



## Rapid onset of bronchodilation with formoterol/beclomethasone Modulite and formoterol/budesonide Turbuhaler as compared to formoterol alone in patients with COPD

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### ABSTRACT

In the present study, we examined whether there is a difference in the onset of bronchodilation between formoterol/beclomethasone 12/200 µg Modulite and formoterol/budesonide 9/320 µg Turbuhaler in patients with COPD. We enrolled 28 patients with stable COPD. Both formoterol/beclomethasone and formoterol/budesonide elicited a larger mean  $FEV_{1-AUC_{0-15min}}$  than formoterol alone, whereas there was no significant difference between their  $FEV_{1-AUC_{0-15min}}$ . Also the change in  $FEV_{1}$  15 min after inhalation of formoterol/beclomethasone combination or formoterol/budesonide combination was greater than that induced by formoterol alone. This study confirms the rapid effect of the inhaled corticosteroid component when combined with formoterol and indicates that the onset of bronchodilation of formoterol/beclomethasone Modulite and formoterol/budesonide Turbuhaler are similar and greater than formoterol alone in patients with COPD.

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### 1. Introduction

Preliminary data from a cross-sectional epidemiological study conducted in 17 European countries indicated that symptoms of COPD (breathlessness, phlegm, coughing, wheezing and chest tightness) are almost troublesome in the morning, either immediately upon waking or later in the morning and often interfere with essential activities such as getting out of bed, washing, drying and dressing [1]. These results have serious implications for helping patients manage their condition effectively. Actually, when asked how many days during the preceding week they needed to use their rescue inhaler to be able to perform morning activities, more than half of the patients needed to use their inhaler [2] and it is well known that the fast onset of bronchodilation is an absolute requirement for any inhaled bronchodilator administered on demand [3].

In a previous study, we documented that the addition of formoterol to budesonide accelerates the onset of action of formoterol in patients with COPD and suggested that this finding

might be explained by actions that can broadly be termed non-genomic [4].

Recently, a hydrofluoroalkane (HFA)-propelled extrafine fixed combination formulation of formoterol/beclomethasone dipropionate 6/100 µg delivered via pMDI has been developed using the Modulite technology. Each actuation of beclomethasone dipropionate/formoterol 100/6 (nominal dose) delivers 86.4 µg of beclomethasone dipropionate and 5 µg of formoterol [5]. In patients suffering from moderate to severe asthma, formoterol/beclomethasone dipropionate 12/200 µg was as rapid as formoterol/budesonide 12/400 µg in term of onset of bronchodilation [6].

In the present study, we examined whether there is a difference in the onset of bronchodilation between the two combinations in patients with COPD.

### 2. Patients and methods

Twenty-eight patients with stable moderate to severe COPD were enrolled. Severity was staged according to  $FEV_{1}$  cut-points as suggested by the American Thoracic Society and European Respiratory Society consensus statement [7]. All patients were >50 years of age, current or former smokers (>10 pack-years), reporting

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chronic cough with or without sputum production and/or dyspnoea when walking quietly on level ground, or both; they had had no change in symptom severity or treatment in the preceding 4 weeks, had shown no signs of a respiratory tract infection in the month preceding or during the trial, had not been taking oral or inhaled corticosteroids for at least three months and had a best post-bronchodilator FEV<sub>1</sub>/FVC of less than 0.7 15 min after salbutamol 200 µg [7]. Patients with allergic rhinitis, atopy, and positive skin test or with a total blood eosinophil count over 400/mm<sup>3</sup> were excluded. Patients were also excluded if they had any coexisting cardiovascular or lung disorder. Table 1 outlines the baseline characteristics of the population studied.

No oral bronchodilators were permitted for 1 week before and during the study, whereas inhaled short-acting bronchodilator drug and inhaled long-acting bronchodilator agent were not permitted for at least 12 and 24 h prior to each test, respectively. Consumption of cola drinks, coffee, tea, and smoking in the hours before and during the investigation were also avoided.

The study was performed using a double-blind, double-dummy, randomized, crossover design. It took place over two non-consecutive days. It was carried out according to the rules of the declaration of Helsinki. The institutional review board approved it. All patients provided written informed consent to participate in the study.

Single doses of formoterol/beclomethasone dipropionate (Foster Modulite) 12/200 (2 × 6/100) µg (metered dose), formoterol/budesonide (Symbicort Turbuhaler) 9/320 (2 × 4.5/160) µg (delivered dose) or formoterol (Oxis Turbuhaler) 9 µg (delivered dose) were administered.

Measurements of FEV<sub>1</sub> were performed before and 3, 6, 10, 15, 20, 30, and 60 min after inhalation of each treatment. In the first 10 min, single FEV<sub>1</sub> measurements were recorded, and from 15 min onwards the best of three recorded FEV<sub>1</sub> manoeuvres was recorded.

Considering data of our previous pilot study that documented a difference between formoterol and formoterol/budesonide in FEV<sub>1</sub>-AUC<sub>0–15min</sub> (area under the FEV<sub>1</sub> curve from 0 to 15 min) of

300 ml [4], the minimum total required sample size was 50, with minimum required sample size per group of 25 given an  $\alpha$ -level of 0.05, an anticipated effect size (Cohen's *d*) of 0.725, and a desired statistical power level of 0.8. The primary objective of this study was to assess the onset of action of formoterol/beclomethasone compared with that of formoterol/budesonide. The primary variable for this comparison was therefore the average FEV<sub>1</sub> during the first 15 min (FEV<sub>1</sub>-AUC<sub>0–15min</sub>). Onset was also compared using the absolute FEV<sub>1</sub> measured 15 min after inhalation of study drugs, and time to onset, defined as the first time to 15% or 200 ml increase in FEV<sub>1</sub> over baseline recorded within 60 min). Comparisons of baseline characteristics among the two treatments were performed by ANOVA analysis and Fisher's exact test. Analysis of spirometric data was performed using the Student's *t*-test for paired variables. The time-averaged changes in the 60-min period following each drug administration were compared by means of the distribution free crossover analysis [8]. The AUCs were calculated for each patient by means of the trapezoidal rule. Comparisons of AUC values among the three treatments were performed by ANOVA analysis with Bonferroni correction for multiple comparisons. A probability level of  $p < 0.05$  was considered significant for all tests.

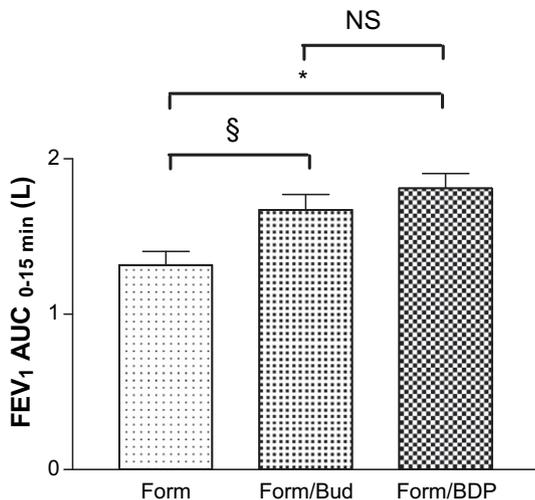
### 3. Results

All patients completed the three-day study. No significant differences occurred between the baseline spirometric values of the three treatment groups for FEV<sub>1</sub> ( $p = 0.2797$ ).

Both formoterol/beclomethasone and formoterol/budesonide elicited a larger mean FEV<sub>1</sub>-AUC<sub>0–15min</sub> than formoterol alone (difference: 0.493 L, 95% CI: 0.170–0.816,  $p < 0.01$ ; and 0.354 L, 95% CI: 0.031–0.677,  $p < 0.05$ , respectively), whereas there was no significant difference between their FEV<sub>1</sub>-AUC<sub>0–15min</sub> (difference: 0.139 L, 95% CI: -0.184–0.4619,  $p > 0.5$ ; Fig. 1). Fig. 2 shows individual changes in FEV<sub>1</sub>-AUC<sub>0–15min</sub> from those induced by

**Table 1**  
Anthropometric data and pulmonary function of patients.

Patient	Sex	Age (years)	Height (cm)	Smoking history (pack/year)	FEV <sub>1</sub> (% predicted)	FVC (% predicted)	% reversibility
1	M	65	165	10/daily (63)	40	49	16
2	M	71	169	Ex (45)	67	75	13
3	M	67	158	Ex (44)	63	71	7
4	F	59	155	30/daily (51)	38	45	11
5	M	62	164	20/daily (66)	40	56	6
6	M	68	169	15/daily (38)	61	67	9
7	M	74	170	Ex (60)	49	72	10
8	M	66	163	10/daily (35)	32	37	14
9	M	63	165	Ex (72)	52	58	8
10	M	57	172	15/daily (39)	59	70	9
11	M	64	170	10/daily (71)	56	62	2
12	F	59	158	30/daily (73)	50	59	13
13	F	70	165	15/daily (41)	66	76	12
14	M	75	162	20 daily (80)	47	58	16
15	F	55	165	30/daily (49)	51	59	8
16	F	73	168	Ex (70)	51	62	17
17	M	71	163	Ex (77)	36	41	13
18	M	67	173	Ex (85)	36	43	3
19	M	63	176	20/daily (45)	34	37	13
20	M	57	166	40/daily (79)	40	52	10
21	M	64	175	Ex (120)	48	70	10
22	F	61	148	20/daily (70)	31	43	19
23	F	67	158	20/daily (45)	71	79	6
24	M	70	164	Ex (70)	62	69	8
25	F	73	146	10/daily (53)	32	39	15
26	M	60	172	Ex (50)	41	48	2
27	M	66	178	15/daily (48)	64	75	3
28	M	69	169	20/daily (65)	52	66	7

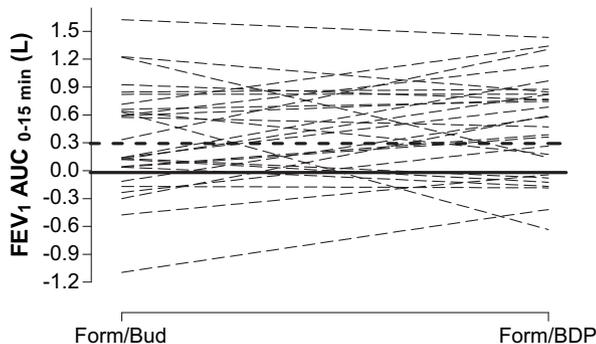


**Fig. 1.** Mean changes in FEV<sub>1</sub> AUC from baseline values to 15 min after inhalation of formoterol (Form) 9 µg via Turbuhaler, Form/budesonide (Bud) 9/320 µg via Turbuhaler or Form/beclomethasone dipropionate (BDP) 12/200 µg via Modulite. Bars are SE: §*p* = 0.0031, \**p* < 0.0001, NS, non significant.

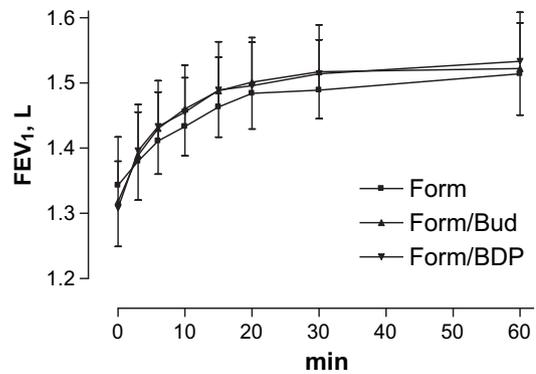
formoterol alone elicited by formoterol/budesonide or formoterol/beclomethasone.

Also the changes in FEV<sub>1</sub> 15 min after inhalation of formoterol/beclomethasone combination (0.178 L; 95% CI: 0.153–0.202) or formoterol/budesonide combination (0.170 L; 95% CI: 0.146–0.194) were greater than that induced by formoterol alone (0.135 L; 95% CI: 0.118–0.152) (Fig. 3). A significant difference was found between the improvement after formoterol/beclomethasone and formoterol alone (0.048 L; 95% CI: 0.020–0.065; *p* = 0.0006) or formoterol/budesonide and formoterol alone (0.035 L; 95% CI: 0.011–0.060; *p* = 0.0063), whereas there was no significant difference between the improvement after formoterol/beclomethasone and that after formoterol/budesonide (*p* = 0.5743).

Thirteen patients out of 28 were unable to achieve a 15% improvement in FEV<sub>1</sub> after formoterol, eleven did not show this change after formoterol/budesonide, and six after formoterol/beclomethasone. In responsive subjects, formoterol was associated with a rise in FEV<sub>1</sub> of at least 15% after 30 min (95% CI: 18–43), formoterol/budesonide after 15 min (95% CI: 11–18), and formoterol/beclomethasone after 17 min (95% CI: 10–24) (Fig. 4). Fourteen out of 28 were unable to achieve a 200 ml improvement in FEV<sub>1</sub> after formoterol and formoterol/budesonide and eight did not



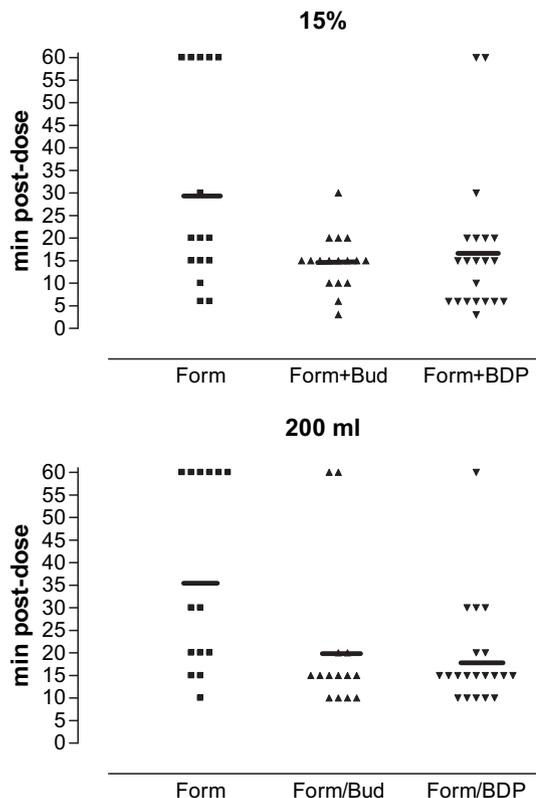
**Fig. 2.** Individual changes in FEV<sub>1</sub>–AUC<sub>0–15min</sub> from those induced by formoterol (Form) 9 µg via Turbuhaler (solid line) elicited by Form/budesonide (Bud) 9/320 µg via Turbuhaler or Form/beclomethasone dipropionate (BDP) 12/200 µg via Modulite. Dotted line indicates the minimal importance difference in FEV<sub>1</sub>–AUC<sub>0–15min</sub> (0.3 L).



**Fig. 3.** Mean changes in FEV<sub>1</sub> (L) from baseline value up to 60 min after inhalation of formoterol (Form) 9 µg via Turbuhaler, Form/budesonide (Bud) 9/320 µg via Turbuhaler or Form/beclomethasone dipropionate (BDP) 12/200 µg via Modulite. Bars are SE. *p* < 0.01 for change of Form vs. baseline at 15 min, *p* < 0.001 for all other changes vs. baseline.

show this change after formoterol/beclomethasone. In responsive patients, formoterol/budesonide induced this increase after 21 min (95% CI: 11–31), formoterol/beclomethasone after 19 min (95% CI: 13–24), and formoterol alone after 37 min (95% CI: 25–49) (Fig. 4).

The mean increases in FEV<sub>1</sub> from baseline were always significant (*p* < 0.01 or *p* < 0.001) with all treatments and higher after formoterol/beclomethasone than budesonide/formoterol or formoterol alone, but differences between combination treatments were not significant (*p* > 0.05) at each explored time point (Fig. 3).



**Fig. 4.** Patients having an increase in FEV<sub>1</sub> of at least 15% or 200 ml over baseline at different time-points within 60 min after inhalation of formoterol (Form) 9 µg via Turbuhaler, Form/budesonide (Bud) 9/320 µg via Turbuhaler or Form/beclomethasone dipropionate (BDP) 12/200 µg via Modulite.

#### 4. Discussion

This study confirms and enlarges the documentation that the addition of budesonide to formoterol influences the fast onset of action of formoterol [4] and, moreover, it shows that also the addition of beclomethasone dipropionate to the same dose of formoterol is able to faster the onset of action of this  $\beta_2$ -agonist. Our results are in keeping with early reports of acute potentiation of rapid bronchodilator actions by corticosteroids [9,10].

It must be mentioned that inhaled corticosteroids alone do not seem to be able to relieve early airway response represented as changes in FEV<sub>1</sub>. For instance, a rather recent study showed that a single dose of budesonide (400  $\mu$ g)/formoterol (12  $\mu$ g) combination or formoterol alone, but not budesonide alone, given few minutes after airway allergen challenge was able to alleviate early airway response (0–3 h) [11]. Other studies showed similar results regarding the effect of inhaled corticosteroids [12,13], although there are also several reports that suggest that corticosteroids can induce rapid improvement in pulmonary function [14–16].

On the contrary, there is some evidence that corticosteroids improve  $\beta_2$ -adrenergic bronchodilation. Through delayed transcriptional action on airway cells, corticosteroids could increase  $\beta_2$ -receptor numbers [17] and restore  $\beta_2$ -receptor coupling to G proteins that mediate adenylyl cyclase stimulation [18]. However, it has been known that after administration of corticosteroids, a minimum of 1–2 h are required for induction of their genomic effects, i.e. appearance of *de novo* synthesised proteins [19] whereas, in our study it is likely that the facilitating action of budesonide and beclomethasone dipropionate was due to a non-genomic effect. In fact, it appeared almost instantaneously, and certainly within a time frame that precluded significant modifications of gene expression.

Corticosteroid actions that occur within seconds to a few minutes have been referred to as non-genomic or rapid action of corticosteroids and are non-classical actions [20]. These rapid non-genomic effects are assumed to be mediated by three mechanisms: (1) physicochemical interactions with cellular membranes (non-specific non-genomic effects) [21,22]; (2) cytosolic glucocorticoid receptor (cGCR)-mediated non-genomic effects [23]; and (3) membrane-bound glucocorticoid receptor (mGCR)-mediated non-genomic effects [24]. It is also possible that inhaled corticosteroids increase the tissue concentration of a cationic  $\beta_2$ -agonist, such as formoterol, by inhibiting its local disposal on the one hand and by delaying the vascular clearance by causing vasoconstriction through diminished local disposal of noradrenaline on the other [25,26].

This clinical study does not allow us to determine which of these actions is that underlying the more rapid onset of bronchodilation of formoterol when it is associated with an inhaled corticosteroid, but it confirms that the presence of an inhaled corticosteroid is crucial for having this effect. It is intriguing that topical corticosteroids at very low concentrations show greater non-genomic potency than systemic corticosteroids likely because they are more lipophilic than systemic corticosteroids due to their esterification at position 17 $\alpha$  and thus better able to diffuse and intercalate into biological membranes [27]. In any case, it has been documented that some corticosteroids have a larger effect on non-genomic mechanisms than others, although the non-genomic selectivity of corticosteroids may be mechanism-dependent [28,29].

We still do not know whether there are substantial differences in non-genomic effects of budesonide and beclomethasone dipropionate. Nonetheless, it is worthy to be highlighted that apparently there is no difference between beclomethasone 200  $\mu$ g and budesonide 400  $\mu$ g (metered doses) in influencing the onset of bronchodilation of formoterol 12  $\mu$ g (metered dose). However, we must underline that beclomethasone dipropionate has been

administered via Modulite and budesonide via Turbuhaler and it is widely accepted that comparisons of inhaled corticosteroids are only scientifically sound when they are given in equivalent doses through comparable delivery devices.

Instead, it is possible that the difference in delivery devices has been important in allowing the same effect with a lower dose of beclomethasone dipropionate. The new fixed beclomethasone dipropionate (100  $\mu$ g per each inhalation) and formoterol (6  $\mu$ g per each inhalation) combination delivered via Modulite lays in the innovative formulation characterised by an extrafine particle size of drug particles [30]. In fact, both beclomethasone dipropionate and formoterol display a mass median aerodynamic diameter (MMAD) in the range of 1.4–1.5  $\mu$ m. Consequently, the amount of drug delivered to the lung, and responsible for the therapeutic effect, is increased whereas the dose of the drug remaining in the upper airways (and potentially responsible for systemic side effects) is reduced. For the same clinical effect, with beclomethasone dipropionate/formoterol HFA extrafine, the beclomethasone dipropionate dose is 2.5-fold lower than the conventional beclomethasone dipropionate chlorofluorocarbon (CFC) product: 400  $\mu$ g beclomethasone dipropionate extrafine was clinically equivalent to 1000  $\mu$ g of the reference beclomethasone dipropionate CFC formulation. This means that a dose of 100  $\mu$ g of beclomethasone dipropionate in extrafine HFA formulation is equivalent, in terms of efficacy, to 250  $\mu$ g of beclomethasone dipropionate in traditional CFC formulation, with a significant lower risk of systemic side effects. It is also important that both components are distributed throughout the lung, including the peripheral airways, which in turn increases the potential for synergistic interaction [31].

In summary, this study confirms the rapid onset of action of formoterol when combined with an inhaled corticosteroid and indicates that the onset of bronchodilation of formoterol/beclomethasone Modulite and formoterol/budesonide Turbuhaler are similar in patients with COPD and greater than formoterol alone. The rapid onset of action may represent a significant benefit for subjects with COPD, especially those with nighttime or early morning symptoms due to reversible bronchospasm.

#### Conflict of interest

This paper describes a spontaneous study, which was not supported by any Drug Company.

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