with 50/250μg. Salmeterol/fluticasone propionate 50/250μg or 50/500μg twice daily significantly improved FEV_1 versus placebo and monotherapy over 24 and 52 weeks (section 4.1.1), with improvements evident within 2 weeks.

Improvements in lung function were generally accompanied by improvements in dyspnoea in recipients of salmeterol/fluticasone propionate, but not always in monotherapy recipients, in whom improvements were numerically smaller. Supplementary salbutamol use by combined-therapy recipients was decreased versus placebo and, generally, versus fluticasone propionate (but not salmeterol) recipients (section 4.1.2). Combined therapy resulted in clinically significant improvements in CRDQ and SGRQ over 24 and 52 weeks (section 4.1.4).

Over 52 weeks, twice-daily salmeterol/fluticasone propionate 50/500μg significantly reduced exacerbations versus placebo, especially in patients with FEV_1 <50% predicted or exacerbations requiring oral corticosteroids (section 4.1.3). Pre-trial withdrawal from inhaled corticosteroids could have increased exacerbations in non-fluticasone propionate recipients in the clinical trials discussed in section 4, but overall exacerbation rates in at least one trial were lower than expected.[48]

In addition, the decrease in exacerbations with salmeterol 50μg monotherapy (and with fluticasone propionate 500μg monotherapy) was significant versus placebo. Over 24 weeks, twice-daily salmeterol/fluticasone propionate 50/250μg did not decrease exacerbations; however, this study was not designed to assess exacerbations. Further trials, ideally comparing twice-daily 50/500 and 50/250μg doses, and including studies of withdrawal from fluticasone propionate, are needed. It would be useful to compare the efficacy of, and withdrawal from, different treatment periods.

Improvements in lung function, dyspnoea and other symptoms were significantly greater with

twice-daily salmeterol/fluticasone 50/250μg than with four-times-daily salbutamol/ipratropium bromide 206/36μg (section 4.2).

The other currently available corticosteroid/β_2-agonist combination available (in the EU) in COPD, budesonide/formoterol 160/4.5μg (delivered dose) via DPI, was compared with corresponding monotherapies and placebo in a large, well designed, 12-month trial in patients with COPD.[74] The combination significantly reduced exacerbations versus formoterol monotherapy and placebo and increased FEV_1 significantly more than budesonide or placebo. PEF and COPD symptoms also decreased significantly versus budesonide and placebo; PEF and some symptoms improved significantly more than with formoterol. Tolerability was similar to that with placebo.[74] Although some pharmacodynamic studies have been undertaken, there are no published long-term clinical trials directly comparing budesonide/formoterol with salmeterol/fluticasone propionate.

Drug-related adverse events in clinical trials of twice-daily salmeterol/fluticasone propionate 50/500 and 50/250μg affected up to 20% of combined-therapy recipients (section 5). No significant increase in salmeterol-related cardiovascular adverse events was reported in clinical trials (section 5).

Long-term use of inhaled fluticasone propionate may reduce cortisol levels; this occurred at a supratherapeutic dosage in patients with COPD and at the recommended dosage in healthy volunteers (section 2.3), as well as in the TRISTAN trial (section 5), where changes were not considered clinically important and were transient in the combination therapy group.[48] The differences in fluticasone propionate pharmacokinetics, particularly absorption, between healthy volunteers and patients with COPD (section 3) may influence the post-treatment serum cortisol levels observed in different recipients (section 2.3).

Preliminary results showed no increase in fractures after fluticasone propionate treatment in one analysis.[62] COPD itself appears to be a risk factor for osteoporosis, regardless of corticosteroid exposure; bone density was significantly reduced in 483 patients with COPD in a double-blind, placebo-controlled study.[75] Further long-term studies in patients with COPD, including those receiving inhaled corticosteroids are needed to clarify this outcome.

Withdrawal of fluticasone propionate appears to cause exacerbations and general worsening of COPD (section 4.3). While corticosteroids may reduce exacerbations (perhaps via their effects on inflammatory mediators in susceptible patients), their withdrawal requires careful management.

Reducing mortality from COPD is a key treatment goal.[2] There is currently a lack of information from randomised, controlled studies on any possible effects of inhaled salmeterol/fluticasone propionate on hospitalisations or mortality in patients with COPD. Three large, retrospective, observational database analyses found significantly reduced mortality in recipients of salmeterol and fluticasone propionate (or any combined long-acting β_2-agonist and inhaled corticosteroid[76]), compared with recipients of other therapies.[76-78] These studies are subject to the usual limitations of observational studies, but were designed to minimise errors in disease classification and assessments of severity, as well as the biases arising from different drug exposures and compounding factors.

The placebo-controlled, 3-year TORCH (TOwards a Revolution in COPD Health) study, with a primary endpoint of all-cause mortality and secondary endpoints of exacerbations and HR-QOL, will assess the long-term effects of inhaled salmeterol/fluticasone propionate 50/500μg twice daily and corresponding monotherapies.[79]

In conclusion, in patients with moderate-to-severe COPD, twice-daily inhaled salmeterol/fluticasone propionate 50/250 or 50/500μg for 24–52 weeks improves predose FEV_1 significantly more than salmeterol monotherapy, improves postdose or postbronchodilator FEV_1 significantly more than fluticasone propionate monotherapy and results in clinically significant improvements in HR-QOL. Salmeterol/fluticasone propionate 50/500μg significantly reduced annual COPD exacerbations, especially in severe COPD. Some corticosteroid-related adverse events were increased in recipients of fluti-

casone propionate with or without salmeterol versus salmeterol monotherapy or placebo; withdrawal from fluticasone propionate, including combination therapy, needs careful management to minimise COPD exacerbations. The DPI combining a corticosteroid and long-acting β_2-agonist provides benefits over monotherapy and may encourage patient compliance in COPD.

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