

A Study on Budesonide/ Formoterol vs. Fluticasone/ Salmeterol Inhaled Combination in Moderate to Severe Asthma

ABSTRACT

Background and Objectives The addition of an inhaled long-acting β_2 -agonist (LABA) to an inhaled corticosteroid (ICS) gives optimal control of asthma in most patients. The LABA salmeterol xinafoate (salmeterol) with inhaled corticosteroid (ICS) fluticasone propionate (fluticasone) and formoterol with budesonide are available as a combination product pMDI in a single aerosol inhaler. This study compared the efficacy and safety of commercially available salmeterol/fluticasone with formoterol/budesonide.

Materials and Methods Patients aged >12 years inclusive of either sex (N = 40) with persistent asthma as defined by NHLBI for >6 months prior to screening were included in the study. After a screening phase (1 week), eligible patients were enrolled in the study with 2 weeks run-in period. Eligible patients were randomized to receive either of the two treatment groups [HFA-propelled pMDI salmeterol/fluticasone (50/100 mcg) or HFA-propelled formoterol/budesonide (6/100 mcg) pMDI] in a ratio of 1:1 for the 12-week treatment period. The primary objective was to demonstrate non-inferiority of salmeterol/fluticasone vs. formoterol/budesonide, measured by mean pre-dose forced expiratory volume in the first second (FEV₁), at week 12.

Results This study provides evidence for the primary efficacy endpoint that salmeterol/fluticasone was statistically as well as clinically non-inferior to formoterol/budesonide in the treatment of patients with persistent asthma. This was supported by secondary endpoints which demonstrate that salmeterol/fluticasone appeared to be comparable to formoterol/budesonide in terms of efficacy for the secondary efficacy endpoints (morning PEFR, evening PEFR, diurnal variability of PEFR, daytime and night-time asthma symptoms score, average need for short-acting β_2 -agonists, proportion of patients that required rescue medication, patients with nocturnal asthma, patients without asthma symptoms of score 0 and average number of days without asthma symptoms of score 0). Salmeterol/fluticasone was safe and well tolerated; and safety profile is comparable to comparator formoterol/budesonide.

Conclusion The results of this study demonstrate that HFA formulations of salmeterol/fluticasone and formoterol/budesonide are clinically interchangeable. Overall, the study indicates that HFA-propelled salmeterol/fluticasone (50/100 mcg) pMDI was safe, well tolerated and non-inferior in efficacy compared to HFA-propelled formoterol/budesonide (6/100 mcg) pMDI.

INTRODUCTION

International guidelines recommend the combination of a long-acting β_2 -agonist (LABA) with low-medium dose inhaled corticosteroids (ICSs) when asthma is not fully controlled by ICS alone, as first choice treatment in moderate asthma¹. 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 symptom control and pulmonary function²⁻⁶. Among the currently available LABAs, both salmeterol and formoterol exhibit a duration of action of at least 12 h, thus being both suitable for a twice-daily regimen in prolonged use. Moreover, formoterol has a faster onset of action⁷ and a higher intrinsic activity compared with salmeterol⁸. Treatment with ICS/LABA combinations in a single inhaler, with the same efficacy and safety profile of

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Sarat Kumar Behera*,
Sudeep Kumar Patra,
Saiprasanna Behera

Department of TB and Chest, Hi-Tech Medical College & Hospital, Pandara, Rasulgarh, Bhubaneswar, Odisha-751025, India

■ Address reprint requests to
*Dr. Sarat Kumar Behera, Associate Professor, Department of TB and Chest, Hi-Tech Medical College & Hospital, Pandara, Rasulgarh, Bhubaneswar, Odisha-751025, India
E-mail: drsarat2010@rediffmail.com

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the two drugs given separately^{9–11} may improve adherence to treatment¹².

Budesonide dipropionate (BDP) is a widely used ICS with a favourable risk/efficacy profile¹³. A new technology using the HFA-134a propellant has been recently developed to obtain extrafine formulation of new drugs as well as reformulation of pre-existing drugs in a pressurized metered dose inhaler (pMDI)¹⁴. The rationale behind an extrafine formulation of an ICS is mainly based on accumulating evidence that in asthma the inflammation and remodelling process take place in all parts of the airways, including peripheral bronchioles¹⁵, and that extrafine formulations might improve delivery to peripheral airways¹⁶. This improved peripheral airway delivery allows a 2.5-fold lower dose when compared with chlorofluorocarbon BDP while maintaining the same efficacy and anti-inflammatory effect (17–21). This technology has been used to develop the first fixed combination containing extra fine BDP and formoterol in a HFA solution with a pMDI device. The aim of this study was to compare the efficacy and tolerability of comparable^{1,22} doses of fixed combination pMDI of beclomethasone/formoterol and fluticasone/salmeterol in patients with moderate to severe asthma whose symptoms were not controlled with ICS alone.

METHODS

Patients

The study was carried out in 12 outpatient respiratory clinics in Europe. Patients aged 18–65 years with moderate to severe persistent asthma according to international guidelines¹, forced expiratory volume in 1 s (FEV1) between 50% and 80% of predicted normal values and a positive response to the reversibility test were eligible. Reversibility was defined as an increase of at least 12% (or, alternatively, of 200 ml) in FEV1 measured 30 min after two puffs (2 × 100 lg) of inhaled salbutamol administered via pMDI. All patients were treated with ICS at a daily dose of 1000 lg of BDP-equivalent and had asthma symptoms not adequately controlled as defined by: presence of daily symptoms less than once a week, night-time symptoms less than twice a month and daily use of short-acting β_2 -agonists. These findings were to be confirmed in the 2-week run in period.

Patients satisfying any of the following criteria were excluded: COPD, current or ex-smokers (≥ 10 packs/year); severe asthma exacerbation or symptomatic infection of the airways in the previous 8 weeks; ≥ 3 courses of oral corticosteroids or hospitalization 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) $>15\%$ in randomization visit, compared with values measured in the screening visit, after the 2-week run-in treatment with up to 1000 lg daily BDP equivalent, were not randomised.

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

This was a phase III, multinational, multicentre, double-blind, randomized, two-arm parallel groups, controlled study. Inhaled rescue salbutamol was permitted at any time but stopped at least 6 h before pulmonary function tests (PFTs). Oral corticosteroids were permitted only in the case of asthma exacerbations; 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 the run-in period, patients whose asthma was not adequately controlled were randomized to either formoterol/budesonide or fluticasone/salmeterol 125/25 Ig pMDI (Seretide[®]; GlaxoSmithKline, Middlesex, UK). Randomisation was in balanced-block design stratified by centres. Both study drugs were administered in two inhalations twice daily (morning and evening) to obtain daily doses of 24 Ig formoterol/400 Ig budesonide or 500 lg fluticasone/100 lg salmeterol. As the shape and colour of the pMDIs differed, inhalers were masked to assure blindness and drug delivery of masked actuators was verified.

Protocol outcome measures

The primary outcome variable was morning predose PEF measured by patients in the last 2 weeks of treatment period (weeks 11 and 12). PFT was performed, in accordance with standard procedure²³, at each visit before study drug intake at least 12 h after the previous evening dose, meaning that the morning dose of study drug was taken onsite after PFT under the investigators supervision and proper inhaler technique was checked. The change in FEV1 and PEF from predose to 5, 15, 30 and 60 min after study drug intake was assessed at baseline and at the end of treatment.

Patients used a portable flow meter (Piko-1; Ferraris, Louisville, CO, USA), in compliance with ATS standard 2004, to measure their PEF and FEV1 in the morning and the evening before study drug intake. Patients recorded asthma symptom score and rescue salbutamol intake twice daily (in the morning for night-time and in the evening for daytime) on a diary card^{5,24}. The daytime symptom score was evaluated in the evening according to a 6-point scale ranging from 0 (no symptoms during

the day) to 5 (symptoms so severe that the patient could not perform normal daily activities). Night-time symptoms were evaluated in the morning according to a 6-point scale ranging from 0 (no symptom during the night or on waking in the morning) to 5 (symptoms so severe that the patient did not sleep at all).

The occurrence of asthma exacerbations was evaluated at all post baseline visits; a mild exacerbation was defined as ≥ 2 consecutive days with morning PEF more than 20% below the baseline value on ≥ 2 consecutive days, or use of >3 additional inhalations of rescue salbutamol for a 24-h period when compared with baseline, or a night-time asthma symptoms score 0-3; a severe exacerbation was defined as: morning PEF more than 30% below the baseline value on ≥ 2 consecutive days, or a deterioration in asthma requiring administration of oral corticosteroids⁴.

Adverse events (AEs) were reported throughout the study period. At visit 2 (baseline) and at the final visit, the 12-h (overnight) urine collection was carried out in a subset of patients for the measurement of the urinary cortisol/creatinine ratio. Vital signs (heart rate and blood pressure) were also measured before study drug administration at all visits. A 12-lead ECG with measurement of the QTc interval (Bazett) was performed before study drug administration at baseline and at the end of the study.

Statistics

The study was designed to evaluate the non-inferiority of formoterol/budesonide vs. fluticasone/salmeterol 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 hypothesis²⁵. An analysis of covariance model with terms for treatment, geographical region and baseline value as covariate was used. Baseline values were the mean values of the last week of the run-in period for variables recorded on diary cards and values measured at the end of run-in visit for variables measured at clinics.

RESULTS

Two hundred and forty-four patients were screened between November 2014 and June 2015. Baseline data (Table 1) of the two groups were well matched. Patient compliance evaluated from diary cards was $>95\%$ in both groups.

Lung function

With regard to the primary outcome, morning predose PEF during the last 2 weeks of the treatment period, the difference between adjusted means (LSMs) of the formoterol/budesonide group (329.6 l/min) and the fluticasone/salmeterol group (333.0 l/min) was 3.32 l/min. The 97.5% unilateral CI for this difference was 17.92, which was within the prespecified limit of 20 l/min, thus showing that formoterol/budesonide was noninferior to fluticasone/salmeterol; moreover, the 95% bilateral CI for the difference between LSMs was 17.92 and 11.28. Change from baseline and comparisons between adjusted means of the last 2-week period for lung function parameters are shown in Table 2 and in Figs. 1 and 2. A significant increase from baseline

Table 1 Baseline characteristics in the two groups.

Sex, n (%)	BDP/F	FP/S
Males	53 (45.3)	47 (42.5)
Females	61 (54.8)	67 (57.5)
Age, years	47.3 \pm 12.6	49.7 \pm 10.2
Time from first diagnosis, years	10.1 \pm 8.6	8.7 \pm 7.7
Allergies, n (%)	47 (40.9)	47 (42.0)
ICS dose before study entry, lg (BDP equivalent)	730.9 \pm 259.3	732.1 \pm 256.5
Morning PEF (l/min)	286.2 \pm 99.1	276.1 \pm 92.6
FEV1 (l)	2.07 \pm 0.54	1.96 \pm 0.48
FEV1 (% predicted)	68.6 \pm 9.57	67.9 \pm 9.59
FEV1 (% change in the reversibility test)	25.2 \pm 14.0	21.2 \pm 12.7
FVC (l)	2.87 \pm 0.88	2.86 \pm 0.82
Daytime (no. puffs of salbutamol)	1.92 \pm 0.81	2.10 \pm 1.17
Night-time (no. puffs of salbutamol)	1.06 \pm 0.77	1.02 \pm 0.74

F/BDP: formoterol/budesonide, FP/S: fluticasone/salmeterol, n: number of observations. All values are mean \pm SD; P = ns between groups for all comparisons.

Table 2 Lung function parameters: changes from baseline (ITT population).

Measure	BDP/F	FP/S	P-value	Between-group P-value
Morning PEF (l/min)	48.91 (56.1)	52.76 (65.9)	<0.001	0.654
Evening PEF (l/min)	47.13 (57.8)	47.17 (63.2)	<0.001	0.928
FEV ₁ (l)	0.43 (0.48)	0.36 (0.38)	<0.001	0.295
FVC (l)	0.46 (0.51)	0.34 (0.44)	<0.001	0.040

F/BDP: formoterol/budesonide, FP/S: fluticasone/salmeterol. All values are mean close to SD. Morning and evening PEF values were collected by the patients with the portable peak flow meter, whereas FEV₁ and FVC were measured at clinic visits. P-values refer to change vs. baseline. Between-group P-values refer to comparison between adjusted values of last visit for FEV₁ and FVC and between the period for the last two weeks for morning and evening PEF.

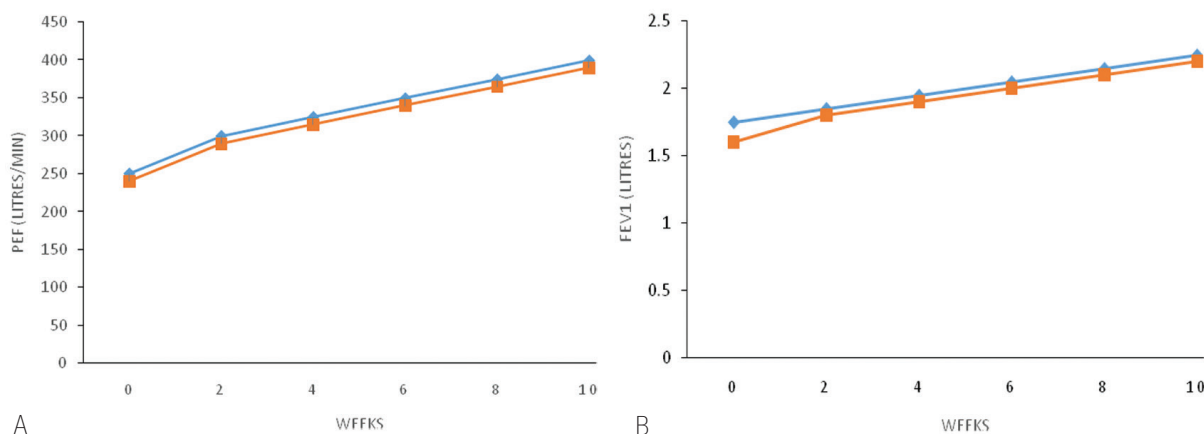


Fig. 1 Mean morning PEF (A) measured daily by patients and FEV₁ (B) measured at clinic visits in the two groups *P < 0.001 vs baseline; \$P = ns\$ between treatments. (formoterol/budesonide: ●—●; fluticasone/salmeterol: e—e).

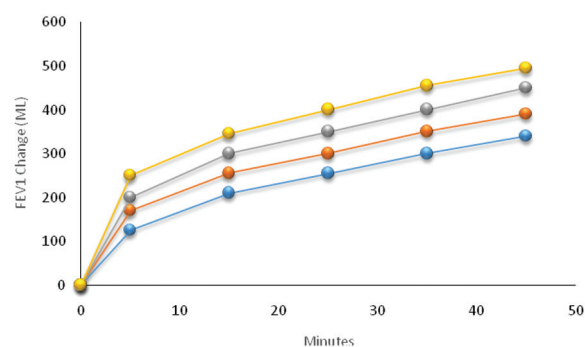


Fig. 2 Change in FEV₁ (ml) measured at clinics from predose to 1 h postdosing in the two groups. Black lines refer to values registered at baseline visit (formoterol/budesonide: ●—●; fluticasone/salmeterol: e—e); grey lines refer to values registered at the end of treatment, last visit (formoterol/budesonide: ●—●; fluticasone/salmeterol: e—e); **P < 0.01 between treatments; *P < 0.05 between treatments.

was shown from the first 2-week period onwards for all parameters. No significant difference between group was shown except for a significant difference in favour of the beclomethasone/formoterol group in predose forced vital capacity (FVC) at the end of treatment (P = 0.040; Table 2). The change in FEV₁ from predose to 5, 15, 30 and 60 min after dosing is shown in Fig. 2.

Changes were at par in the formoterol/budesonide group as in the fluticasone/salmeterol group; a non-significant difference between treatments was shown at all time points (from 5 to 60 min postdosing) either at the baseline visit or at the last visit.

Symptoms

Symptom score, symptom-free days and use of rescue salbutamol are shown in Table 3. No significant difference between groups was found in comparing adjusted mean values of the last 2 weeks of treatment. Compared with baseline, clinical symptom score and rescue medication use significantly decreased, whereas symptom-free days significantly increased (P < 0.001) from the first 2-week period onwards, in both groups.

Exacerbations

Asthma exacerbations occurred in 20 patients, 8 (7.0%) in the formoterol/budesonide group and 12 (10.7%) in the fluticasone/salmeterol group. Severe exacerbations were reported in two patients in the formoterol/budesonide group and six patients in the fluticasone/salmeterol group; oral corticosteroids were used in one and two cases respectively. No statistically significant difference was found between groups in the time to the

Table 3 Symptoms and rescue medication use: values at baseline and at the end of the study (ITT population).

Measure	BDP/F		FP/S		Between-group P-value
	Baseline	Last 2 weeks	Baseline	Last 2 weeks	
Daytime symptom score	1.71 (0.56)	0.57 (0.70)	1.80 (0.65)	0.55 (0.70)	0.382
Night-time symptom score	1.21 (0.68)	0.44 (0.64)	1.26 (0.76)	0.48 (0.63)	0.834
Symptom-free days (%)	0.25 (1.88)	55.52 (38.89)	0.84 (6.55)	54.25 (38.35)	0.706
Day time use of rescue medication (puffs)	1.92 (0.81)	0.51 (0.66)	2.10 (1.17)	0.50 (0.75)	0.611

BDP/F: formoterol/budesonide, FP/S: fluticasone/salmeterol. All values are mean \pm SD. P-values refer to comparison between groups in final adjusted values (weeks 11 and 12).

first exacerbation ($P = 0.358$) with the Kaplan–Meier survival estimate.

Tolerability

Adverse events were reported in 21 (18.3%) patients in the formoterol/budesonide group and 16 (14.2%) in the fluticasone/salmeterol group. No significant difference was found between groups in the proportion of patients with AEs and adverse drug reactions; no serious AEs were observed for the total study period and no patient had to discontinue the study because of AEs. No changes in heart rate and systolic blood pressure were observed in both groups, apart from a small and not clinically relevant decrease in diastolic blood pressure in the formoterol/budesonide group at the end of treatment (1.85 ± 6.94 mmHg; 95% CI: 3.14 to 0.57; $P = 0.005$). With regard to ECG, no evidence of QTc interval prolongation was reported in both groups; only one patient in the fluticasone/salmeterol group had normal ECG at baseline and abnormal findings at the final visit.

Fifty-four patients in the formoterol/budesonide group and 53 in the fluticasone/salmeterol group had both baseline and final measurement of 12-h overnight urinary cortisol/creatinine ratio. The mean changes from baseline to the final visit were 4.72 ± 80.2 lg/g*12 h (95% CI: 17.2 to 26.6) in the formoterol/budesonide group and 2.16 ± 67.55 lg/g*12 h (95% CI: 20.8 to 16.46) in the fluticasone/salmeterol group; the difference between groups was not statistically significant ($P = 0.767$).

DISCUSSION

The results of the study show that formoterol/budesonide 400/24 lg/day is not inferior to fluticasone/salmeterol 500/100 lg/day with regard to both primary outcome, morning PEF in the last 2 weeks of treatment period, and secondary outcomes, e.g. other lung function and clinical efficacy variables.

Both treatment groups had a real potential to improve from baseline to endpoint, as demonstrated by the significant increases in lung function during the course of the study, confirming that recruited patients, unstable with a daily dose of up to 1000 lg BDP equivalent, were in the need for step-up therapy with combination,

i.e. were at least moderate asthmatics. This provides reassurance that the equivalence was not due to lack of efficacy for both treatments or to maximal lung function potential already achieved at the end of the run-in period²⁶. 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 power to detect any potential difference between groups, although the minimum dose required to achieve asthma control was not established in the study. 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, except for a significant difference in favour of formoterol/budesonide in the last 2 weeks of treatment period in FVC. The greater improvement in FVC at the end of the treatment period with the formoterol/budesonide combination reported in this study is consistent with a greater reduction in air trapping and small airways obstruction^{27–30}. A similar trend for FVC has been recently described in a study comparing extrafine BDP with fluticasone in asthmatic children³¹. Reduced air trapping has been previously reported with BDP extrafine compared with non-extrafine BDP and it has been hypothesised that this may be associated with more effective suppression of small airways inflammation, and consequently greater peripheral airways patency³⁰.

The onset of bronchodilation was more rapid with beclomethasone/formoterol as shown by the change in FEV1 from predose to 60 min after dosing that was significantly greater at all-time points (from 5 to 60 min postdosing) when compared with fluticasone/salmeterol due to the pharmacodynamic properties of formoterol. The more rapid improvement in bronchodilation in the formoterol/budesonide group was still present at the end of treatment when compared with fluticasone/salmeterol, even if the absolute change from predose was smaller for both drugs when compared with the evaluation at the beginning of the treatment period due to the improved predose values.

Comparable improvements in the two groups were 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. However, exposure time was limited in this study, and more patients are generally needed for detecting the potential differences between treatments.

The two combination treatments showed similar tolerability profiles. No evidence of detrimental effects on ECG (except for one patient in the fluticasone/salmeterol group) or QTc interval prolongation, a potential cardiovascular effect of beta2-adrenergic drugs³², was reported. No differences in cardiovascular effects (heart rate and blood pressure) were observed between groups.

In conclusion, this study shows that the new pMDI containing budesonide and formoterol is an effective and safe alternative combination for the treatment of asthma. Thanks to the pharmacodynamic properties of formoterol contained in the combination formulation, the product offers the added advantage of a more rapid bronchodilation compared with fluticasone/salmeterol.

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