Effect on lung function and morning activities of budesonide/formoterol versus salmeterol/fluticasone in patients with COPD

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Abstract:
Background: Patients with chronic obstructive pulmonary disease (COPD) often experience symptoms and problems with activities early in the morning. This is the first study to compare the effect of budesonide/formoterol and salmeterol/fluticasone on lung function, symptoms and activities early in the morning.

Methods: Lung function [peak expiratory flow [PEF] and forced expiratory volume in 1 second [FEV1]] and symptoms were measured at bedtime and activities were measured during the morning using a six-item questionnaire concerning basic morning routines. In a randomised, double-blind, multicentre, cross-over study, 442 patients with COPD aged \( \geq 40 \) years (pre-bronchodilator FEV1 \( \leq 50\% \); FEV1/vital capacity <70\%) received budesonide/formoterol (320/9 \( \mu \)g, one inhalation twice daily) dry powder inhaler (DPI) or salmeterol/fluticasone (50/500 \( \mu \)g, one inhalation twice daily) DPI daily, for 1 week each, separated by a 1- to 2-week washout. Lung function [PEF and FEV1] shortly after rising from bed in the morning, symptoms and basic morning activities were assessed by electronic diary (e-Diary) recordings.

Results: Budesonide/formoterol and salmeterol/fluticasone treatment increased morning PEF 5 minutes post-dose, measured as a mean improvement from baseline over the full study period (primary endpoint; adjusted mean change: 15.1 l/min and 14.2 l/min, respectively [difference 1.0 l/min; \( p = 0.603 \)]. Mean morning FEV1 improved more following budesonide/formoterol treatment versus salmeterol/fluticasone at 5 minutes (0.12 l versus 0.09 l; \( p = 0.090 \)) and 15 minutes (0.14 l versus 0.10 l; \( p < 0.05 \)) post-dose. Budesonide/formoterol demonstrated a more rapid onset of effect as reflected by increases in e-Diary-recorded PEF and FEV1 from pre-dose to 5 and 15 minutes post-dose (all \( p < 0.001 \)) and spirometry at the clinic measured after the first dose [FEV1 \( p < 0.001 \); 5 minutes post-dose]. Improvements in symptom scores within 15 minutes after drug administration were similar for both drugs, but budesonide/formoterol treatment resulted in significantly greater improvements in total morning activities score (getting washed, dried, dressed, eating breakfast and walking around the home; 0.22 versus 0.12 respectively, \( p < 0.05 \)). Both treatments were well tolerated.

Conclusions: Short-term treatment with budesonide/formoterol DPI or salmeterol/fluticasone DPI was effective in patients with COPD. Budesonide/formoterol had a more rapid onset of effect compared with salmeterol/fluticasone and resulted in greater improvements in ability to perform morning activities despite the lower inhaled corticosteroid dose.

Keywords: budesonide/formoterol, COPD, morning activities, salmeterol/fluticasone, tolerability

Introduction
Chronic obstructive pulmonary disease (COPD) is characterised by a progressive decline in lung function and an increase in symptoms such as dyspnoea, cough and sputum production [Global Initiative for Chronic Obstructive Lung Disease, 2008, http://www.goldcopd.com accessed July 2009]. Patients with COPD may
also experience activity limitation, which becomes more problematic as the disease advances. In addition, during the more advanced stages of the disease, exacerbations increase in severity and frequency, leading to a further decline in patient quality of life, activities relating to daily living as well as overall well-being [Global Initiative for Chronic Obstructive Lung Disease, 2008]. Exacerbations have, importantly, been a major focus of COPD management; however, a more comprehensive understanding of the impact of this disease on patients’ day-to-day life is warranted and may provide further opportunity for better-targeted strategies and patient-centred care.

Increasing clinical experience reveals that, similar to asthma, patients with COPD may experience diurnal variation in lung function: forced expiratory volume in 1 second (FEV₁); forced vital capacity; peak expiratory flow (PEF); and symptoms (fatigue, dyspnoea) [McCarley et al. 2007; van Noord et al. 2006; Calverley et al. 2003b; Postma et al. 1985]. This is further supported by data indicating symptoms such as dyspnoea, as well as patients’ abilities to perform morning activities, are particularly problematic for patients with COPD in the morning compared with other times of the day [Partridge et al. 2009; Partridge and Karlsson, 2008].

While the ultimate aim is disease prevention, one of the main goals of effective COPD management, once COPD has been diagnosed, is to achieve optimal COPD control for the patient by relieving symptoms; improving lung function, patients’ ability to undertake activities of daily living and quality of life (i.e. addressing their present best control); and reducing future risk of exacerbations, decreasing the decline in lung function and health status and reducing long-term side effects. For patients with more severe COPD, defined as having an FEV₁ <50% predicted, current guidelines recommend treatment with a combination of inhaled corticosteroid (ICS) and a long-acting β₂-agonist (LABA), due to their improved efficacy when combined over the individual components alone [Global Initiative for Chronic Obstructive Lung Disease, 2008; National Institute for Clinical Excellence, 2004].

There are currently two fixed-dose ICS/LABA combinations available for the treatment of COPD: budesonide/formoterol (Symbicort™, AstraZeneca, Lund, Sweden) and salmeterol/fluticasone (Seretide™, GlaxoSmithKline, Greenford, UK). A number of large, randomised, double-blind clinical studies have demonstrated their benefits in patients with COPD with respect to improving lung function and reducing the number of exacerbations compared with placebo or monotherapy [Calverley et al. 2007; Calverley et al. 2003a, 2003c; Szafranski et al. 2003].

Collectively, patients’ insights into living with COPD have highlighted the importance of being able to engage in activities, particularly in the morning, and how the speed of symptom relief is central to their treatment expectations [Miravitlles et al. 2007; Williams et al. 2007]. Formoterol has been shown to have an onset of effect that is comparable to the short-acting β₂-agonist salbutamol and more rapid than salmeterol, in patients with COPD [Lindberg et al. 2007]. Improvements in lung function have been shown to be evident as early as the first day of treatment with budesonide/formoterol, suggesting that this combination has a rapid onset of effect [Szafranski et al. 2003]. Taken together, a question that remains to be answered is whether the more rapid onset of effect of budesonide/formoterol compared with salmeterol/fluticasone would give patients with COPD a better start in the morning, measured as greater improvements in morning lung function, morning symptoms and morning activities. To address this question, a study to evaluate the effect of budesonide/formoterol compared with salmeterol/fluticasone was conducted, examining effects on lung function, symptoms measured at the bedside and results from a morning activities questionnaire.

Methods

Patients

Patients with COPD ≥40 years of age, with a clinical diagnosis of COPD, with symptoms for at least 2 years, at least one COPD exacerbation requiring oral steroids and/or antibiotics in the previous 12 months, being current or previous smokers with a smoking history of at least 10 pack-years, FEV₁ ≤50% of predicted normal value and FEV₁/vital capacity <70% pre-bronchodilator and who had previously used a short-acting bronchodilator (β₂-agonist or anticholinergic) as reliever medication were recruited. This population is similar to COPD patient populations in other ICS/LABA studies [Szafranski et al. 2003].
The main exclusion criteria included a current respiratory infection, a history of seasonal rhinitis before 40 years of age, a history of asthma, an exacerbation of COPD within 4 weeks prior to or during the run-in period requiring hospitalisation, a course of oral corticosteroids and/or ICS and/or antibiotics, or significant or unstable cardiovascular disease. LABAs were withdrawn before entry to the run-in period, but ICS treatment was allowed during both the run-in and the washout period, if used before the study. Terbutaline was provided as a reliever medication throughout the study period.

**Study design**

This was a randomised, double-blind, double-dummy, cross-over study (ClinicalTrials.gov identifier: NCT00542880) with two 1-week treatment periods, conducted in 66 centres in nine countries: Argentina (five centres), Australia (seven centres), Belgium (three centres), Brazil (nine centres), Denmark (eight centres), Germany (eight centres), India (four centres), Philippines (six centres) and the United Kingdom (16 centres) (Figure 1). The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written, informed consent was obtained from all patients. The study was approved by local research ethics boards for all sites.

Following enrolment (Visit 1), baseline pulmonary function tests and physical examinations were performed and eligible patients entered a 1-week run-in period (Visits 2–3) during which their regular COPD medications were withdrawn with the exception of ICS. Following run-in, eligible patients were randomised to the treatment sequence. The randomisation schedule was computer-generated at AstraZeneca, Lund, Sweden.

For each treatment period (Visits 3–4 and Visits 5–6) patients received, according to their randomised treatment sequence, one inhalation twice daily of either budesonide/formoterol (320/9 µg; Symbicort Turbuhaler®,¹) plus placebo by Diskus™ (GlaxoSmithKline, Greenford, UK) or salmeterol/fluticasone (50/500 µg; Seretide Diskus, GlaxoSmithKline, Greenford, UK) plus placebo by Turbuhaler. The treatment periods were separated by a 1–2-week washout period during which the patients used their prescribed ICS in the same manner as during the run-in period. Terbutaline 0.5 mg/inhalation (Bricanyl® Turbuhaler, AstraZeneca, Lund, Sweden) was prescribed as reliever medication throughout the study.

**Outcome measures**

Lung function in the morning was assessed via PEF and FEV₁ at home shortly after rising from bed, both before and after drug

¹Symbicort® and Turbuhaler® are trademarks owned by AstraZeneca. The Symbicort dry powder formulation Turbuhaler is not currently approved in the US.
administration by peak flow meter (Esense™, Piko®, PHT Corporation Sarl, Geneva, Switzerland). The patient was instructed to perform at least three measurements and the highest recording was transmitted wirelessly to an electronic diary (e-Diary). For standardisation reasons, patients were instructed to complete the assessments without interruption and measurements were conducted within 30 minutes after getting out of bed, but before bathing, showering or washing, and before getting dressed and having breakfast. The primary endpoint was PEF 5 minutes post-morning dose, evaluated as the change between the mean value from the baseline/wash-out period to the mean over the 1-week treatment period.

The secondary outcome variables included PEF and FEV₁ before as well as at 5 and 15 minutes after morning dose and before evening dose, all measured at home. Before each lung function measurement in the morning at 5 and 15 minutes post-dose, symptoms were assessed using the Global Chest Symptoms Questionnaire (GCSQ) consisting of two questions (Box 1A). Morning activities such as getting bathed, dried, dressed, eating breakfast and walking around the house were assessed using a second questionnaire, the Capacity of Daily Living during the Morning (CDLM) questionnaire; the CDLM questionnaire was assessed in the morning after all morning activities were completed (Box 1B).

The responses were recorded in the e-Diary. The GCSQ and CDLM questionnaire have both demonstrated good internal consistency, test/retest reliability and validity, and have reported minimal important differences (MID) of 0.15 and 0.20, respectively (data on file).

In addition, spirometry was measured in the clinic at Visits 3 and 5, clinical control was assessed using the self-administered Clinical COPD Questionnaire (CCQ) [Van der Molen et al. 2003] in the evening before intake of study medication, reliever medication use was recorded throughout the study period and the modified St George’s Respiratory Questionnaire for COPD patients (SGRQ-C) was completed at the beginning and end of the treatment period [Meguro et al. 2007]. All of the above endpoints were recorded in the e-Diary. Patients received training and written and verbal instruction (Visit 2, start of run-in) on how to fill in the e-Diary and handle the device, and were informed that electronic recordings could not be carried out retrospectively or prospectively, but only during prespecified time slots.

**Tolerability**

Tolerability was evaluated at each clinic visit by documenting all adverse events and vital signs (pulse and blood pressure).

**Statistical analysis**

All efficacy and safety analyses were for the intention-to-treat population (all patients receiving at least one dose of the randomised study medication). The statistical analyses of e-Diary data were based on period means. For each variable and patient, four means (arithmetic averages) were calculated over the two treatment periods and over the last 7 days of the run-in and washout periods. The primary variable (the change in average e-Diary-recorded PEF from the last 7 days of the run-in period and the washout period, respectively, to 5 minutes post-dose over the whole subsequent treatment period) was analysed by analysis of variance (ANOVA) using a model with patient, treatment, period and treatment order as factors and the pretreatment average as a covariate. The other variables recorded in the e-Diary (e-Diary PEF, e-Diary FEV₁, use of reliever medication, morning activities questionnaire, symptoms questionnaire and CCQ) were analysed in a similar way as for the primary variable. Onset of effect (i.e. the mean changes from pre-dose to 5 and 15 minutes post-dose in

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**Box 1. Patient-reported outcomes questionnaires.**

**A: Global Chest Symptoms Questionnaire (GCSQ)**

1. How short of breath are you feeling right now?
2. How tight does your chest feel right now?

**B: Capacity of Daily Living during the Morning (CDLM) questionnaire**

Thinking of your chest condition:

1. Did you wash yourself this morning other than your face (i.e. body wash, shower or bath)?
2. Did you dry yourself with a towel after washing this morning?
3. Did you get dressed this morning?
4. Did you eat breakfast this morning?
5. Did you walk around your home this morning after taking your medicine?
6. Did you walk around your home later this morning?

[(A) The GCSQ consisted of two questions on symptoms. Patient responses were: not at all, a little, moderately, very, or extremely.
(B) The CDLM questionnaire consisted of six questions. If the patient answered ‘Yes, I did it by myself’ (question 1–3) or ‘Yes, I did’ (question 4–6), the question was followed by: ‘How difficult was it to complete the activity?’ (patient responses: not at all, a little, moderately, very or extremely). Each item in the CDLM questionnaire was scored on a scale ranging from 0 (so difficult that the activity could not be carried out by the patient themselves) to 5 (activity not at all difficult to carry out).]
e-Diary PEF and e-Diary FEV$_1$) was analysed using a multivariate ANOVA with the pre-dose mean as baseline with patient, treatment, period and treatment order as factors, and the mean morning value from run-in as covariate. Adverse events were analysed by means of descriptive statistics and qualitative analysis.

**Results**

**Patients**

Enrolment began in September 2007 and the last subject completed in August 2008. A total of 706 outpatients with COPD were recruited from 66 centres across nine countries, of whom 442 received treatment (Figure 2). During the study, 13 patients in the budesonide/formoterol–salmetol/fluticasone group and 24 in the salmeterol/fluticasone–budesonide/formoterol group withdrew after randomisation (Figure 2). Demographic data and baseline characteristics were comparable between the two treatment order groups (Table 1) and were in line with COPD patient populations in other ICS/LABA studies [Calverley et al. 2003a; Szafranski et al. 2003].

**Efficacy outcomes**

**Lung function in the morning: mean over the study period.** The primary variable (morning PEF measured at home, 5 minutes after dose) was analysed using the corresponding run-in/washout morning mean measurements as baseline, over the full study period (Figure 3a). The estimated increase from baseline was 15.1 l/min for budesonide/formoterol and 14.2 l/min for salmeterol/fluticasone treatment (mean difference: 1.0 l/min; 95% confidence interval [CI]: −2.7, 4.7; p = 0.603).

The secondary efficacy variable (mean morning FEV$_1$ measured at home over the full study period) improved more with budesonide/formoterol treatment compared with salmeterol/fluticasone at 5 minutes post-dose (0.12 l versus 0.09 l, respectively [p = 0.090]) and significantly so at 15 minutes post-dose (0.14 l versus 0.10 l,
Table 1. Demographics and patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All [n = 442]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>316 (71)</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>63 (40–86)</td>
</tr>
<tr>
<td>Time since diagnosis, median years (range)</td>
<td>6.3 (0–52)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Previous/occasional/habitual, %</td>
<td></td>
</tr>
<tr>
<td>Pack-years, median (range)</td>
<td>40 (10–172)</td>
</tr>
<tr>
<td>ICS at study entry, n (%)</td>
<td>359 (81)</td>
</tr>
<tr>
<td>ICS at study entry, µg/day</td>
<td>640 (160–1600)</td>
</tr>
<tr>
<td>FEV₁, l</td>
<td>1.0 (0.4–2.0)</td>
</tr>
<tr>
<td>FEV₁, % predicted normal</td>
<td>36.1 (13–51)</td>
</tr>
<tr>
<td>FEV₁ reversibility, % predicted normal (SD)</td>
<td>5.2 (5.7)</td>
</tr>
<tr>
<td>Patients by GOLD severity stage: FEV₁ %</td>
<td></td>
</tr>
<tr>
<td>Stage I ≥50 to &lt;80%</td>
<td>98 (22)</td>
</tr>
<tr>
<td>Stage II ≥30 to &lt;50%</td>
<td>261 (59)</td>
</tr>
<tr>
<td>Stage IV &lt;30%</td>
<td>82 (19)</td>
</tr>
<tr>
<td>Reliever use, no. inhalations/24 h</td>
<td>5.7 (0–25.2)</td>
</tr>
<tr>
<td>Medication group use at entry, n (%)</td>
<td></td>
</tr>
<tr>
<td>Anticholinergics*</td>
<td>210 (48)</td>
</tr>
<tr>
<td>SAMA</td>
<td>114 (26)</td>
</tr>
<tr>
<td>LAMA</td>
<td>128 (29)</td>
</tr>
<tr>
<td>SABA</td>
<td>386 (87)</td>
</tr>
<tr>
<td>LABA</td>
<td>282 (64)</td>
</tr>
<tr>
<td>LABA + ICS</td>
<td>232 (52)</td>
</tr>
<tr>
<td>LABA + LAMA</td>
<td>104 (24)</td>
</tr>
<tr>
<td>LABA + LAMA + ICS</td>
<td>103 (23)</td>
</tr>
<tr>
<td>Mucolytics</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Xanthines</td>
<td>42 (10)</td>
</tr>
</tbody>
</table>

Data expressed as mean [range] unless otherwise indicated. *Separately or in combination. The COPD patient population is within the budesonide/formoterol (Symbicort Turbuhaler) label for COPD [FEV₁ <50% of predicted normal and a history of exacerbations] [Calverley et al. 2003d]. FEV₁, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β₂-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

respectively \( p < 0.05 \) (Figure 3b). There were no statistically significant differences in morning pre-dose lung function.

**Lung function in the morning: onset of effect.** e-Diary-recorded morning PEF and FEV₁ (5 and 15 minutes post-dose versus pre-dose) showed greater improvements for budesonide/formoterol compared with salmeterol/fluticasone (Figure 4a), indicating a more rapid onset of effect. The increase in e-Diary PEF 5 minutes post-dose was 12.01/min for budesonide/formoterol and 6.31/min for salmeterol/fluticasone \( p < 0.001 \), and 16.31/min and 9.81/min \( p < 0.001 \) at 15 minutes, respectively. Similar results for e-Diary morning FEV₁ were observed (Figure 4b). Compared with pre-dose, morning FEV₁ 5 minutes post-dose increased by 0.10 l with budesonide/formoterol and 0.04 l with salmeterol/fluticasone \( p < 0.001 \), and after 15 minutes by 0.11 l and 0.04 l, respectively \( p < 0.001 \). Significantly greater improvement in FEV₁ was also demonstrated with budesonide/formoterol, 5 minutes post-dose at the clinic (Figure 4b), indicating a faster onset of effect than salmeterol/fluticasone. No differences in spirometric parameters measured at the clinic 60 minutes post-dose were observed.

**Symptoms and activities in the morning.** At 5 and 15 minutes post-dose, budesonide/formoterol treatment had numerically greater improvements in both symptom variables (breathlessness and chest tightness) compared with salmeterol/fluticasone, with no statistical significance (data not shown). On comparing patients’ abilities to perform morning activities, treatment with budesonide/formoterol resulted in statistically significant improvements compared...
Table 1.

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Medication group use at entry, Reliever use, no. inhalations/24 h 5.7 (0

Smoking status

ICS at study entry, ICS at study entry, history of exacerbations) [Calverley

Time since diagnosis, median years (range) 6.3 (0

Age, years (range) 63 (40

FEV1 reversibility, % predicted normal (SD) 5.2 (5.7)

FEV1, % predicted normal 36.1 (13

Predicted normal postbronchodilator,

Mucolytics 4 (1)

LABA + LAMA 104 (24)

LABA + ICS 232 (52)

SABA 386 (87)

LAMA 128 (29)

SAMA 114 (26)

Anticholinergics* 210 (48)

<

Stage III

Pack-years, median (range) 40 (10

Previous/occasional/habitual, %

<

50 to

30% 82 (19)

<

50% 261 (59)

<

80% 98 (22)

<

66/3/31

n =

442)

p < 0.05) (Figure 3b). There were

<

b.i.d., twice daily; BUD/FORM, budesonide/formoterol; SAL/FLU, salmeterol/fluticasone.

(b) Mean morning forced expiratory volume in 1 second (FEV1) after morning dose; (b) Lung function assessed at clinic; onset: increase in clinic FEV1 after the first dose. Vertical bars represent standard errors.

Figure 4. Onset of effect. [a] Lung function variables assessed using electronic diary; onset: increase in morning peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV1) after morning dose; [b] Lung function assessed at clinic; onset: increase in clinic FEV1 after the first dose. Vertical bars represent standard errors. b.i.d., twice daily; BUD/FORM, budesonide/formoterol; SAL/FLU, salmeterol/fluticasone.

Figure 4. Onset of effect. [a] Lung function variables assessed using electronic diary; onset: increase in morning peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV1) after morning dose; [b] Lung function assessed at clinic; onset: increase in clinic FEV1 after the first dose. Vertical bars represent standard errors. b.i.d., twice daily; BUD/FORM, budesonide/formoterol; SAL/FLU, salmeterol/fluticasone.

with salmeterol/fluticasone in total score on the CDLM questionnaire (0.22 versus 0.12 respectively, mean difference: 0.10; 95% CI: 0.01, 0.19; p < 0.05). In addition, numerically greater improvements were observed with budesonide/formoterol than with salmeterol/fluticasone for the individual morning activities that comprised the total score (getting washed, dried, dressed, eating breakfast, walking around the house early and walking around the house later [Figure 5]).

Although statistically significant, the observed mean difference between treatments on this measure (0.10) was below the MID of 0.20. However, with budesonide/formoterol, the mean absolute change in CDLM questionnaire score (0.22) was above the MID, whereas with salmeterol/fluticasone, the mean absolute change was below the MID (0.12) (data on file).

Other clinical assessments. On analysing patients’ health status, improvements were noted for both budesonide/formoterol and salmeterol/fluticasone. Overall CCQ scores and SGRQ-C total scores were comparable between the budesonide/formoterol and salmeterol/fluticasone treatment arms, with no significant differences (data not shown). The total number of inhalations of reliever medication used was comparable with no notable differences between the two treatment groups (mean difference: 0.21 inhalations; p = 0.12).
maintenance therapies and there were no notable between-group differences because of adverse events and five were due to death during the study: 22 discontinuations were reported. In total, 37 of the randomised patients discontinued the study, 12 of them due to adverse events and one due to inadequate compliance. So, 22/37 patients (60%) were lost to follow-up.

Safety outcomes
In total, 37 of the randomised patients discontinued the study: 22 due to adverse events and five due to study-specific discontinuation criteria (Figure 2). Both treatment groups were well tolerated, and there were no notable between-group differences in the frequency or severity of adverse events.

Discussion
This study compared two highly effective COPD maintenance therapies — budesonide/formoterol dry powder inhaler (DPI) and salmeterol/fluticasone DPI. It was the first study to compare these two ICS/LABA products in terms of improvement of lung function at the bedside and morning activities. Both treatments were well tolerated and similar improvements in the primary outcome (mean morning PEF 5 minutes post-dose), symptoms, clinical control and health status were observed in both treatment arms. However, treatment with budesonide/formoterol was associated with a more rapid onset of effect, and significantly greater improvements in evening FEV1 and patients’ ability to perform basic morning activities compared with salmeterol/fluticasone after only 1 week of treatment.

In a recent quantitative study, most patients with COPD indicated morning as the time of day when symptoms, such as dyspnoea, were particularly severe. This was found to place a major burden on patients, and their abilities to carry out morning routines and everyday activities [Partridge et al. 2009]. Indeed, in a separate study, the most important aspect of COPD from the patient’s perspective was the effect the disease had on normal daily life activities, with more than half of the respondents claiming that they were unable to complete the activities they would like to because of COPD [Miravitlles et al. 2007]. These findings, combined with the knowledge that the speed of symptom relief is central to patients’ treatment expectations and adherence [Bourbeau and Bartlett, 2008; Miravitlles et al. 2007], raises the question of whether a treatment with a rapid onset of effect would lead to improved outcomes in patients with COPD first thing in the morning.

Self-administered PEF and FEV1 measurements were used for the first time in this study, as an endpoint in a clinical trial comparing combination products in the morning. PEF, which has been previously used as an endpoint in clinical trials, was used as the primary endpoint. Self-assessed PEF was favoured over FEV1 as there is limited experience of measuring FEV1 at home in an unsupervised manner. Additionally, a higher level of respiratory effort is required to conduct a technically acceptable measurement [Miller et al. 2005].

In the present study, treatment with budesonide/formoterol significantly improved average morning lung function measured by FEV1 compared with salmeterol/fluticasone, with no significant difference seen in evaluated PEF. This may indicate that PEF measurements underestimate the degree of airflow obstruction occurring in COPD [Rennard et al. 2002]. These results demonstrate that when patients are correctly instructed, FEV1 measurement can be a valuable method to evaluate lung function in an unsupervised manner at home. Onset of effect, measured as change from pre-dose to post-dose morning PEF or FEV1 at home, was more rapid for budesonide/formoterol than for salmeterol/fluticasone, consistent with a comparator study between these drugs [Lindberg et al. 2007].

In this study, a reliable, valid questionnaire consisting of six questions and reflecting usual morning activities was used. The development and validation of this tool is described elsewhere [Partridge et al. 2008, data on file]. Budesonide/formoterol treatment resulted in a better ability
to perform basic morning activities compared with salmeterol/fluticasone. There was a significant difference between treatments in the degree of improvement in total morning activities score, while the absolute difference from run-in to the end of treatment was above the MID for the questionnaire for budesonide/formoterol but not for salmeterol/fluticasone. Numerical differences in favour of budesonide/formoterol were also observed for improvements in the individual morning activities that comprise the total score. These differences were seen after 1 week of treatment, consistent with findings from another study, which used the tool in a similar patient population, and showed significant differences after 1 week and further improvements following 12 weeks of treatment [Welte et al. 2009].

While treatment with budesonide/formoterol had a more rapid onset of effect and resulted in significant improvements in some morning activities, little effect was observed on patient perception of symptoms, as reflected by results from the GCSQ post-drug administration. A possible explanation for this disparity could be that in order to see the full effect of study drugs on morning symptoms, a longer period of time than the 5 and 15 minutes post-dose is required. The lack of effect of study drugs on symptoms may also be due to patients with COPD not experiencing perceivable differences in symptoms as they become accustomed to them. The patients may also adapt their lifestyles to their symptoms over time and, consequently, they may find it difficult to perceive meaningful changes unless they are deteriorating.

Despite the possibility that (1) the study duration may have been too short to allow treatment benefits to translate into improved health status, or that (2) the observed differences in favour of budesonide/formoterol may have been smaller over time, the data presented may have important clinical implications. Evidence from other studies suggests that patients are infrequently asked about their symptoms in the morning [Partridge et al. 2009], leaving physicians unable to assess the impact of their disease and adjust management accordingly. Physicians should therefore try to question patients more about morning symptoms and activity limitations, and provide advice on how they could adapt their routines, for example, by adjusting the timing of their medications, since many patients appear to be taking medications too late in the day to benefit from their potential effects. Indeed, in this present study, such improvements were evident even after 1 week, supporting the use of early morning treatment.

In conclusion, both budesonide/formoterol DPI and salmeterol/fluticasone DPI treatment combinations were effective in showing overall improvements in lung function and other clinical endpoints. Although differences between the drugs were not seen with mean PEF 5 minutes post-dose, budesonide/formoterol demonstrated greater improvements in morning mean FEV1, a more rapid onset of effect on all lung function parameters, and enabled patients to perform basic morning activities better than salmeterol/fluticasone. This study provides important insights into the short-term treatment effects in patients with COPD and indicates the value of maintenance drugs with a rapid onset of effect that may improve patient performance in the morning.

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Conflict of interest statement
M.R. Partridge has received fees for giving lectures and ad hoc consultancies from GlaxoSmithKline, AstraZeneca, Chiesi, Cipla, Teva and Novartis and received departmental research funding from AstraZeneca, and help with publication of a history of asthma charities from Novartis.

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