Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide™ (50/250 μg bd Diskus™ vs. formoterol (12 μg bd) and budesonide (800 μg bd) given concurrently (both via Turbuhaler™) in patients with moderate-to-severe asthma

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Abstract  The aim of this study was to compare the efficacy, safety and cost of Seretide™ (salmeterol/fluticasone propionate (Salm/FP), 50/250 μg bd) via Diskus™ with formoterol (Form; 12 μg bd) and budesonide (Bud; 800 μg bd) given concurrently (Form+Bud) via Turbuhaler™ in patients with moderate-to-severe asthma who were uncontrolled on existing corticosteroid therapy. The study used a randomised, double-blind, double-dummy, parallel-group design, consisting of a 2-week run-in period on current corticosteroid therapy (1000–1600 μg/day of BDP or equivalent) and a 12-week treatment period. Symptomatic patients (n=428) with FEV₁ of 50–85% predicted and increased symptom scores or reliever use during run-in were randomly allocated to receive either Salm/FP (50/250 μg bd) via a single Diskus™ inhaler or Form+Bud (12+800 μg bd) via separate Turbuhalers™. Clinic, diary card and asthma-related health-care resource utilisation data were collected. Improvement in mean morning peak expiratory flow (PEF₃₃) was similar in the Salm/FP and Form+Bud groups. Both PEF₃₃ and mean evening PEF (PEFₑₚ) increased by a clinically significant amount (> 20 L/min) from baseline in both treatment groups. The mean rate of exacerbations (mild, moderate or severe) was significantly lower in the Salm/FP group (0.472) compared with the Form+Bud group (0.735) (ratio = 0.64; P < 0.001), despite the three-fold lower microgram inhaled corticosteroid dose in the Salm/FP group. Patients in the Salm/FP group also experienced significantly fewer nocturnal symptoms, with a higher median percentage of symptom-free nights (P = 0.04), nights with a symptom score < 2 (P = 0.03), and nights with no awakenings (P = 0.02). Total asthma-related health-care costs were significantly lower in the Salm/FP group than the Form+Bud group (P < 0.05). Both treatments were well tolerated, with a similar low incidence of adverse events. This study showed that in symptomatic patients with moderate-to-severe asthma, Salm/FP (50/250 μg bd), administered in a single convenient device (Diskus™), was at least as effective as an approximately three-fold higher microgram corticosteroid dose of Bud (800 μg bd) given concurrently with Form (12 μg bd) in terms of improvement in PEF₃₃ and superior at reducing exacerbations and nights with symptoms or night-time awakenings. Salm/FP was also the less costly treatment due primarily to lower hospitalisation and drug costs. © 2002 Elsevier Science Ltd. All rights reserved.

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Keywords Seretide™; salmeterol/fluticasone propionate; budesonide; formoterol; asthma; exacerbations; PEF; combination therapy.
INTRODUCTION

The addition of a long-acting β2-agonist (LABA) to an inhaled corticosteroid (ICS) is a recommended strategy for patients with persistent symptoms of asthma who remain inadequately controlled on existing corticosteroid therapy (1). It is now well established that this combination provides a greater improvement in lung function, exacerbations and symptom control than doubling the dose of inhaled corticosteroid in patients with persistent asthma (2–7).

In recognition of this, a combination therapy has been developed (Seretide™/Advair™/Viani™) which delivers 50 µg salmeterol xinafoate (Salm) in combination with 100, 250 or 500 µg fluticasone propionate (FP) in a single inhaler (Salm/FP). Previous studies have shown the Salm/FP combination to be as effective and well tolerated as treatment with salmeterol and FP given concurrently via separate Diskus™ inhalers (8–11), more effective than FP or salmeterol alone (11–13), and superior to higher doses of budesonide (Bud) alone (14,15). An alternative LABA/ICS therapy was examined by the FACET study (16), which showed that adding formoterol (Form) to Bud reduced asthma symptoms and exacerbation rate and improved lung function in patients with persistent asthma, but by less than using a four-fold higher dose of Bud alone (16).

Despite increasing evidence for the use of LABA/ICS combinations and their commercial availability comparative trials are lacking: this is the first to directly compare the efficacy and safety of two different combinations of LABA and ICS. Our comparison of Salm/FP 50/250 µg bd (via a single Diskus™ inhaler) with Form+Bud 12+800 µg bd (via separate Turbuhalers™) aimed to demonstrate similar efficacy between both treatments, but using less than one-third of the microgram steroid dose in the Salm/FP arm.

METHODS

Study design

This was a randomised, double-blind, double-dummy, parallel-group study. Patients attended clinic at the start of run-in (Visit 1), at the start of treatment (Visit 2, after 2 weeks of run-in), and at 4 (Visit 3), 8 (Visit 4) and 12 (Visit 5) weeks after the start of treatment. Between visits patients completed diary record cards (DRCs) with daily PEF and asthma symptom data. The run-in was used to determine patient baseline characteristics and confirm the need for additional treatment with LABAs. The study protocol was approved by the Ethics Committee at each study centre and was conducted according to good clinical practice (GCP) and in accordance with the declaration of Helsinki (1996). Each patient gave written informed consent before enrolment into the study.

Randomisation and blinding

A randomisation code was generated using the Glaxo Wellcome computer program 'Patient Allocation for Clinical Trials' (block size of 4) and non-overlapping sets of treatment numbers were allocated to each centre. Treatment numbers were allocated at Visit 2 in consecutive order, starting with the lowest number available at that centre. Numbered treatment packs of study drugs were labelled to ensure that both patients and investigators were blinded to the treatment allocation, and the randomisation codes were not revealed to investigators or other study participants until after recruitment, treatment, data collection and analyses were complete.

Study population

Patients were recruited in 11 European countries at primary care practices and hospital respiratory units. Male and female patients aged 16–75 years with a clinical history of reversible airways obstruction and who were symptomatic on 1000–1600 µg/day of Bud, beclomethasone dipropionate (BDP) or flunisolide (Flu), or 500–800 µg/day of FP, were recruited. Reversibility was defined as an increase in forced expiratory volume in one second (FEV1) of ≥15% from baseline, 15 min after inhaling 400 µg of salbutamol. Patients were excluded if they had changed their ICS dose or received oral corticosteroids, leukotriene modifiers or nasal corticosteroids (other than FP, permitted due to its low bioavailability (17)) in the 4 weeks before Visit 1, or any LABAs in the 2 weeks before Visit 1; had a recent history of upper or lower respiratory tract infection; were smokers with a history of 10 pack years or more; or had an acute asthma exacerbation within 1 month before Visit 1.

To be randomised to treatment at Visit 2, patients also had to have a predicted FEV1 of 50–85%, and either a symptom score (day and night combined, Table I) of ≥2 or use of salbutamol for symptomatic relief (not prophylaxis) on ≥2 occasions, on ≥4 of the last 7 evaluable days of the run-in period. This was to confirm that patients were symptomatic on ICS and so required more treatment, such as adding a LABA.

The only pre-defined reason for early withdrawal from the study was discontinuation of study drug, defined as intended permanent discontinuation or failure to take more than three consecutive doses at any time. Patients could withdraw freely or be withdrawn at an investigator’s discretion at any time.

Treatment

During the run-in patients continued on their pre-study ICS without change of dose. At Visit 2, all eligible patients
were randomly assigned to one of the following treatment groups for 12 weeks:

- Salm/FP (50/250 µg bd) via Diskus™ inhaler and two placebo Turbuhalers™ (bd).
- Form (12 µg bd) and Bud (800 µg bd) via two Turbuhalers™ and placebo via Diskus™ (bd).

The dose of Bud was chosen to maintain the anti-inflammatory treatment of patients on the highest inclusion criteria doses at the same level, while the dose of Form was that used in the FACET study. The dose of Salm/FP selected was the middle strength and from previous studies of the individual components was considered likely to provide non-inferior efficacy to these doses of Form+Bud.

Patients were instructed to take one inhalation from each inhaler in the morning and evening, using the Diskus™ first, followed by the two Turbuhalers™, with no more than 2 min to elapse between each inhaler. Placebo devices were rendered externally identical to active ones by relabelling but contained no active contents, only lactose (Diskus™) or desiccant (Turbuhaler™). Salbutamol (delivery device according to individual preference) was provided as relief medication on an “as required” basis.

**Primary efficacy measure**

The primary efficacy measure was mean PEF<sub>am</sub> over the week prior to the end of treatment (Week 12). Patients recorded on DRCs the highest of three readings using a Mini-Wright peak flow meter before taking any rescue and/or study medication.

**Secondary efficacy measures**

Secondary efficacy measures included: PEF<sub>am</sub> and PEF<sub>pm</sub> at other timepoints; PEF % diurnal variation, clinic FEV<sub>1</sub>; rate and severity of exacerbations; day- and night-time symptom scores; night-time awakenings; use of rescue salbutamol; withdrawals from the study; and asthma-related health-care resource utilisation.

**Lung function**

PEF<sub>am</sub> and PEF<sub>pm</sub> were recorded on DRCs as above and the mean calculated over the 12 weeks of treatment. FEV<sub>1</sub> (the highest of three technically acceptable measurements) was measured at each clinic visit. If possible, patients withheld salbutamol for at least 6 h before each clinic visit and did not take their study medication on that morning.

**Exacerbations**

The occurrence and severity of asthma exacerbations (mild, moderate or severe) were assessed by physicians reviewing DRC entries and taking patient histories at clinic visits. The definitions used are given in Table 2 and are mostly similar to those in FACET, although exacerbations defined as severe in FACET were classed as moderate in this study and the term “severe” used for exacerbations requiring emergency hospital treatment.

**Symptom, awakenings and relief medication**

Symptom scores were recorded by patients every morning and evening on DRCs using the scales in Table 1. The number of awakenings and the number of occasions on which rescue salbutamol was taken were also recorded in the DRCs on a daily basis.

**Health-care resource utilisation**

Unscheduled asthma-related health-care resource utilisation data were collected throughout the study. These were defined as events occurring as a result of a patient’s asthma that required additional intervention by a healthcare professional, including asthma-related in-patient hospitalisations, emergency room visits, specialist outpatient consultations and contacts with primary-care physicians. Protocol-driven visits and routine clinic attendance were excluded from the analysis. Data were collected from all patients and costed from the perspective of the Norwegian health-care system (using unit costs at 1999 prices, when most patient visits took

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Day</td>
<td>No symptoms during the day</td>
</tr>
<tr>
<td>1</td>
<td>Symptoms for one short period during the day</td>
</tr>
<tr>
<td>2</td>
<td>Symptoms for two or more short periods during the day</td>
</tr>
<tr>
<td>3</td>
<td>Symptoms for most of the day which did not affect my daily activities</td>
</tr>
<tr>
<td>4</td>
<td>Symptoms for most of the day which did affect my normal daily activities</td>
</tr>
<tr>
<td>5</td>
<td>Symptoms so severe that I could not go to work or perform normal daily activities</td>
</tr>
<tr>
<td>Night</td>
<td>No symptoms during the night</td>
</tr>
<tr>
<td>1</td>
<td>Symptoms causing me to wake once or to wake early</td>
</tr>
<tr>
<td>2</td>
<td>Symptoms causing me to wake twice or more (including waking early)</td>
</tr>
<tr>
<td>3</td>
<td>Symptoms causing me to be awake for most of the night</td>
</tr>
<tr>
<td>4</td>
<td>Symptoms causing me to be awake for most of the night</td>
</tr>
<tr>
<td>5</td>
<td>Symptoms so severe that I did not sleep at all</td>
</tr>
</tbody>
</table>
place) as this was the highest-recruiting country. Total health-care costs were calculated for each treatment arm and reported as mean and median costs per patient per day. Conversion to U.S. dollars was at the rate of U.S. $1=7.797 Norwegian Krone, current at the time of the analysis.

Safety assessment

An adverse event (AE) was defined as any untoward medical occurrence irrespective of causality. All AEs were classified by the investigator as serious or non-serious, and the cause assessed as unrelated, unlikely, possibly, probably or almost certainly related to the study drugs. All AEs were documented. Withdrawals from the study were also recorded and classified according to cause. Patients were instructed to take suitable contraceptive precautions where appropriate and any pregnancies were followed beyond the birth to determine the outcome.

Statistical analyses

The pre-defined primary objective was to demonstrate that Salm/FP 50/250 μg bd was non-inferior to Form 12+Bud 800 μg bd. This was defined as the lower limit of the 95% confidence interval (CI) for the difference in mean PEF_{am} over week 12 being −15 L/min or above. Assuming a residual standard deviation (σ) of 50 L/min for PEF_{am} in either treatment group, a total of 470 evaluable patients (235 per group) was expected to provide approximately 90% power for assessing this.

Analysis of primary and secondary efficacy measures was based on the intent-to-treat (ITT) population. For mean PEF_{am}, only, the analysis was repeated on the per-protocol population. Mean PEF_{am}, PEF_{pm} and clinic FEV_{1} were all analysed by analysis of covariance, adjusting for age, sex, country of recruitment and baseline value. For PEF the mean over week 2 of the run-in was used as a baseline value. Analysis of exacerbations was based on a Poisson model, adjusting for age. By way of a sensitivity analysis, the model was refitted with exacerbations beyond the sixth for any given individual disregarded. Health-care resource utilisation over the 12 week treatment period was compared using the method of Hodges–Lehmann to construct a 95% CI. Other secondary efficacy measures were analysed using the Wilcoxon rank sum test, adjusted for country of recruitment by the van Elteren method. Treatment differences for these measures were calculated as the median of all the pairwise differences with the 95% CIs calculated using the Hodges–Lehman method. Safety measures were presented as summary statistics.

RESULTS

Of the 520 patients recruited, 428 were randomised to treatment (212 to Salm/FP, 216 to Form+Bud). After randomisation 49 patients (23 Salm/FP, 26 Form+Bud) were withdrawn before completing treatment, but all were included in the ITT analysis (Fig. 1). Fifty patients (29 Salm/ FP, 21 Form+Bud) were judged to be protocol violators prior to unblinding treatment allocation, mainly due to taking non-study doses of corticosteroids or excluded drugs during the run-in period. Patient baseline characteristics, including number of patients taking each steroid at randomisation and the mean dose, are given in Table 3. The treatment groups were well matched at baseline, with the exception of higher median night-time awakenings in the Form+Bud group (night-time symptom scores were the same, however). Mean exposure to study treatments (σ) was 79 (17.6) days on Salm/FP and 79 (17.8) days on Form+Bud, with almost 90% of patients exposed for 77 days (11 weeks) or above.

Primary efficacy measure (Week 12 PEF_{am})

Mean PEF_{am} in the per protocol population increased from 343 L/min at baseline to 386 L/min over Week 12 in the Salm/FP group (\( \psi = 157 \)) and from 348 L/min to 389 L/min in the Form+Bud group (\( \psi = 167 \)). The difference between the two over week 12 was −3.2 L/min (95%CI −15.0, 8.6; \( p = 0.593 \)). Similar mean increases from
baseline were seen in the ITT population (43 L/min on Salm/FP and 47 L/min on Form+Bud).

Secondary efficacy measures

Lung function at other timepoints

Both combinations produced similar increases in PEF_{am} over the whole of treatment (Fig. 2). They were also similar over the first 7 days, with non-significant differences of 0.7 L/min on Day 1 (95% CI = −7.2, 8.6) and 0.3 L/min on Day 7 (95% CI = −8.2, 8.9) (n = 196–204). Mean PEF_{pm} followed a similar pattern to PEF_{am}.

Median percent diurnal variation in PEF decreased from 7.8% at baseline to 4.7% over Month 3 on Salm/FP (n = 187) and from 8% at baseline to 5.1% on Form+Bud (n = 192) (difference = −0.3, 95% CI = −1.0, 0.3; P = 0.295). Mean clinic-measured FEV1 increased from 2.18 l at baseline to 2.45 l after 12 weeks of Salm/FP (n = 189), and from 2.20 l to 2.46 l on Form+Bud (n = 194) (difference at 12 weeks = −0.01 l; 95% CI = −0.09, 0.07; P = 0.796).

Exacerbations

The total number of asthma exacerbations during treatment was considerably lower on Salm/FP than on Form+Bud (129 vs. 206) (Fig. 3). The corresponding figures for the run-in period were 42 (Salm/FP) and 49 (Form+Bud). The mean rate of exacerbation (mild, moderate or severe) per patient per 84 days of treatment, according to the Poisson model, was significantly lower on Salm/FP (0.472; n = 211) than on Form+Bud (0.735; n = 215) (ratio = 0.64; 95% CI = 0.51, 0.80; P < 0.001), corresponding to a 36% risk reduction. This difference in favour of Salm/FP was largely maintained (31% risk reduction) even when the effect of outliers was reduced by censoring the number of exacerbations per patient at 6 (0.473 vs. 0.686; ratio = 0.69; 95% CI = 0.55, 0.87; P = 0.002), indicating that the difference was not driven strongly by outlying values.

Symptoms, awakenings and relief medication

Patients in the Salm/FP group experienced a significantly higher percentage of nights without awakenings (difference = 4.9; 95% CI = 0.0, 12.0; P = 0.02), without symptoms (difference = 2.7; 95% CI = 0.0, 8.4; P = 0.04), and with a symptom score < 2 (difference = 0.0; 95% CI = 0.0, 1.2; P = 0.03) than patients in the Form+Bud group over the 12 weeks of treatment (Fig. 4). The distribution of the percentage of patients with each
percentage rate of response (over the 12 weeks of treatment) is presented in Fig. 5. When the night-time awakenings analysis was re-run with baseline rather than country as the adjusting factor (to test whether an apparent baseline difference between treatments [median 28.6% Salm/FP vs. 16.7% Form+Bud] had influenced the results) the P-value changed from 0.02 to 0.01 in favour of Salm/FP. As night-time awakenings was one of the measures used to define exacerbations, the effect of baseline awakenings on exacerbation rates was also assessed. To account for the apparent baseline imbalance, a sensitivity analysis adjusting for night-time awakenings was performed that confirmed the significance of the main results (P < 0.001). A significant reduction in the number of night-time awakenings was present even over the first month of treatment (difference = 3.7; 95% CI = 0.0, 14.3; P = 0.02 whether stratified by country or by baseline). Patients in both groups showed similar improvements in day-time symptoms and similar use of relief salbutamol, with no significant differences.

**Asthma-related health-care resource utilisation**

There were more than twice as many in-patient hospital days and unscheduled specialist visits in the Form+Bud group compared with the Salm/FP group, while the Salm/FP group had a higher number of primary-care visits (Table 4).

Total asthma-related health-care costs were significantly lower in the Salm/FP group. Mean cost per patient per day was 15.60 Norwegian Krone (NOK) (approximately U.S.$2.00; median = 13.32 NOK) in the Salm/FP group compared with 23.79 NOK (U.S.$3.02; median = 18.26 NOK) in the Form+Bud group (Fig. 6). The
between group median difference was $-4.84$ NOK (95% CI = $-4.97, -4.76$; $P < 0.05$), indicating a median daily direct cost saving per patient per day of $4.84$ NOK (U.S.$0.57$) on Salm/FP relative to Form+Bud (95% CI 4.76, 4.97 NOK). This was primarily due to the lower study drug costs of Salm/FP (12.84 NOK/day) compared with Form+Bud (17.57 NOK/day), and the lower costs of asthma-related hospitalisations in the Salm/FP group (1.40 NOK/day, vs. 4.95 NOK/day in the Form+Bud group).

**Safety measures**

Both treatments were well tolerated throughout the study. Patients in the Salm/FP group reported 91 adverse events (AEs) compared with 78 in the Form+Bud group. The most common AE was “upper respiratory tract infection”, which was reported 26 times on Salm/FP and 18 times on Form+Bud. Only one AE caused 1% or more of...
patients to withdraw, which was “asthma” (asthma resurgence/loss of asthma control) in 6/216 (3%) of the Form+Bud group and 1/212 (<1%) of the Salm/FP group. Eighteen AEs in the Salm/FP group and 23 in the Form+Bud group were considered by investigators to be possibly drug related, the most common of which were: candidiasis of the mouth and throat (1 Salm/FP, 9 Form+Bud), hoarseness/dysphonia (6 Salm/FP, 2 Form+Bud), throat irritation (4 Salm/FP, 1 Form+Bud), worsening of asthma control (4 Form+Bud), tremors (3 Form+Bud), tachycardia (3 Salm/FP), and muscle cramps and spasms (3 Form+Bud). Two throat swabs from Salm/FP patients were culture positive for Candida species (both at randomisation) and 10 from Form+Bud patients (four at randomisation, six during treatment).

There was one serious AE reported during the run-in (exacerbation of asthma) and five reported after randomisation: two in the Salm/FP group (one exacerbation of asthma; one polymyalgia) and three in the Form+Bud group (one exacerbation of asthma; one pneumonia; one chest symptoms). One of these (polymyalgia; Salm/FP group) was considered to be possibly related to therapy. No birth defects were reported for either of the two pregnancies during the study (both in the Salm/FP group).

**DISCUSSION**

The superiority of the Salm/FP combination over a higher microgram steroid dose of Bud in improving PEF_{am} in mild-to-moderate (14) and moderate-to-severe (15) asthmatics, and of adding salmeterol (3,7) or formoterol (16) to ICS over increasing the steroid dose, has lead international asthma treatment guidelines to progressively adopt combination therapy with LABA and ICS. Variations in study design and patient characteristics have made comparison of the different LABA/ICS combinations difficult, however, so it has become increasingly important to evaluate the different combinations within a single study.

Our study is the first large-scale comparison of different LABA/ICS combinations to be reported. We showed that in patients with symptomatic moderate-to-severe asthma Salm/FP produced similar improvements in PEF_{am}, PEF_{pm} and FEV_{1} to Form+Bud containing three times the microgram corticosteroid dose from the first day of treatment. Patients on Salm/FP also experienced a significantly reduced rate of exacerbations compared with Form+Bud, and significantly fewer nights with symptoms or awakenings. Salm/FP was also significantly less costly than Form+Bud, mainly due to fewer hospitalisations and lower drug costs. The safety profile was good on both treatments and comparable to previous studies, with oropharyngeal candidiasis the most common drug-related adverse event.

Despite the difference in steroid dose used we found that Salm/FP was at least as effective as Form+Bud in improving mean PEF_{am}. Similar results were seen for PEF_{pm} and FEV_{1} although these were not formally tested for non-inferiority. Both treatments produced clinically significant improvements from baseline in all three parameters, indicating that combination therapy can improve lung function even in patients already receiving moderate-to-high corticosteroid doses (in the case of Salm/FP, at a lower mean steroid dose than baseline). Previous work has shown that salmeterol can improve lung function while allowing reduction of the steroid dose (18) while in a meta-analysis, FP at half the microgram dose of Bud or less was significantly more effective than Bud in improving mean PEF_{am} irrespective of delivery device (19). The non-inferiority in PEF_{am} despite the difference in steroid dose may therefore have been a consequence of differences in either the β_{2}-agonist or steroid components or both.

Asthma exacerbations cause extensive morbidity, elevated health-care costs and sometimes mortality (20) and so are of prime importance in assessing the efficacy of a treatment. In patients with persistent asthma adding salmeterol to FP reduced the rate and severity of exacerbations by more than doubling the dose of FP (21), whereas in the FACET study, adding Form to Bud (100 µg bd) was less effective at reducing the rate of (severe) exacerbations than taking a four-fold higher dose of Bud (400 µg bd) (16). These studies are not directly comparable, however, as the definitions of exacerbations used were different, and FACET-stabilised patients on a high dose of steroid (800 µg bd) then dropped the dose significantly (to as little as one-eighth), which is not typical clinical practice and may lead to unusually high levels of exacerbation. In our study, using similar definitions to those in FACET and the same add-on therapy design for both treatments, Salm/FP significantly reduced the rate of exacerbations by over one-third compared with concurrent Form+Bud.

This might be attributable to both the ICS and LABA components of Salm/FP. As asthma exacerbations are associated with increased eosinophilic inflammation (22,23) and FP is a more potent inhibitor of eosinophil survival than Bud (24,25), part of the difference may be due to this. In addition, although both salmeterol and formoterol inhibit many processes involved in lung inflammation (26–31), salmeterol has a concentration-independent duration of action, resists superfusion and persists at the β_{2}-adrenoceptor for longer than formoterol (32,33), while the duration of action of formoterol is affected by its concentration (34). These pharmacological differences may be clinically relevant over a 12 h treatment period. Taken together this suggests that, at the doses studied, the combination of salmeterol with FP is more effective than that of formoterol with BUD with respect to the prevention of exacerbations.
Symptoms and night-time awakenings have a substantial negative impact on quality of life (35,36). In our study Salm/FP gave significantly better nocturnal asthma control than Form+Bud, with patients experiencing significantly fewer nights with awakenings or symptoms. As with exacerbations, this improved nocturnal control may in part be due to the pharmacological differences discussed above. The dose-dependent duration of formoterol (34) might have allowed patients in the Form+Bud group to experience “break-through” nocturnal symptoms. The superior efficacy of FP compared with Bud with respect to lung function and symptoms has not been observed when treating fever oropharyngeal candidiasis, which was more common on Form+Bud and probably resulted from the higher steroid doses and the significant post-randomisation improvement in both groups suggests that neither was previously ever-treated with ICS and that the non-inferiority of Salm/FP was not simply due to lack of scope to see any differences, particularly as Salm/FP showed superiority in a number of other endpoints. Recruitment was from a mixture of primary and secondary care sites (roughly half of the patients from each), suggesting that our findings would be applicable to a range of health-care delivery settings.

We compared combination Salm/FP with concurrent Form+Bud, but recently a combination of Form+Bud in one device has become available (6 μg Form/200 μg Bud), with a current maximum daily dose of Form 24 μg/Bud 800 μg. Previous experience with Salm/FP (39) has shown that the combination in one device is significantly better than concurrent therapy, suggesting a possible synergistic effect of the two drugs. Recent data on the Form+Bud combination suggest that this was not the case there (40), however, and the dose of Bud used was lower than the one studied here, although the dose of Form was the same. There is nothing to suggest that the main conclusions from our study would not also apply to the Form+Bud combination given twice daily at its current maximum dose, although that would have to be confirmed by another study.

Our study is the first to compare two different inhaled corticosteroid and long-acting β2-agonist therapies, one given in combination and the other concurrently. It found that patients treated with Salm/FP 50/250 μg bd experienced significantly fewer exacerbations and night-time symptoms than those on Form+Bud 12+800 μg bd (who received three times the microgram corticosteroid dose) while achieving similar PEF and FEV1 values, indicating that similarity in lung function may not preclude important benefits in other areas. Our results suggest that patients symptomatic on inhaled corticosteroid alone experience important
Acknowledgements

Funding for the study (protocol number: SAS40002/SERL05) was provided by Glaxo Wellcome Research and Development. We thank Dr Ruth B. Murray for writing and editing assistance during the preparation of this manuscript. We thank the following investigators of the EDICT study group for their invaluable input during the running of this study: Dr W. Wanka, Dr I. Schiller-Freuhhich, Dr A. Schuhliehm, Dr H. Artner (Austria); Dr J. Auermann, Dr J. Benoit Martinot, Dr I. Monsieur, Dr O. Van Cutsem (Belgium); Dr D. Plavec, Prof. F. Pavičić (Croatia); Dr L. Laursen, Dr E. Frausing, Dr V. Backer, Dr N. Hyldebrandt, Dr J. Korsgaard (Denmark); Dr K. Järvinen, Dr K. Tamminen, Dr O. Suohonen, Dr K. Ämmäälä (Finland); Dr W. Feussner, Dr R. Gebhardt, Dr H. Leiner, Dr U. Reinert, Dr M. Rolke, Dr R. Schnorr, Dr G. Scholz, Dr K-M. Schussman (Germany); Dr P. Grandi, Prof. M. Polverino (Italy); Dr O. Horgen, Dr A. Eivindson, Dr K. Risberg, Dr O. Rystad (Norway); Prof. A. Tsou (Russia); Dr J. Komada, Dr R. Benedik (Slovakia); Dr M. Barnard, Dr S. Bassett, Dr M. Blagden, Dr R. Gwilym Bowen, Dr H. Charles, Dr C. Clayton-Payne, Dr A. Darragh, Dr E. Davies, Dr M. Doyle, Dr S. Fearns, Dr A. George, Dr B. Glancy, Dr S. Holgate, Dr M. Johnson, Dr S. Jones, Dr C. Kyle, Dr P. Lowry, Dr J. McBride, Dr A. McFarland, Dr H. McGoldrick, Dr K. Millar, Dr N. Sinclair, Dr K. Thompson, Dr A. Williams, Dr W. Wilson (UK.). The study was previously presented at the American Thoracic Society Meeting: 2000 May 5–10; Toronto, Canada, the European Respiratory Society Congress; 2000 August 30–September 3; Florence, Italy, and the American Thoracic Society Meeting; 2001 May 18–23; San Francisco, U.S.A. Abstracts were published in Am J Respir Crit Care Med 2000; 161(3 part 2 Suppl. I): A196; Eur Resp J 2000; 16 (Suppl 31): 353s; and Am J Respir Crit Care Med 2001; 163: A866. Seretide™/Advair™/Viani™ and Diskus™/Accuhaler™ are trademarks of the GlaxoSmithKline group of companies. Turbuhaler™ is a trademark owned by Astrazeneca.

REFERENCES


