Faster onset of bronchodilation with formoterol than with salmeterol in patients with stable, moderate to severe COPD: Results of a randomized, double-blind clinical study

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OBJECTIVES: To compare the onset and magnitude of bronchodilation after dry powder inhalations of formoterol fumarate (Foradil Aerolizer) versus salmeterol xinofoate (Serevent Diskus) with respect to normalized (*) forced expiratory volume in 1 s area under the curve 0 to 1 h after inhalation (FEV_1 $AUC^*_{0\text{-}1\ h}$).
DESIGN: A double-blind, double-dummy, multicentre, randomized, placebo controlled, single-dose, five-period crossover study.
SETTING: Five centres in four countries – one centre each in France, Greece and Italy, and two centres in the Netherlands.
PATIENTS: Forty-seven patients aged 42 to 80 years (mean age 63.5 years) with chronic obstructive pulmonary disease (COPD) stage II and III, and mean baseline FEV_1 1.17 L (range 0.56 to 1.77 L).
INTERVENTIONS: Patients inhaled single doses of formoterol dry powder (12 and 24 μg), single doses of salmeterol (50 and 100 μg) and matching placebo on five separate days.
MAIN RESULTS: The estimates of treatment difference in absolute terms (0.086 L) and percentage change from predose baseline (7.8%) for the primary end point, FEV_1 $AUC^*_{0\text{-}1\ h}$, showed that formoterol 12 μg was statistically significantly superior to salmeterol 50 μg (P=0.0044 and P=0.0021, respectively). In addition, both doses of formoterol were statistically superior to placebo for both absolute improvement and percentage change (P=0.0001). The analysis of secondary variables also confirmed the superiority of formoterol over salmeterol.
CONCLUSIONS: Formoterol is associated with a faster onset of bronchodilation than salmeterol in patients with COPD.

Key Words: *$Beta_2$-agonists; Bronchodilators; Chronic obstructive pulmonary disease; Clinical trial; COPD; Formoterol; Salmeterol*

Résumé à la page suivante

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Amorce plus rapide de la bronchodilatation avec le formotérol qu'avec le salmétérol chez des patients atteints d'une BPCO modérée ou grave : résultats d'un essai clinique à double insu avec répartition aléatoire

OBJECTIF : Comparer l'amorce et l'importance de la bronchodilatation provoquée par l'inhalation de fumarate de formotérol en poudre sèche (Foradil Aerolizer) au xinafoate de salmétérol (Serevent Diskus) en tenant compte de l'aire sous la courbe (ASC) normalisée* du VEMS (volume expiratoire maximal par seconde) de 0 à 1 h après l'inhalation (VEMS ASC*$_{0\text{-}1\ h}$).

PLAN D'ÉTUDE : Essai multicentrique, à double insu et à double placebo, avec répartition aléatoire, croisé avec cinq périodes et à dose unique.

LIEU : Cinq centres dans quatre pays : un en France, en Grèce et en Italie respectivement et deux aux Pays-Bas.

PATIENTS : Quarante-sept patients âgés de 42 à 80 ans (âge moyen : 63,5 ans), atteints d'une BPCO (bronchopneumopathie chronique obstructive) de stade II ou III et ayant un VEMS moyen au départ de 1,17 l (intervalle de 0,56 à 1,77 l) ont participé à l'étude.

INTERVENTIONS : Les patients ont inhalé une dose unique de formotérol en poudre sèche (12 et 24 µg), une dose unique de salmétérol (50 et 100 µg) et un placebo correspondant au cours de cinq jours différents.

PRINCIPAUX RÉSULTATS : Les estimations de différences entre traitements, en valeurs absolues (0,086 l) et en pourcentage (7,8 %) par rapport aux valeurs de départ avant l'administration des doses, montrent, en ce qui concerne le principal critère d'évaluation (VEMS ASC*$_{0\text{-}1\ h}$), que le formotérol 12 µg s'est avéré statistiquement supérieur au salmétérol (50 µg) (P=0,0044 et P=0,0021 respectivement). De plus, les deux doses de formotérol se sont également révélées supérieures au placebo, et ce, tant pour l'amélioration absolue que pour les variations de pourcentage (P=0,0001). L'analyse des variables secondaires a aussi confirmé la supériorité du formotérol sur le salmétérol.

CONCLUSION : Le formotérol est associé à une amorce plus rapide de la bronchodilatation que le salmétérol chez des patients atteints d'une BPCO.

In patients with asthma, formoterol has a rapid onset of action that is similar to salbutamol (albuterol). Single-dose studies in adults with asthma have shown that inhalation of 12 or 24 µg of formoterol (as an aerosol or dry powder) provides prompt bronchodilation, with onset of action observed within 1 to 3 min of administration (1-5). In contrast, salmeterol xinofoate, a long-acting beta$_2$-agonist, has a slower onset of bronchodilating action – 7 to 17 min after inhalation (6,7).

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction caused by chronic bronchitis and emphysema. Unlike patients with asthma, patients with COPD present with poorly reversible bronchoconstriction, which is the result of irreversible changes in the lung parenchyma and airways due, in most cases, to cumulative exposure to tobacco smoke. Pharmacotherapy in COPD is given to improve symptoms and reduce complications, and bronchodilators are central to the management of symptoms, used on an as-needed basis or regularly (8). In patients with COPD, regular beta$_2$-agonist treatment is intended to provide relief from existing symptoms, unlike asthma, in which regular beta$_2$-agonist treatment is focused on protecting the airways from challenge and preventing symptoms.

Both formoterol and salmeterol have been shown to be effective in the treatment of COPD (9-14), demonstrating improvements in symptoms (particularly dyspnea) and quality of life. However, because these two long-acting beta$_2$-sympathomimetic drugs differ from one another with respect to a number of pharmacological properties (15), the speed of onset of bronchodilation and symptom relief is likely to be of great importance to the patient with COPD. In this context, the present study was conducted to investigate the speed of onset of effect of formoterol delivered by a dry powder inhaler (Foradil Aerolizer, Norvartis Pharma AG, Switzerland) compared with inhaled salmeterol xinofoate dry powder (Serevent Diskus, GlaxoSmithKline, United Kingdom) in patients with stable, moderate to severe COPD (stages II and III).

PATIENTS AND METHODS

Study design

This was a multicentre, randomized, double-blind, double-dummy, placebo controlled, single-dose, five-period crossover study in male and female patients with stage II and III COPD diagnosed according to American Thoracic Society criteria, ie, forced expiratory volume in 1 s (FEV_1) less than 50% of the predicted value (8). This design minimized bias and allowed for a within-patient, placebo controlled comparison. To blind the trial, a double-dummy technique was employed, using the study treatments as follows: formoterol dry powder capsules, each containing 12 µg formoterol fumarate (Foradil) delivered via the Aerolizer device; salmeterol 50 µg metered dose delivered via dry powder inhaler (Serevent Diskus); placebo dry powder (lactose) capsules matched to formoterol dry powder capsules delivered via the Aerolizer device; and placebo Serevent Diskus (empty). To ensure that lack of taste with (single-dose) placebo Diskus inhalation did not lead to unblinding, formoterol (either active or placebo) was always administered first. This was considered to blunt the perception of any lack of taste on the part of the patient and thus ensure treatment blinding.

At visit 1 (screening), spirometry was performed to help to determine disease severity. In addition, a reversibility test with dry powder salbutamol 400 µg (Ventodisk; GlaxoSmithKline, United Kingdom; 200 µg per inhalation) was carried out. Eligible patients had to demonstrate an increase in FEV_1 (30 min after inhalation of salbutamol) of 5% or greater from the baseline value, but not greater than 12% of the patient's predicted normal value, allowing for most measurements to fall within the normal variability of the FEV_1 measurement (16,17).

At visit 2, patients were randomly assigned to one of the sequences of treatments from a 5×5 Latin square design comparing single doses of formoterol dry powder (12 and 24 µg) with single doses of salmeterol dry powder (50 and 100 µg)

and placebo. All treatments were administered in a double-blind manner, so that at each dosing interval, every patient received four separate inhalations – two dry powder capsules (formoterol or matching placebo), each inhaled from a separate Aerolizer device, plus one inhalation from each of two separate Diskus inhalers (salmeterol or placebo). Eligible patients attended the clinic on five test days (visits 2 to 6), with each consecutive pair of visits three to five days apart.

During visits 2 to 6, the baseline values of the FEV_1 had to be within the range of 85% to 115% of the baseline FEV_1 measured at visit 1. If, on any day, the predose FEV_1 value did not meet this requirement or the patient had taken rescue bronchodilator medication within the predefined washout period before baseline spirometry, the patient was instructed to return to repeat the spirometry no later than 10 days after their previously fully completed visit.

At each clinic visit, FEV_1, forced vital capacity (FVC), inspiratory capacity (IC) and maximal mid-expiratory flow ($FEF_{25-75\%}$) were measured predose, as well as at 5, 10, 15, 30 and 60 min, and 2, 3 and 4 h postdose. At visits 2 to 6, patients were asked to rate any perceived changes in dyspnea by using two visual analogue scales (vertical straight line, 100 mm long) – the first for the sense of effort required to breathe, and the second for the degree of discomfort associated with breathing before dosing, and at 1 and 4 h postdose. In addition, at visits 2 to 6, patients rated their perception of change in breathlessness 1 and 4 h postdose on a –5 to +5 scale (13,18,19).

Interventions

Each patient received single doses of inhaled formoterol dry powder (12 and 24 μg), single doses of inhaled salmeterol xinofoate (50 and 100 μg) and matching placebo in a randomized sequence. The primary comparison was between the 12 μg dose of formoterol and the 50 μg dose of salmeterol, because these are the most commonly prescribed doses (7,20).

The study treatments were provided as formoterol dry powder capsules, each containing 12 μg formoterol fumarate (Foradil); salmeterol 50 μg metered dose (Serevent) delivered via the Diskus dry powder inhaler; placebo dry powder capsules; and placebo Serevent Diskus. All dry powder capsules were identical in appearance and were inhaled through the Aerolizer, a breath-actuated dry powder inhalation device. In addition, salbutamol dry powder was provided for use in reversibility testing at screening (Ventodisks 200 μg/blister plus Diskhaler device). The study drugs were administered in the morning (07:00 to 10:00), and all four inhalations had to be taken at the same time and in the sequence outlined as follows: two capsules delivered by the Aerolizer followed by two inhalations from the Diskus device.

Patients were expected to avoid using bronchodilators during the 4 h test periods at visits 2 to 6 and during the washout periods before these visits. Treatment with inhaled or nasal corticosteroids and stable doses of oral modified-release theophylline or a derivative was allowed.

Efficacy evaluations

The primary efficacy parameter was the normalized (*) FEV_1 area under the curve in the first hour (FEV_1 $AUC^*_{0\text{-}1\,h}$) after drug inhalation in the morning. The first hour after dosing was considered to be of paramount importance for patients with COPD under regular, twice daily $beta_2$-agonist treatment because of the need of these patients for fast symptom relief. Secondary efficacy parameters included other measures of lung function, dyspnea ratings, and monitoring for safety and tolerability at various time points up to and including 4 h postinhalation. These were normalized FEV_1 AUC over the 4 h period (FEV_1 $AUC^*_{0\text{-}4\,h}$), peak FEV_1 and FEV_1 at all time points. FVC, IC and $FEV_{25-75\%}$ were all considered in the same way. In addition, the following secondary parameters were evaluated: time to 10%, 12% and 15% change in all of these parameters from baseline; number of responders with a 10%, 12%, 15% and greater than 15% change in all of these parameters from baseline at 5, 10 and 15 min; and change in dyspnea ratings at 1 h and 4 h. All efficacy measurements and ratings evaluated the capacity of both agonists to induce bronchodilation, reductions in the work of breathing, symptom relief, and enhancement of the individual's ability for work and exercise. A total duration of 4 h was chosen as this time interval and was considered to be sufficient to allow the study medication to achieve peak effect. In addition, this evaluation period was not too prolonged and was not expected to hinder patient compliance.

To reduce the variability of observations induced by known diurnal variation, measurements were taken at approximately the same time at each visit. Three determinations for the expiratory indexes were performed at each time point, and the best reading was recorded (21).

Patients

A minimum of 50 patients diagnosed with COPD of stage II and III severity according to the American Thoracic Society criteria were to be randomly assigned (8). All patients gave written informed consent. Inclusion criteria were: age 40 years or older; current or previous smoker (more than 20 pack-years); prebronchodilator baseline FEV_1 of less than 50% of the predicted normal value and at least 0.7 L (if less than 0.7 L then 40% or greater of predicted normal); prebronchodilator FEV_1/FVC of 70% or less; an increase in FEV_1 30 min after inhalation of 400 μg salbutamol dry powder at screening of 5% or greater from the baseline value and 12% or less from the patient's predicted normal value; a complaint of dyspnea of at least two months' duration before screening. European Respiratory Society standards were used to determine the predicted values for FEV_1 and the FEV_1/FVC ratio required to meet the study entry criteria (21).

Exclusion criteria included current or childhood asthma (21); a history of allergic rhinitis or another atopic disease; a total blood eosinophil count higher than 400/μL; a respiratory tract infection within one month before screening; hospitalization or emergency room treatment for an acute

TABLE 1
Baseline demographics and spirometry for 47 patients with stable, moderate to severe chronic obstructive pulmonary disease included in a randomized, double-blind study comparing single doses of formoterol and salmeterol

Demographic variable		
Age (years)	Mean ± SD	63.5±8.6
	Range	42-80
Sex	Male	38 (81%)
	Female	9 (19%)
Current smokers		28 (60%)
Spirometric test		
Pretreatment FEV_1 (L)	Mean ± SD	1.17±0.29
	Range	0.56-1.77
FEV_1 reversibility* (%)	Mean ± SD	17.7±7.2
	Range	6.0-34.0
FEV_1 reversibility* (% of predicted)	Mean ± SD	7.1±2.7
	Range	3.0-13.0

**30 min after inhalation of salbutamol 400 μg. FEV_1 Forced expiratory volume in 1 s*

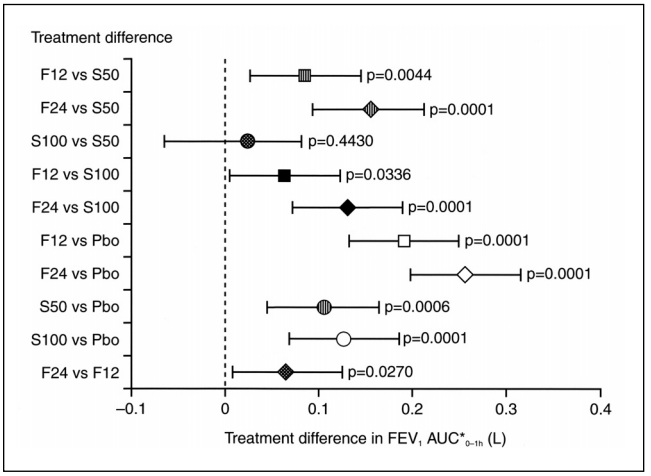

Figure 1) *Treatment differences in normalized forced expiratory volume in 1 s area under the curve (FEV_1 $AUC^*_{0\text{-}1\ h}$) for the intent-to-treat population. Results are shown as estimated treatment differences and 95% CIs using ANCOVA based on the model AUC* = μ + treatment + predose FEV_1 + centre + period. F12 Formoterol 12 μg; F24 Formoterol 24 μg; Pbo Placebo; S50 Salmeterol 50 μg; S100 Salmeterol 100 μg; vs Versus*

COPD exacerbation in the month before screening; any clinically significant condition; long term oxygen therapy; or an inability to stop treatment with a usual bronchodilator before screening.

Statistical analysis

The primary and most of the secondary efficacy variables were analyzed using ANCOVA. Analyses were performed on both the intent-to-treat and per-protocol populations. Because of the crossover design, the intent-to-treat population was defined as all randomly assigned patients who provided postdose measurements on at least two different study days. The per-protocol population was defined as all patients completing the study without any major protocol deviations such as the incorrect selection of the patient at screening or the use of prohibited concomitant medications during the trial.

The primary efficacy variable was the FEV_1 $AUC^*_{0\text{-}1\ h}$, standardized with respect to the length of time during which the patient provided serial spirometry measurements. The results of normalization, in which the AUC is divided by the measurement period, are therefore expressed either in litres (AUC in L/min divided by 60 for $AUC_{0\text{-}1\ h}$ or divided by 240 for $AUC_{0\text{-}4\ h}$) or as a percentage value (AUC for the percentage increase, divided by time). Throughout the present article, normalized values are designated using an asterisk as AUC*. The ANCOVA used a fixed effects model, fitting treatment, centre and period as main effects, with the treatment baseline (visit predose value) fitted as a covariate. All 10 pairwise contrasts were estimated, but the comparison of formoterol 12 μg and salmeterol 50 μg was considered to be of prime interest. Analysis of secondary variables was carried out in a similar way.

For the estimation of the sample size, a difference of 5% (assuming an SD of 10%) between formoterol 12 μg and salmeterol 50 μg in terms of the primary variable, FEV_1 $AUC^*_{0\text{-}1\ h}$, was considered to be clinically important. To demonstrate superiority with 85% power (significance level 5%, two-sided), a minimum of 38 evaluable patients were needed. Consequently, it was decided to recruit a minimum of 50 patients to allow for patients who discontinued the trial prematurely.

RESULTS

Patients

Five centres in four countries participated in the study – one centre each in France, Greece and Italy, and two centres in the Netherlands. Sixty-eight patients were screened, and 47 were randomly assigned and treated. A summary of patient demographics is presented in Table 1. All patients who were included achieved the minimum value of 5% reversibility, and only one patient failed to meet the inclusion criterion maximum limit for reversibility (12%), with an increase of 13% of predicted normal. This patient was not excluded from the per-protocol evaluation, because the deviation was considered to be slight.

Efficacy

The superiority of formoterol 12 μg over salmeterol 50 μg with respect to the primary efficacy variable, FEV_1 $AUC^*_{0\text{-}1\ h}$, was demonstrated by a statistically significant difference for both absolute values of FEV_1 and for the percentage change from predose value, with estimated treatment differences of 0.086 L (P=0.0044) and 7.8% (P=0.0021), respectively, for the intent-to-treat population (Figure 1). This was confirmed by the results for the per-protocol population, which

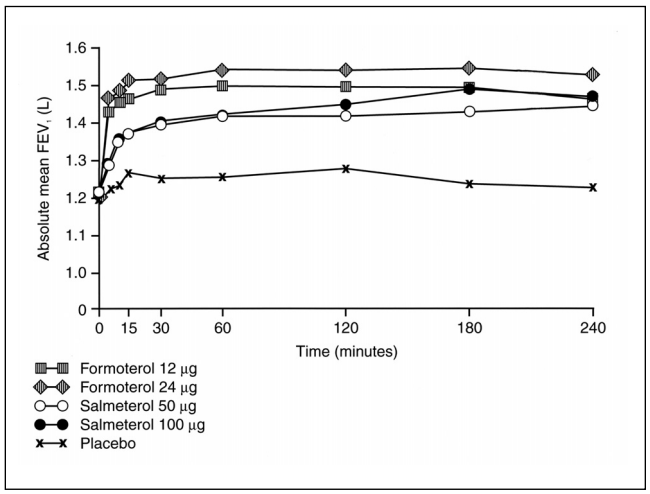

Figure 2) *Mean forced expiratory volume in 1 s (FEV_1) over time after administration of formoterol 12 µg or 24 µg, salmeterol 50 µg or 100 µg, or placebo as single dose dry powder inhalations in the intent-to-treat population*

gave very similar estimates of 0.087 L (P=0.0100) and 7.1% (P=0.0088). The higher dose of formoterol (24 µg) was also shown to be statistically superior to the higher dose of salmeterol (100 µg), with estimated treatment differences of 0.130 L (P=0.0001) and 12.4% (P=0.0001). Both doses of formoterol were statistically significant compared with placebo, confirming the sensitivity of the trial. These results for the primary variable support the claim that the effect of formoterol is superior to that of salmeterol during the first hour after dosing.

Analysis of the FEV_1 at individual time points up to 4 h also highlighted the rapid onset of action of formoterol compared with salmeterol, with statistically significant differences between formoterol 12 µg and salmeterol 50 µg at 5, 10, 15, 30 and 60 min postdose (Figure 2). At these time points, estimated mean treatment differences were 0.130 L (P=0.0001), 0.115 L (P=0.0003), 0.089 L (P=0.0123), 0.092 L (P=0.0105) and 0.073 L (P=0.0349), respectively.

The estimated treatment difference for the main contrast of formoterol 12 µg versus salmeterol 50 µg in FEV_1 $AUC^*_{0\text{-}4\ h}$ was 0.067 L (mean absolute difference), but did not achieve statistical significance (P=0.0577). However, the estimated difference in terms of percentage change – 6.1% – was statistically significant (P=0.0350).

For peak FEV_1 in the intent-to-treat population, the main contrast (formoterol 12 µg versus salmeterol 50 µg) did not achieve statistical significance (estimated mean difference formoterol – salmeterol 0.076 L, P=0.0948). The comparison of formoterol 24 µg with salmeterol 50 µg (estimated mean difference 0.164 L) was statistically significant (P=0.0004). Patients treated with formoterol 24 µg reached the highest mean peak FEV_1 value (1.63 L) followed by patients treated with formoterol 12 µg (1.58 L). The mean peak FEV_1 values for salmeterol were 1.54 L for the 100 µg dose and 1.49 L for the 50 µg dose. Patients showed a mean peak FEV_1 of 1.36 L with placebo.

Formoterol also had a faster onset of action than salmeterol when evaluated in temporal terms (Table 2). The median times to 10%, 12%, 15% and maximum percentage change in FEV_1 from predose levels were shorter for formoterol 12 and 24 µg compared with salmeterol 50 and 100 µg and placebo. In addition, more formoterol recipients achieved a 10%, 12% or 15% change (Table 2), and almost twice as many formoterol than salmeterol recipients reached a 10%, 12% or 15% change from predose levels at 5 min (Table 3).

While FEV_1 is the most commonly used measure for assessing bronchodilation, other spirometric indices are also important. The mean treatment differences in FVC

TABLE 2
Time* (min) to 10%, 12%, 15% and maximum change from baseline forced expiratory volume in 1 s for the intent-to-treat population in a randomized, double-blind study comparing single doses of formoterol and salmeterol in patients with chronic obstructive pulmonary disease

		Formoterol 12 µg	Formoterol 24 µg	Salmeterol 50 µg	Salmeterol 100 µg	Placebo
10%	n (%)	41 (83)	44 (98)	39 (87)	39 (85)	29 (64)
	Median	5	5	10	10	15
	Range	5-180	5-120	5-240	5-240	5-120
12%	n (%)	41 (93)	44 (98)	36 (80)	36 (78)	23 (51)
	Median	5	5	10	10	15
	Range	5-180	5-180	5-240	5-120	5-180
15%	n (%)	39 (89)	43 (96)	32 (71)	34 (74)	18 (40)
	Median	5	5	15	10	22.5
	Range	5-180	5-180	5-240	5-240	5-120
Maximum	n (%)	44 (100)	45 (100)	45 (100)	46 (100)	45 (100)
	Median	60	60	120	150	30
	Range	5-240	5-240	10-240	5-240	5-240

**The first postdose assessment was performed at 5 min; therefore, the medians are probably overestimating time to onset*

TABLE 3
Number of responders classified by percentage change from baseline forced expiratory volume in 1 s at 5 min for the intent-to-treat population in a randomized, double-blind study comparing single doses of formoterol and salmeterol in patients with chronic obstructive pulmonary disease

	Formoterol 12 µg (n=44) (%)	Formoterol 24 µg (n=45) (%)	Salmeterol 50 µg (n=45) (%)	Salmeterol 100 µg (n=46) (%)	Placebo (n=45) (%)
10%	31 (76)	39 (89)	12 (31)	19 (49)	5 (17)
12%	26 (63)	37 (84)	10 (28)	13 (36)	4 (17)
15%	23 (59)	32 (74)	7 (22)	9 (27)	3 (17)

TABLE 4
ANCOVA of the absolute changes in effort to breathe and degree of breathing discomfort from predose for the intent-to-treat population in a randomized, double-blind study comparing single doses of formoterol and salmeterol in patients with chronic obstructive pulmonary disease

Contrast (difference)	Time point (h)	Estimated difference (mm)*	95% CI	P
Effort to breathe				
Formoterol 12 µg – salmeterol 50 µg	1	–4.546	(–9.731 to 0.638)	0.0853
	4	–3.827	(–9.674 to 2.020)	0.1984
Degree of breathing discomfort				
Formoterol 12 µg – salmeterol 50 µg	1	–5.201	(–10.720 to 0.318)	0.0646
	4	–4.404	(–10.440 to 1.632)	0.1519

**Based on the model: Visual analogue scale (VAS) (time) – VAS predose = µ + treatment + VAS (at predose) + centre + period*

$AUC^*_{0\text{-}1\ h}$ results for the intent-to-treat population showed that formoterol was statistically significantly superior to salmeterol and placebo for all pair contrasts; the two formoterol doses did not differ significantly. For the main contrast (formoterol 12 µg versus salmeterol 50 µg), the mean $AUC^*_{0\text{-}1\ h}$ difference for FVC was 0.137 L (P=0.0135) in absolute terms. The difference between these two treatments was most marked at 5 min (estimated treatment difference 0.293 L, P=0.0001) and 10 min (0.247 L, P=0.0012). Both doses of formoterol show statistically significant differences versus placebo at each time point after dosing.

For IC $AUC^*_{0\text{-}1\ h}$, the estimated difference between formoterol 12 µg and salmeterol 50 µg (the main treatment contrast) was 0.142 L (P=0.0096). In addition, for IC $AUC^*_{0\text{-}1\ h}$, the estimated differences were not statistically significant for the contrast between the two formoterol doses and the two salmeterol doses, and for the contrast between formoterol 12 µg and salmeterol 100 µg.

All treatment pairs for the mean $FEF_{25\text{-}75\%}$ $AUC^*_{0\text{-}1\ h}$ contrasts for the intent-to-treat population showed statistical superiority for formoterol compared with salmeterol or placebo. For the main contrast (formoterol 12 µg versus salmeterol 50 µg), the estimated mean AUC* difference was 0.058 L/min using actual values or 11.3% using percentage change from predose in favour of formoterol (P=0.078 and P=0.0187, respectively).

Subjective assessments by patients of relief from dyspnea were also investigated. The results for the main contrast (formoterol 12 µg versus salmeterol 50 µg) for absolute changes in effort to breathe and degree of breathing discomfort from predose for the intent-to-treat population are shown in Table 4. For effort to breathe, there were no statistically significant differences between treatments, and similarly, the primary contrast for degree of breathing discomfort was not statistically significant. For change in effort to breathe, the reduction in effort was also similar for the formoterol and salmeterol treatment groups at 1 and 4 h postdose (Table 5).

Safety

Five patients (10.6%) reported eight adverse events, none of which was considered to be related to the study drug. Five adverse events were classed as moderate in intensity, two as mild and one as severe. Two patients had adverse events that led to discontinuation. Both patients experienced a COPD exacerbation of moderate severity that was judged to be unrelated to the study drug; one patient received formoterol 24 µg and the other salmeterol 100 µg. There were no differences in blood pressure and pulse rate measurements.

DISCUSSION

The results of the present study indicate that formoterol has a significantly faster onset of effect than salmeterol in patients with COPD. For those doses most frequently used in patients with COPD (formoterol 12 µg and salmeterol 50 µg), primary efficacy results with respect to the FEV_1 $AUC^*_{0\text{-}1\ h}$ showed a statistically significant difference of 0.086 L. In addition, the FEV_1 was statistically significantly

TABLE 5
The effects of formoterol and salmeterol on the sense of effort required to breathe (the results are shown as the changes in score from predose values, assessed on a visual analogue scale [mm])

	Formoterol 12 µg (n=44)	Formoterol 24 µg (n=45)	Salmeterol 50 µg (n=45)	Salmeterol 100 µg (n=46)	Placebo (n=45)
1 h postdose					
n (%)	40 (90.9)	41 (91.1)	41 (91.1)	42 (91.3)	42 (93.3)
Mean	–1.4	–1.4	–1.1	–1.0	–0.7
SD	1.3	1.4	1.3	1.3	1.2
Median	–1.0	–1.0	–1.0	–1.0	–1.0
Range	–4.0 to 1.0	–5.0 to 1.0	–5.0 to 0.0	–4.0 to 2.0	–3.0 to 3.0
4 h postdose					
n (%)	40 (90.9)	41 (91.1)	41 (91.1)	43 (93.5)	41 (91.1)
Mean	–0.8	–0.8	–0.6	–0.8	–0.2
SD	1.2	1.4	1.0	1.4	1.1
Median	0.0	0.0	0.0	–1.0	0.0
Range	–5.0 to 1.0	–5.0 to 1.0	–4.0 to 1.0	–4.0 to 3.0	–3.0 to 3.0

higher with formoterol than with salmeterol at all time points from 5 min up to and including 60 min postdose. The reliability of these study results was confirmed by the statistically significantly better results of both formoterol doses over placebo. Also, the time to 10%, 12%, 15% and maximum change in FEV_1 from its baseline value, and the number of patients responding with such changes, though not statistically tested between treatments, indicate a faster onset of effect with formoterol 12 µg during the first hour postdose. The median time to 15% increase in FEV_1 from predose (a bronchodilatory response that is generally accepted as significant) for both formoterol doses was 5 min, whereas for salmeterol 50 µg, it was 15 min, and for salmeterol 100 µg, it was 10 min. It should, however, be noted that the first postdose FEV_1 assessment was performed at 5 min, suggesting the possibility that an earlier assessment would result in more marked differences between the two drugs tested.

A bronchodilator with a rapid onset of effect may be particularly important in patients with COPD, in which patients experience progressive and long term debilitating symptoms. This is because such a bronchodilator would result in a fast enhancement of exertion tolerance (22), with a corresponding reduction in the work of breathing and rapid relief of symptoms (23), and such rapid effects, readily discernible by the patient, would provide reassurance. Thus, these effects may improve compliance. In the context of the results of the present investigation, however, the obvious question is: what is the clinical relevance of the observed difference of 0.086 L with formoterol 12 µg during the first hour postdose? In this trial, three scales were used to evaluate dyspnea ratings to relate any improvement in lung function with clinically meaningful outcomes. The results from these subjective assessments showed small advantages with active treatments over placebo, but no statistically significant difference between the primary treatment contrasts for the sense of effort required to breathe or the degree of discomfort associated with breathing. In addition, change in perception of breathlessness from predose to 1 and 4 h postdose showed no statistical difference between the treatment groups. Although these results suggest that the observed improvement in lung function was not associated with any meaningful clinical improvements, the assessments of dyspnea were performed at 1 and 4 h postdose, and not during the first hour postdose, when the faster onset of effect associated with formoterol was more pronounced. Thus, earlier assessment of dyspnea may have revealed a meaningful outcome. More importantly, patients with COPD tend to adopt relatively sedentary lifestyles with low levels of activity to avoid symptoms; thus, the clinical significance of 0.086 L in FEV_1 AUC* during the first hour after dosing can only really be judged in an experimental exercise setting.

It has become apparent that changes in FEV_1 are unlikely to produce a reliable guide to symptomatic improvement in COPD, and some investigators believe that measurement of IC may correlate better with improvements in exercise endurance and dyspnea after bronchodilator therapy, because they provide an indirect measure of dynamic changes in lung hyperinflation (24,25). Because serial measurements of IC during exercise may be problematic for many physicians who manage patients with COPD, O'Donnell et al (24) have recently investigated the value of resting IC measurement in evaluating clinical response, and have shown that these correlate well with improvements in exercise endurance and dyspnea after anticholinergic therapy in patients with severe COPD. In the present study, IC $AUC^*_{0\text{-}1\ h}$ results showed a statistically significant difference between the main treatment contrast of 0.142 L, which may be suggestive of a greater clinical response from formoterol compared with salmeterol.

The results of the present study suggest that further, more in-depth investigations would be valuable. In patients with advanced disease, even modest improvements in symptoms can lead to quite important perceived benefits and can have a real impact on quality of life. In particular, further studies are needed to assess any potential differences between formoterol and salmeterol in terms of improvements in breathlessness during exercise, and to relate these to assessments of quality of life. The rapid onset of action of formoterol shown in this study confirms previous results by Dahl et al (9,10), who showed an onset of action of less than 5 min in a study comparing formoterol with ipratropium bromide in patients with COPD. Results from comparative studies in patients with COPD have also shown that the onset of action in terms of FEV_1 increase is greater for formoterol than salmeterol (26) and similar to that of salbutamol (27). Our results do not, however, reproduce the results of Cazzola et al (28), who showed formoterol to be slower in onset than salbutamol and similar to salmeterol in patients with COPD. The difference in results seen in the Cazzola study (28) may be attributable to differences in methodology, patient population studied and inhalers used. With respect to the latter, all medications were administered via metered dose inhalers in the Cazzola study (28), whereas in the present study, formoterol and salmeterol were administered via dry powder inhalers (Aerolizer for formoterol, Diskus for salmeterol). A recent study by Benhamou et al (29) also refuted the findings of Cazzola et al (28); it showed that formoterol 24 μg and salbutamol 400 μg had a similar onset of action in patients with COPD; both drugs produced similar bronchodilation by 5 min, which became near maximal at 30 min (29). Overall, these findings do not support the argument posed by Cazzola and Donner (30) that the discrepancy is due to greater activity of salmeterol than formoterol in patients with severe COPD.

CONCLUSIONS

In patients with COPD, formoterol is associated with a faster onset of effect during the first hour postdose compared with salmeterol. The clinical relevance of this finding warrants further investigation by means of properly designed, longer term clinical trials looking at the impact of treatment with formoterol on quality of life and exertion endurance.

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