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BECLOMETHASONE/FORMOTEROL *VS* BUDESONIDE/FORMOTEROL COMBINATION THERAPY IN ASTHMA

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ABSTRACT (189)

The present study was designed to compare the fixed combination of beclomethasone and formoterol in HFA Modulite® pMDI, with the combination of budesonide and formoterol given via the Turbuhaler® dry powder inhaler.

This was a phase III, multinational, multicentre, double-blind, double-dummy, randomised, two-arm parallel groups, controlled study design. After a 2-week run-in period, 219 patients with moderate to severe asthma were randomised to a 12-week treatment with beclomethasone 200 mcg plus formoterol 12 mcg bid delivered via a pressurised metered dose inhaler or budesonide 400 mcg plus formoterol 12 mcg bid delivered via a dry powder inhaler.

The analysis of non-inferiority on primary outcome, morning peak expiratory flow in the last 2 weeks of treatment, showed no difference between groups. A statistically significant improvement from baseline in lung function, symptoms and rescue medication use was observed in both groups at all time points. No differences were observed between treatments in either rates of asthma exacerbations or frequency of adverse events.

The new fixed combination of beclomethasone and formoterol in HFA Modulite® pMDI is equivalent to the marketed combination of budesonide and formoterol in terms of efficacy and tolerability profile.

INTRODUCTION

International guidelines recommend the addition of a long-acting beta$_2$-agonist (LABA) to low-medium dose inhaled corticosteroids (ICS) in patients whose asthma is not fully controlled by ICS alone [1]. Several clinical trials have shown that the addition of a LABA to ICS is more beneficial than increasing the dose of ICS alone in terms of both symptom control and pulmonary function [2-6]. Treatment with an ICS/LABA combination in a single inhaler, with the same efficacy and safety profile as the two drugs given separately, may also produce a better adherence to treatment [7-9].

Beclomethasone dipropionate (BDP) is a widely used ICS with a favourable risk/efficacy profile [10]. BDP has been recently developed as an extra-fine formulation with hydrofluoroalkane (HFA) propellant which has been shown to be effective in controlling asthma symptoms in both adults and children at a 2.5-fold lower daily dose as compared to chlorofluorocarbon (CFC)-BDP [11-13]. The rationale behind an extra-fine formulation of an ICS is mainly based on accumulating evidence that in asthma the inflammation and remodelling process takes place in all parts of the airways, including peripheral bronchioles [14-20]. Since extra-fine formulations result in drug delivery to both central and peripheral airways [21], airway inflammation could be treated uniformly throughout the lower respiratory tract. A reduced ICS dose implies a lower systemic exposure and a lower overall risk of steroid specific side effects [22]. A new technology called Modulite® using the HFA-134a propellant has been recently developed to obtain an extra-fine formulation of new drugs as well as reformulation of pre-existing drugs in a pressurized metered dose inhaler (pMDI) [23]. This technology has been used to develop the first fixed combination containing extra-fine BDP and formoterol in HFA solution with pMDI device.

The main aim of the present study was to assess whether the efficacy and tolerability of the fixed combination beclomethasone/formoterol pMDI HFA Modulite® are non-inferior when

compared with those of budesonide/formoterol Turbuhaler® dry powder inhaler (DPI) in patients with moderate to severe asthma whose symptoms are not controlled with ICS alone.

Budesonide/formoterol combination has been selected as comparator because it contains the same LABA, formoterol. Since the extra-fine BDP formulation allows for a higher percentage of the nominal dose to be delivered to the lungs, the BDP dose used in this study is half the budesonide dose, and in accordance with GINA international guidelines , daily doses of 400 mcg extra-fine BDP and 800 mcg budesonide are equivalent [1].

PATIENTS AND METHODS

Patients

The study was carried out in 13 centres in Europe. Adult patients aged 18-65 years with moderate to severe persistent asthma, and with a forced expiratory volume in one second (FEV_1) between 50% and 80% of predicted normal values were eligible to take part in the study. All patients were previously treated with ICS at a daily dose ≤ 1000 mcg of BDP-equivalent and had asthma symptoms not adequately controlled defined as: presence of daily asthma symptoms > once a week, night-time asthma symptoms > twice a month, and daily use of short-acting β2-agonists. Thus, because these patients were not controlled by moderate-high doses of inhaled corticosteroids, according to international guidelines [1] they were classified as moderate persistent asthmatics. These findings were based on recent medical history and were to be confirmed in the 2-week run-in period.

Patients satisfying any of the following criteria were excluded from the study: COPD, current or ex-smokers (≥ 10 pack/years); severe asthma exacerbation or symptomatic infection of the airways in the previous 8 weeks; ≥ 3 courses of oral corticosteroids or hospitalisation due to asthma in the previous 6 months; treatment with LABAs, anticholinergics or antihistamines in the previous 2 weeks, and/or with topical or intranasal corticosteroids and leukotriene antagonists in the previous 4 weeks; change of ICS dose in the previous 4 weeks. Patients with asthma exacerbation during the run-in did not enter the treatment phase. Moreover, patients with

an increase in peak expiratory flow (PEF) > 15% as compared to values measured in the screening visit, after 2 weeks run in treatment with up to 1000 mcg daily BDP equivalent, were not randomised. This cut-off value was taken as an indicator of the positive response to ICS suggesting that they might not require combination therapy.

The study was performed in accordance with the Good Clinical Practice guidelines recommended by the International Conference on Harmonization of Technical Requirements. The protocol was approved by the institutional review board of each centre and written informed consent was obtained from each participant prior to study initiation.

Study Design

The study was designed to evaluate the non-inferiority of beclomethasone/formoterol combination versus equipotent doses of the combination of budesonide/formoterol.
This was a phase III, multinational, multicentre, double-blind, double-dummy, randomised, two-arm parallel groups, controlled study design. Enrolled patients entered a 2-week run-in period before being randomised to study groups. Inhaled rescue salbutamol was permitted at any time but at least 6 hours before pulmonary function tests (PFT). Oral corticosteroids were permitted only in the case of asthma exacerbations; inhaled or oral sodium cromoglycate or nedocromil sodium, and theophyllines taken at study entry were permitted at a constant dose throughout the study period. ICS were continued at unchanged dose during run-in, while all the other anti-asthma medications were not permitted at any time.

At the end of run-in period, symptoms and rescue medication use were reviewed and patients whose asthma was not adequately controlled were randomised to the 12-week treatment phase with beclomethasone/formoterol 100/6 mcg pMDI (FOSTER™, Chiesi Farmaceutici, Parma, Italy) or budesonide/formoterol 200/6 mcg DPI (Symbicort®Turbuhaler®, AstraZeneca, Lund, Sweden) . Both study drugs were administered in two inhalations twice daily (morning and evening) to obtain daily doses of 400/24 µg beclomethasone/formoterol or 800/24 µg budesonide/formoterol. As the formulation of the study drugs differed, patients from each group were also given placebo inhalers of the respective pMDI and DPI devices to ensure the double blind (double dummy) design. Devices and respective placebo were identical in shape and colour and patients were instructed to take two inhalations from each device in the morning and in the evening.

Patients were asked to visit the clinic six times, at the following scheduled times: study entry (visit 1, beginning of run-in period), end of run-in period/start of treatment period (visit 2, randomisation) and after 2, 4, 8 and 12 weeks of treatment (visits 3, 4, 5 and 6).

Protocol outcome measures

The primary outcome variable was morning pre-dose PEF measured by patients, at least 12 hours after previous evening dose, in the last two weeks of treatment period (weeks 11-12). PFT was performed at each visit before study drug intake at least 12 hours after previous evening dose, meaning that the morning dose of study drug was taken onsite after PFT. The following PFT were measured in accordance with standard procedure [24]: FEV_1, L, forced vital capacity (FVC, L), PEF, L/min and mid expiratory flow at 50% vital capacity (MEF_{50}, L/sec). The best of three values was used for analysis.

Patients used a portable flow meter (Piko-1, Qubisoft, Padova, Italy), in compliance with ATS standard 2004, to measure their pre-dose PEF and FEV_1 morning and evening. The best of three readings was used for data analysis. Patients recorded asthma symptom scores and rescue salbutamol intake twice daily (in the morning for night time and in the evening for daytime) on a diary card [5]. The percentage of symptom-free and salbutamol-free days (i.e. without 24-hour symptoms or without use of salbutamol) was calculated.

The occurrence of asthma exacerbations was evaluated at all post-baseline visits; exacerbations were categorized as mild, moderate or severe as previously described [4].

Adverse events (AEs) were reported throughout the study period . Vital signs (heart rate and blood pressure) were also measured at all visits. A 12-lead ECG with measurement of the QTc interval was performed at baseline and at the end of the study. Patients recorded their twice daily intake of study drugs on diary cards; a range between 75-125% of scheduled administrations was considered as adequate for a satisfactory level of adherence.

Statistics

The study was designed to be able to evaluate the non-inferiority of beclomethasone/formoterol versus budesonide/formoterol and the sample size calculation was made by defining the limit for non-inferiority as the lower limit of the unilateral 97.5% confidence interval (CI) for the difference between least square means (LSMs) of morning PEF

being -20 L/min or greater. Estimating a standard deviation of 45 L/min and an expected difference between means equal to zero, a total of 90 patients in each group were required to have >80% power for satisfying the above hypothesis [25]. Beclomethasone/formoterol was defined as non-inferior to budesonide/formoterol if the lower limit of the unilateral 97.5% CI for the difference between LSMs was ≥ -20 L/min.

Data analysis was carried out in the following populations: safety population (SAF), defined as all randomised patients for which there was evidence of drug intake; intention-to-treat (ITT), i.e. all randomised patients who received at least one dose of study drug and with post-baseline data; modified ITT (M-ITT), i.e. excluding data measured in the 30 days after the intake of oral corticosteroids for asthma exacerbation; and per-protocol (PP), i.e. all patients in the ITT analysis set without major protocol violations (e.g. poor compliance to study drug or procedures, use of non permitted medications). Post-baseline missing values were replaced with the last observation carried forward (LOCF) method. The same method was used to replace data measured in the 30 days after the intake of oral corticosteroids for the M-ITT population. Baseline values were the mean values of the last week of the run-in period for variables recorded daily by patients on diary cards and values measured at the end of run-in visit for variables measured at clinics; two-weekly means were also calculated during the entire study period for variables recorded on diary cards. Demographic and baseline characteristics were summarised by means of descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum) or frequency distributions (number and percent), as appropriate. For the primary efficacy analysis, the one-sided 97.5% confidence interval for the difference between beclomethasone/formoterol and budesonide/formoterol in final PEF recorded by patients into diary cards was used in order to demonstrate the non-inferiority. An analysis of covariance (ANCOVA) model with terms for treatment, geographic region and baseline value as covariate was used. For the secondary efficacy variables, the same ANCOVA model was used.

The number of patients with asthma exacerbation in the two groups was summarised by means of frequency distribution and a Chi square test was used to compare the two treatment groups. Time to first exacerbation was compared by means of Kaplan-Meier curves. The number of patients with AEs occurred during treatment period was summarised by means of frequency distribution. Differences between treatment groups were evaluated using Chi square test or two-tailed Fisher's exact test. The results of the ECG were presented in terms of

normal/abnormal findings, while QTc interval was analysed using the 95% CI for the final values from an ANCOVA model.

RESULTS

Patient flow and baseline characteristics are shown in Figure 1a and Table 1. Two hundred and forty patients were screened and 219 were randomised while 21 were considered not eligible. One hundred and nine patients (47.8%) were randomly assigned to the beclomethasone/formoterol arm and 110 (52.2%) to the budesonide/formoterol arm. Six patients in the beclomethasone/formoterol group and 13 patients in the budesonide/formoterol group were withdrawn from the study and 103 patients in the beclomethasone/formoterol group and 97 patients in the budesonide/formoterol group completed the 3 months study period. One patient in the budesonide/formoterol group did not show intake of study drug, thus the safety population included 218 patients (109 in each group). Two beclomethasone/formoterol-treated patients did not have post-baseline data and were excluded from the ITT analysis set. Four patients in the beclomethasone/formoterol group and 10 in the budesonide/formoterol group were also excluded from the PP analysis due to major protocol violation. Considering the small difference in the number of patients in the ITT and PP populations (figure 1b), results are shown for the ITT population only.

Baseline data (Table 1) of the two groups were well matched in terms of demographics, pulmonary function, symptoms and time from first asthma diagnosis. The two groups had comparable baseline asthma severity and there were no differences between groups in mean ICS dose.

Patient compliance in both groups was similar, with mean percentage of administered drug being 96.8 ± 3.2 % in the beclomethasone/formoterol group and 95.6 ± 7.8 % in the budesonide/formoterol group.

EFFICACY

Lung function

With respect to the primary outcome, morning pre-dose PEF during the last two weeks of the treatment period, the difference between adjusted means (Least Square Means, LSMs) of the beclomethasone/formoterol group (338.3 L/min) and the budesonide/formoterol group (337.8 L/min) was 0.49 L/min. The 97.5% unilateral CI for this difference was -11.97, which was within the pre-specified limit of -20 L/min, thus showing that beclomethasone/formoterol was non-inferior to budesonide/formoterol; moreover, the 95% bilateral CI for the difference between LSMs was -11.97 to 12.95.

As compared to baseline, both groups showed marked and significant improvements in morning PEF; the mean increases from baseline to endpoint were 29.43 ± 52.8 L/min (95% CI: 19.31 to 39.54) in the beclomethasone/formoterol group and 28.63 ± 43.4 L/min (95% CI: 20.39 to 36.87) in the budesonide/formoterol group (Figure 2). Similarly, no significant difference between groups was observed in evening PEF at the end of treatment, and a significant increase as compared to baseline was shown in both groups: the mean improvements in the final 2-week period were 27.50 ± 53.35 L/min in the beclomethasone/formoterol group and 27.43 ± 39.39 L/min in the budesonide/formoterol group (95% CI for the difference between LSMs: -12.26 to 11.94). A significant increase vs. baseline was shown in daily FEV_1 measured by patients in both groups with no significant difference between groups at the end of treatment.

The results of the PFT measured at the on-site visits (FEV_1, FVC, PEF and MEF_{50}) are shown in Table 2, and in Figure 3. Statistically significant improvements from baseline were found in both groups from week 2 onwards in all lung function parameters with no significant difference between groups at the end of treatment.

Symptoms

Clinical symptoms' scores significantly decreased from baseline in both groups from the first two-week period onwards as well as daily use of rescue salbutamol, with no significant difference between groups at the end of treatment. The mean decreases from baseline to endpoint (weeks 11-12) in daytime symptoms' scores were -0.93 ± 0.78 U and -0.86 ± 0.86 U in the beclomethasone/formoterol and in the budesonide/formoterol groups respectively ($p<0.001$ vs baseline). The mean changes from baseline to the end of treatment in night-time symptoms' score were -0.73 ± 0.75 U and -0.66 ± 0.84 U in the beclomethasone/formoterol and in the

budesonide/formoterol groups respectively ($p<0.001$ vs baseline). Daily use of rescue medication significantly decreased from 2.16 ± 1.15 puffs/day in the last week of run-in to 0.76 ± 0.92 puffs/day in the last two weeks of treatment period in the beclomethasone/formoterol group and from 2.28 ± 1.50 puffs/day to 0.87 ± 1.04 in the budesonide/formoterol group.

The mean percentages of symptom-free days and of days without need of rescue salbutamol over the entire treatment period are shown in Figure 4. As can be seen, there are no significant differences between the two groups, but statistical significance is reached in both groups when the data are compared to baseline ($p<0.001$).

Exacerbations

Asthma exacerbations occurred in 29 patients, 17 (15.9%) in the beclomethasone/formoterol group and 12 (11.0%) in the budesonide/formoterol group. No severe exacerbations occurred, while moderate exacerbations requiring one course of oral corticosteroids were reported only in 2 patients in each group. The ratio days of exacerbation/days of exposure was 0.013 (0.04) in the beclomethasone/formoterol group and 0.023 (0.11) in the budesonide/formoterol group ($p=0.38$), ie not statistically different. The median time to the first exacerbation was 29 days (range 1-77) in the beclomethasone/formoterol group and 24 days (range 1-69) in the budesonide/formoterol group ($p = 0.342$ between groups in the Kaplan-Meier estimate for survival curves).

Tolerability

No significant differences were observed between the two treatment groups as reported in Table 3. AEs were reported by 15 (13.8%) patients in the beclomethasone/formoterol group and 18 (16.5%) in the budesonide/formoterol group (p=ns), but none was classified as serious. Only one patient in the budesonide/formoterol group discontinued the study due to throat pain, palpitation and hand tremors.

No changes in blood pressure were observed in either group during the study period. A small but significant increase in heart rate was observed only at visit 3 in the budesonide/formoterol group (1.67 ± 6.71 bpm; 95% CI: 0.39 to 2.95); no other significant changes were observed in either group

No evidence of ECG changes or QTc interval prolongation was reported in either group.

DISCUSSION

In this study, the effects of the new pMDI containing the beclomethasone/formoterol combination were compared with those of the DPI Turbuhaler® containing combined budesonide/formoterol in moderate to severe asthma patients over a 3month period. The results of the study showed that beclomethasone/formoterol pMDI 400/24 mcg/day was as effective as budesonide/formoterol 800/24 mcg/day in morning PEF in the last two weeks of treatment period and this was confirmed also by the other lung function and clinical efficacy variables evaluated.

The two treatment groups were well matched in terms of asthma severity and baseline values of all outcome measures evaluated. The population in both treatment groups had a real potential to improve from baseline to endpoint as demonstrated by increases in lung function during the course of the study, showing real equivalence between the two study treatments. In addition, reassurance is provided that the equivalence was not due to lack of efficacy for both treatments or to maximal lung function potential already being present prior to dosing [26]. The increases obtained in both groups in the primary efficacy variable were both statistically and clinically significant, supporting the fact that this study had the potential to detect any potential differences between groups.

The results of the other pulmonary function parameters, either measured by patients twice daily or measured at the site visits, showed comparable increases in the two groups, with no significant differences between treatments being observed. Comparable improvements in the two groups were also observed in the assessment of clinical symptoms and in the use of rescue salbutamol, which significantly decreased from baseline with no difference between groups. Similarly, no difference was found in the rates of asthma exacerbations and in time to first exacerbation. It was however not possible to treat exacerbation rate as a primary endpoint in this study because exposure time was limited, and more patients are needed in order to detect potential differences between treatments.

The two combination treatments showed similar tolerability profile. During the 3-month study period, the new beclomethasone/formoterol combination was at least as well tolerated as the standard combination containing budesonide, an ICS that exhibits low systemic activity [27]. Worsening of asthma and upper/lower respiratory tract infections were the most common events, likely due to seasonal affections rather than to drug tolerability concerns as suggested by their

similar frequency in the two groups. No evidence of detrimental effects on ECG or QTc interval prolongation, a potential cardiovascular effect of beta2-adrenergic drugs [28], was reported.

Both patient compliance and long-term pulmonary function benefit from single inhaler treatment with LABA and ICS [3, 29]. This treatment regimen allows the patient to perceive the relief of symptoms provided by the LABA, thus enhancing compliance, while receiving a maintenance dose of the ICS that acts on the chronic airways inflammation hence improving disease control. Moreover, the use of fixed combinations reduces the direct and indirect treatment costs compared with the administration of the same drugs given by separate inhalers [9]. Taking into consideration the evidence-based advantages offered by the combined administration of LABA/ICS the new beclomethasone/formoterol combination is a valid alternative in the treatment of asthma. In view of the fact that BDP delivered via a pMDI is an established ICS used worldwide, the availability of a new beclomethasone/formoterol combination may also allow patients not adequately controlled with ICS alone to continue using the same device with the same inhalation technique and the same molecule.

Although the daily nominal dose of beclomethasone used in the study was two-fold lower than the equipotent daily dose of budesonide present in the budesonide/formoterol combination, we cannot claim that extra-fine beclomethasone was twice as potent as budesonide, as the minimum dose required to achieve asthma control was not established in the study.

Similarly, the difference in corticosteroids dose between the two treatment groups does not imply a difference in systemic exposure, as this depends not only on the nominal dose but also on the amount of drug reaching the lungs and on the pharmacokinetics properties of the two corticosteroids. Previous studies indicated that the fine particle dose of budesonide, ie the amount of drug supposed to reach the lower airways, after 1 inhalation of DPI combination 200/6 mcg budesonide/formoterol, is 46,0 mcg [30], whereas the fine particle dose of beclomethasone, after 1 inhalation of extra-fine 100/6 mcg beclomethasone/formoterol, is 34,5 mcg [31].

In conclusion, our study is the first trial to compare the efficacy and safety of a new pMDI containing the combination beclomethasone/formoterol with a standard combination of budesonide/formoterol in patients with moderate to severe asthma whose symptoms were not adequately controlled with ICS alone. The results have shown that the two tested combinations produced equivalent benefits in lung function and in clinical symptoms, and led to a significant decrease in use of rescue medications. In addition, no significant differences were observed

between groups in terms of rates of asthma exacerbation and/or the need of additional prevention therapy.

The study shows that the new pMDI containing the beclomethasone/formoterol combination is a valid alternative for the treatment of asthma.

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G.Nicolini is an employee of the sponsor

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Table 1. Baseline characteristics in the two groups; BDP/F=beclomethasone/formoterol; BUD/F=budesonide/formoterol; n=number of observations; all values are mean ± SD; p=ns between groups for all comparisons

	BDP/F	**BUD/F**
Sex:		
Males (*n*)	45 (42.1%)	46 (42.2%)
Females (*n*)	62 (57.9%)	63 (57.8%)
Age, *years*	43.4 ± 12.3	46.0 ± 11.1
Weight, *kg*	72.2 ± 12.9	75.6 ± 16.3
Height, *cm*	168.8 ± 9.6	168.7 ± 9.8
Allergies	69(64.5%)	70(64.2%)
ICS dose, mcg (BDP equivalent)	787.9 ± 257.2	808.0 ± 262.7
Time from first diagnosis, *years*	11.8 ± 9.5	12.4 ± 10.4
FEV_1, *% predicted*	70.5 ± 10.7	69.3 ± 9.7
FEV_1, L	2.30±0.71	2.21±0.64
FEV_1, *% change in the reversibility test*	23.6 ± 10.1	26.5 ± 12.1
Morning PEF, *L/min*	308.9 ± 106.6	305.2 ± 100.0
Evening PEF, *L/min*	317.5 ± 112.1	315.0 ± 98.5

Table 2: Pulmonary function tests in the two groups measured at the on-site visits: mean changes from baseline (ITT population); BDP/F=beclomethasone/formoterol; BUD/F=budesonide/formoterol; p values refer to comparison between groups in final values (week 12, last visit)

Measure	**Group**	**Week 2 (mean ± SD)**	**Week 4 (mean ± SD)**	**Week 8 (mean ± SD)**	**Week 12 (mean ± SD)**	**p value**
FEV_1 (*L*)	BDP/F	0.26 ± 0.38	0.29 ± 0.46	0.33 ± 0.49	0.28 ± 0.47	0.354
	BUD/F	0.33 ± 0.41	0.37 ± 0.44	0.40 ± 0.44	0.33 ± 0.44	
FVC (*L*)	BDP/F	0.23 ± 0.47	0.27 ± 0.53	0.33 ± 0.54	0.26 ± 0.52	0.557
	BUD/F	0.26 ± 0.49	0.31 ± 0.53	0.34 ± 0.52	0.21 ± 0.52	
PEF (*L/min*)	BDP/F	52.29 ± 72.81	59.99 ± 74.03	63.66 ± 74.28	56.04 ± 72.97	0.806
	BUD/F	55.71 ± 74.35	57.47 ± 71.25	64.36 ± 75.94	53.16 ± 77.29	
MEF50 (*L/sec*)	BDP/F	0.42 ± 0.66	0.43 ± 0.71	0.48 ± 0.84	0.43 ± 0.82	0.512
	BUD/F	0.48 ± 0.69	0.53 ± 0.75	0.63 ± 0.86	0.50 ± 0.80	

Table 3. Adverse events observed in > 2% of patients (numbers and percentages in the population analysed for safety); BDP/F=beclomethasone/formoterol; BUD/F=budesonide/formoterol;

Adverse event	**BDP/F(n = 109)**	**BUD/F (n = 109)**
Worsening of asthma	16 (14.7%)	12 (11.0%)
Respiratory tract infections	6 (5.5%)	7 (6.4%)
Bronchitis	7 (6.4%)	5 (4.6%)
Nasopharingitis	2 (1.8%)	5 (4.6%)
Herpes simplex infection	3 (2.8%)	1 (0.9%)
Tremor	1 (0.9%)	3 (2.8%)

FIGURE LEGENDS

Figure 1a: Patient flow; BDP/F=beclomethasone/formoterol; BUD/F=budesonide/formoterol;

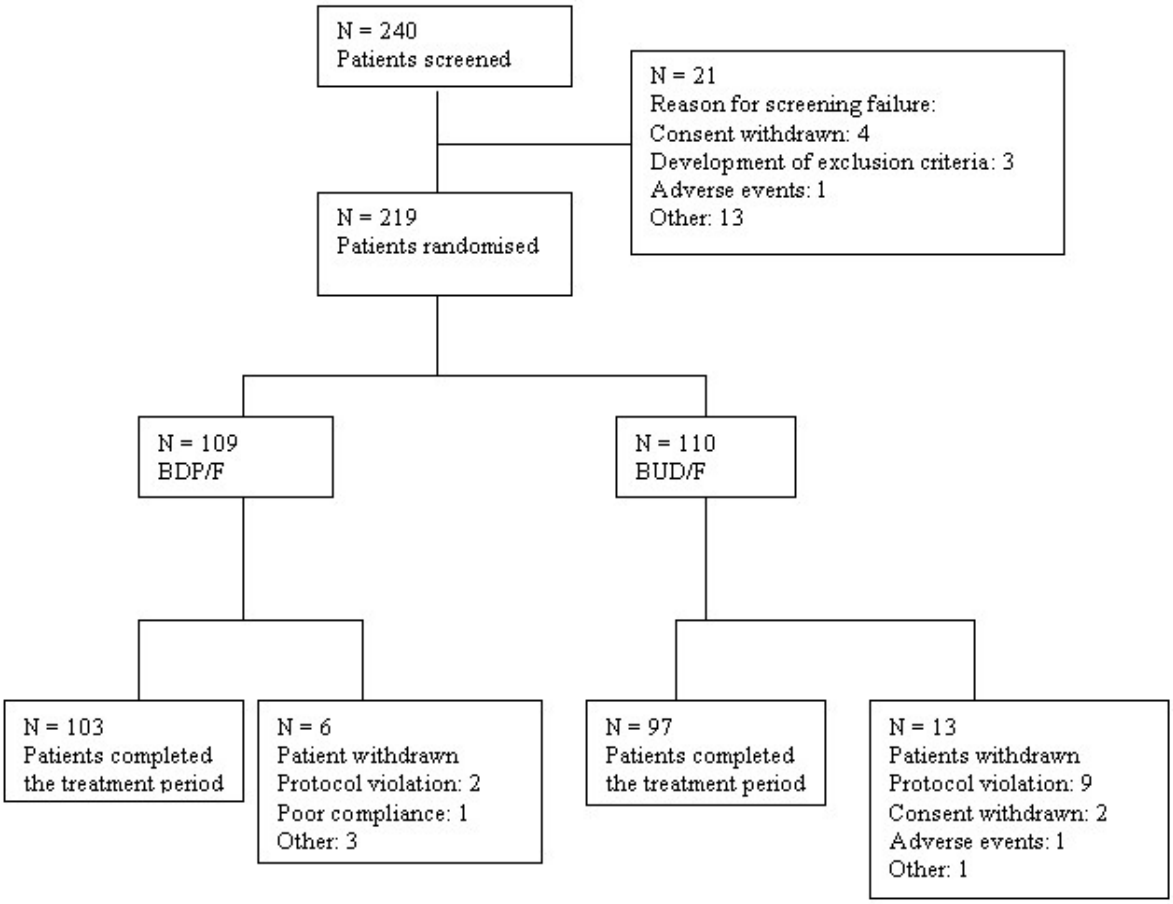

Figure 1b: Populations for analysis; BDP/F=beclomethasone/formoterol; BUD/F=budesonide/formoterol; Patients can have more than one reason for exclusion

	BDP/F	BUD/F
Randomised	109	110
SAF	109	109 1 patient had no evidence of drug intake (randomised and immediately withdrawn, the diary card was not filled in)
ITT	107 2 patients had no post-baseline data for the primary efficacy variable	109
M-ITT	107	109
PP	103 (4 patients excluded) 2 patients due to increase in PEF at visit 2>20% with respect to visit 1 2 patients had a time window between the last 2 visits > 5 days 1 patient had no intake of salbutamol during the run-in > 5 days	99 (10 patients excluded) 4 patients due to increase in PEF at visit 2>20% with respect to visit 1 3 patients due to poor compliance to study medication 2 patients had no intake of salbutamol during the run-in > 5 days 1 patient due to significant and unreliable discrepancies between pulmonary function tests (i.e. FEV1 and PEF) monitored daily by patients and measured at sites 1 patient due to study drug exposure to < 2 weeks

Figure 2: Mean morning PEF (L/min) measured daily by patients in the two groups (beclomethasone/formoterol: ●──●; budesonide/formoterol: ◊----◊) ; *p<0.001 vs baseline; §NS between treatments

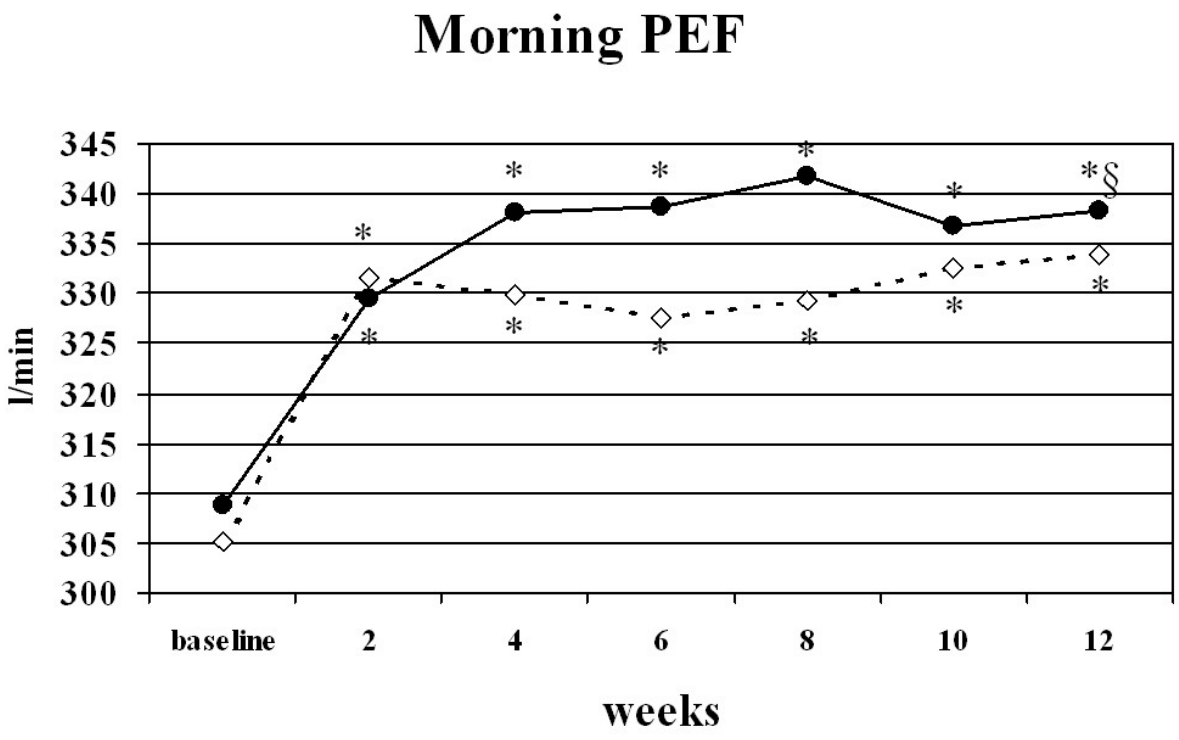

Figure 3: FEV_1 (L) measured at clinics in the two groups (beclomethasone/formoterol: ●——●; budesonide/formoterol: ◊----◊) ; *p<0.001 vs baseline; §NS between treatments

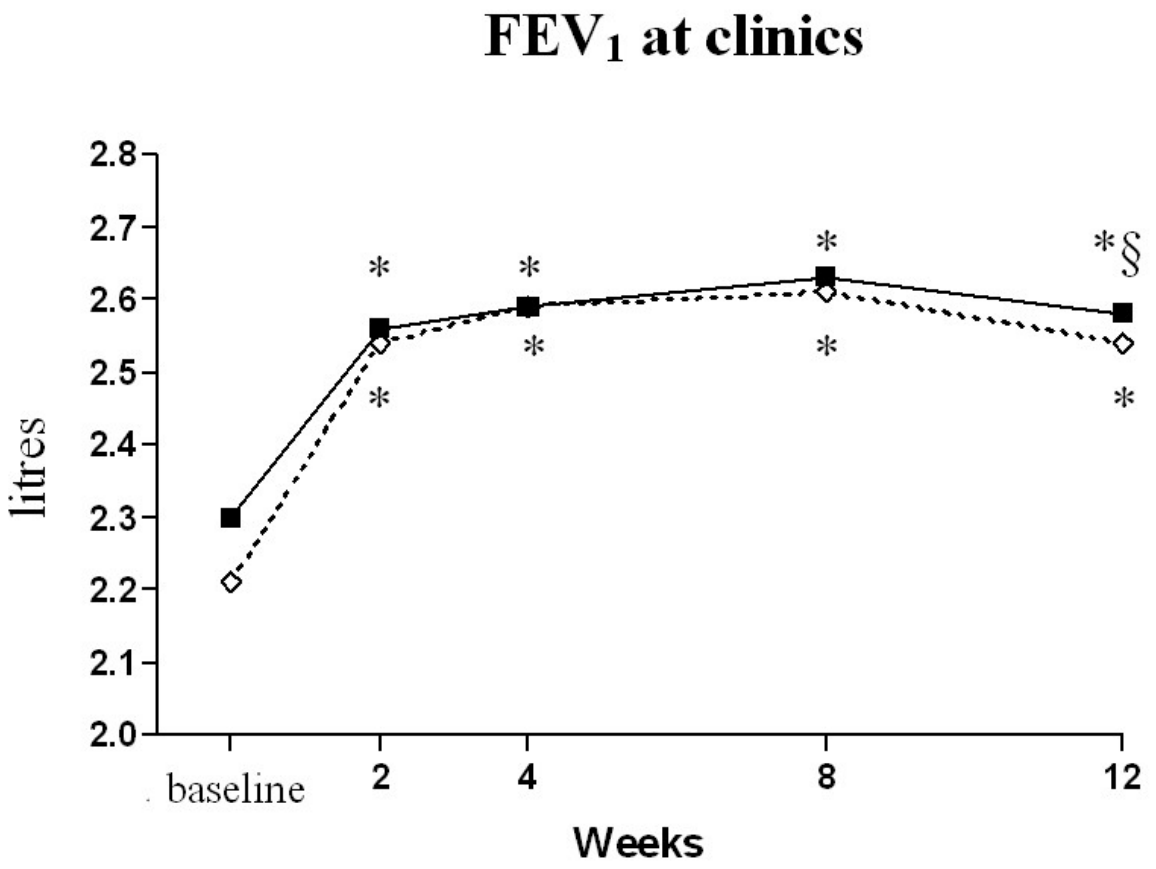

Figure 4: Percentage of symptom-free days and of days with no intake of rescue salbutamol in the treatment phase; NS in the comparisons between groups (beclomethasone/formoterol: ■; budesonide/formoterol: □)