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Clinical efficacy and safety of fluticasone propionate 1 mg twice daily administered via a HFA 134a pressurized metered dose inhaler to patients with severe asthma

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A randomized, double-blind, cross-over study was conducted to assess the efficacy and safety of fluticasone propionate 1 mg twice daily administered via a pressurized metered dose inhaler (pMDI) containing the new non-chlorofluorocarbon (CFC) propellant (HFA 134a), or the established CFC propellants 11 and 12 in patients with severe asthma. The study comprised a 2-week run-in period followed by two 6-week treatment periods, with no washout period in between. One hundred and nineteen symptomatic adult patients with severe asthma, who were receiving inhaled beclomethasone 2–4 mg day^{-1} or equivalent, were randomized to treatment.

Patients were randomized to one of two sequence groups (sequence 1: HFA 134a pMDI then CFC pMDI or sequence 2: CFC pMDI then HFA 134a pMDI). The sequence groups differed with respect to mean peak expiratory flow (PEF) at baseline; however, the magnitude of the increase in PEF from baseline during treatment was similar in the two sequence groups. Mean PEF at baseline was 334 l min^{-1} in sequence group 1 (HFA 134a→CFC pMDI) and this increased to 357 l min^{-1} and 366 l min^{-1} during treatment with the HFA 134a and CFC pMDI, respectively. In sequence group 2 (CFC→HFA 134a pMDI) mean PEF at baseline was 297 l min^{-1} and this increased to 336 l min^{-1} and 328 l min^{-1} during treatment with the HFA 134a and CFC pMDI, respectively.

Based on an overall analysis of the two treatment groups at week 6, equivalence was demonstrated; the mean treatment difference (HFA 134a-CFC pMDI) in morning PEF was 0 l min^{-1} (90% confidence interval (CI), for difference between groups: −7, 6 l min^{-1}). There was a comparable improvement in secondary efficacy variables, including clinic lung function measurements, in the two treatment groups. The incidence and type of most adverse events were similar in the two treatment groups. There was no difference in the adjusted geometric mean morning serum cortisol levels after treatment with the HFA 134a and CFC pMDI.

Therefore, the fluticasone propionate HFA 134a pMDI constitutes a suitable replacement for the established CFC pMDI at a microgram equivalent dose.

Key words: fluticasone propionate; chlorofluorocarbons; CFC; hydrofluoroalkane 134a; HFA 134a; severe asthma.

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Introduction

Fluticasone propionate is indicated for the prophylactic management of asthma of all severities (1–3). At a microgram equivalent dose, high-dose fluticasone propionate (2 mg day^{-1}) is significantly more effective than budesonide (2 mg day^{-1}) in terms of an improvement in lung function and symptom control in patients with severe asthma (4). Fluticasone propionate, in common with all other inhaled corticosteroids, also has an oral steroid-sparing effect and has been reported to reduce or eliminate the need for oral corticosteroid therapy while improving lung function and quality of life in patients with severe asthma (5).

With the need to phase out chlorofluorocarbons (CFC) as propellants in pressurized metered dose inhalers (pMDIs), there has been a need to find a safe replacement

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propellant. As part of this transition, hydrofluoroalkane (HFA) propellants have been introduced. For fluticasone propionate, a 250 μg pressurized metered dose inhaler (pMDI) formulation has been developed as a microgram equivalent replacement for the traditional CFC pMDI. This study was designed to determine if a change in the pMDI propellant from CFC to HFA 134a would affect the efficacy and safety of fluticasone propionate 1000 μg administered twice daily to patients with severe asthma.

Methods

STUDY DESIGN AND TREATMENT

The study was of a multi-centre, randomized, double-blind, cross-over design with no washout period. During a 2-week run-in period, patients continued to use their usual asthma medication but replaced their short-acting β_2-agonist with a salbutamol CFC pMDI (Ventolin^{TM}) to be used on an as-required basis for symptomatic relief. At the end of the run-in period, patients discontinued their current inhaled corticosteriod therapy and were randomized to fluticasone propionate 1 mg twice daily administered via a CFC pMDI (containing propellants 11 and 12) or a non-CFC pMDI, containing the propellant HFA 134a, for the first 6 weeks of the study. At the end of this period patients immediately crossed over to the second 6-week treatment period and received the alternative fluticasone propionate pMDI. This was followed by a 2-week follow-up period.

During both treatment periods, patients received four actuations of fluticasone propionate 250 μg administered via a pMDI in the morning and evening. With the exception of β_2-agonist therapy, all other concurrent asthma medications, including oral steroids ($\leq 10\,mg\,day^{-1}$), were permitted providing that the dose remained constant throughout the study. Large volume spacer devices (Volumatic^{TM}) were provided if required. Patients attended the clinic on seven occasions: at the start and end of the run-in period, after week 3 and 6 of each treatment period, and at the end of the 2-week follow-up period.

PATIENTS

The study recruited patients from 12 hospital centres in the U.K. All patients had a documented clinical history of severe reversible airways obstruction requiring and responding to high doses of inhaled corticosteroids and β_2-agonist therapy. The patients were treated on an outpatient basis and were eligible for inclusion in the study if they were aged >16 years and required 2–4 mg day^{-1} of inhaled beclomethasone dipropionate or budesonide, or ≤ 1 mg day^{-1} of inhaled fluticasone propionate. Patients were excluded if, in the 4 weeks preceding the study, they had changed their regular asthma medication, required antibiotics, been hospitalized for respiratory disease or received oral corticosteroids at a dose of >10 mg day^{-1} on any one day. Current cigarette smokers, patients who had smoked cigarettes within the previous 6 months and patients treated with depot corticosteroids in the previous 3 months were also ineligible.

In addition, at the end of the run-in period, patients had to demonstrate a forced expiratory volume in 1 sec (FEV_1) of $\leq$90% of the predicted value (6). They also had to show 'room for improvement', a criterion necessary to help establish clinical equivalence (7). Room for improvement was defined as a demonstrable reversibility of peak expiratory flow (PEF) or FEV_1 of $\geq$15% and a requirement for rescue salbutamol on at least four of the last 7 days of the run-in period. The $\geq$15% reversibility of lung function could have been historically documented within the previous 6 months or demonstrated at the beginning of the study after inhalation of salbutamol 400 μg.

The study was approved by the appropriate local ethics committee for each centre, and all subjects gave written informed consent before entering the study.

DAILY RECORD CARDS

Patients were given a mini-Wright peak flow meter and daily record cards. Patients were asked to record the following information in the diary card each day during the run-in and treatment periods: the highest of three PEF readings in the morning and evening before taking the study medication and preferably after withholding salbutamol for 4 h; daytime symptom scores measured on a six-point scale (0 = no symptoms; 5 = symptoms so severe that normal daily activities could not be performed); night-time symptoms on a five-point scale (0 = no symptoms; 4 = symptoms so severe that the patient could not sleep); and use of as-required salbutamol.

CLINIC LUNG FUNCTION

At each clinic visit, the best of three PEF and FEV_1 measurements were recorded. PEF was measured using the peak flow meter issued to the patient at the start of the run-in period. In order to investigate paradoxical bronchospasm, which occurs with pressurized CFC inhalers, (8,9) a second PEF measurement was recorded 5 min after taking the first dose of inhaled corticosteroid medication in each treatment period.

SAFETY EVALUATION

Venous blood and urine samples were collected at the start and end of the run-in period and at the end of each 6-week treatment period for standard haematological and biochemical analysis. Blood samples were collected from fasted patients between 08·00 and 10·00 hours. Serum samples were also analysed for cortisol concentrations and urine samples, collected for up to 12 h before the same clinic visits, were analysed for urinary free cortisol excretion. Compliance with this procedure was not assessed. Repeat blood or urine samples were collected at the follow-up visit if any initial abnormality was detected. All samples were analysed by West Middlesex Laboratory, Isleworth, Middlesex, U.K.

At the start of the run-in and after each 6-week treatment period, the investigators conducted a standard physical examination of each patient and assessed vital signs (heart rate and blood pressure). Once treatment had commenced, the oropharynx was examined at each visit to check for the visible presence of *Candida albicans* and dysphonia. The severity of dysphonia was rated by the patient as follows: 1 = absent, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe.

STATISTICAL ANALYSIS

The analysis was performed on both the intent-to-treat population and on a predefined efficacy population, in line with current best practice for equivalence studies (10). Equivalence between formulations was established if the 90% confidence intervals (CI) for the treatment difference of mean morning PEF were within ± 15 l min^{-1}. Based on a residual standard deviation for PEF of ≤ 45 l min^{-1}, 150 evaluable patients were required to ensure a power of 80%.

For both treatment periods, the first 2 weeks were disregarded to account for the lack of any formal washout period. Although only those patients who provided data for both treatment periods were included in the statistical analysis, all the data were summarized.

Each variable was compared between treatments during weeks 3–6 and at week 6. Morning and evening PEF (recorded in diary cards) and clinic visit FEV_1 and PEF were analysed using an analysis of variance (ANOVA) model for two-way cross-over designs without baselines (11). The terms in the model were patient, period and treatment. After log-transformation, serum cortisol data were also analysed using ANOVA. Urinary cortisol data were log-transformed and summarized.

Symptom scores, additional brochodilator medication and dysphonia severity scores were analysed using the method of Koch proposed for a cross-over design and the Wilcoxon rank sum test (12).

Results

One hundred and nineteen patients were randomized to receive study treatment, 60 received the fluticasone propionate HFA 134a pMDI followed by the CFC pMDI and 59 received the alternative treatment sequence. Table 1 presents baseline demographics for each sequence group. Twenty patients were withdrawn from the study after randomization, 11 were receiving the HFA 134a pMDI and nine the CFC pMDI. Reasons for withdrawal included: adverse events (six and five patients, respectively, receiving the HFA 134a and CFC pMDI); failure to return (five and three patients); unspecified (one patient receiving the CFC pMDI).

DAILY RECORD CARD DATA

During the run-in period there was evidence of a baseline difference between the treatment sequence groups. Patients who received the HFA 134a pMDI during the first treatment period had higher mean values for morning and evening PEF at baseline (i.e. pretreatment) than those patients who received the CFC pMDI (Table 2). The

TABLE 1. Demographic characteristics of the patients

	FP HFA 134a→CFC pMDI	FP CFC→HFA 134a pMDI	Total
No. of patients	60	59	119
Male (%)	27 (45%)	24 (41%)	51 (43%)
Female (%)	33 (55%)	35 (59%)	68 (57%)
Age (years)			
Mean	48	50	49
Range	18–71	18–78	18–78
Volumatic™ spacer (no. of pts)			
Yes	48 (80%)	44 (75%)	92 (77%)
No	12 (20%)	15 (25%)	27 (23%)
Baseline FEV_1 (l) [mean ± SD]	1·95 ± 0·9	1·69 ± 0·75	1·82 ± 0·83
Medication continued into the study (no. of pts):			
Oral steroids	6 (10%)	6 (10%)	12 (10%)
Methylxanthines	20 (33%)	9 (15%)	29 (24%)
Anticholinergics	14 (23%)	11 (19%)	25 (21%)
Sodium cromoglycate	1 (2%)	1 (2%)	2 (2%)

CFC, chlorofluorocarbons; HFA, hydrofluoroalkane; FEV_1 forced expiratory volume in 1 sec; FP, fluticasone propionate; pMDI, pressurized metered dose inhaler; SD, standard deviation.

TABLE 2. Diary card morning peak expiratory flow (l min^{-1})

Mean morning PEF (l min^{-1})	FP HFA 134a→CFC pMDI		FP CFC→HFA 134a pMDI	
	HFA 134a pMDI	CFC pMDI	CFC pMDI	HFA 134a pMDI
Baseline ± SD (*n*)	334±97		297±102	
*n**	60		58	
Mean† ± SE				
weeks 3–6	355±13	360±13	325±4	333±13
week 6	357±14	366±14	328±14	336±13

*Number of patients who provided data.
†Analysis based on patients who completed both treatment periods.
CFC, chlorofluorocarbons; FP, fluticasone propionate; HFA, hydrofluoroalkane; pMDI, pressurized metered dose inhaler; SE, standard error; SD, standard deviation.

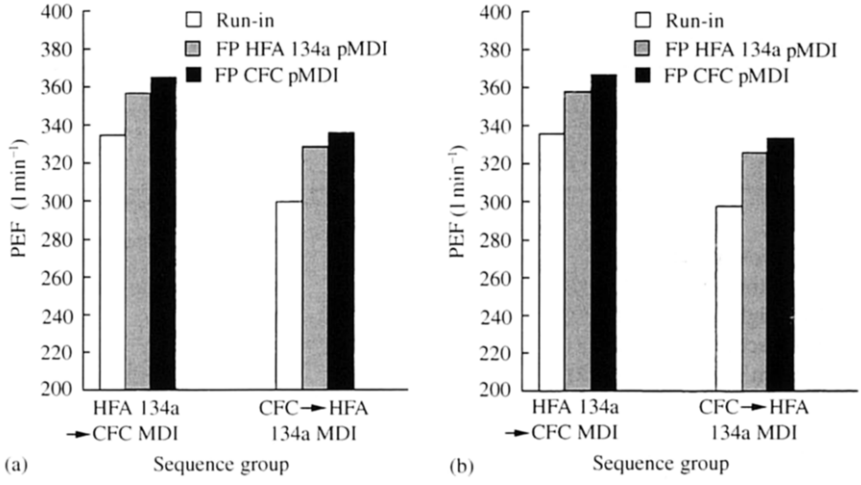

FIG. 1. Mean morning peak expiratory flow (PEF) for patients treated with fluticasone propionate (FP) 2 mg day^{-1} via a hydrofluoroalkane (HFA) 134a pressurized metered dose inhaler (pMDI) followed by FP 2 mg day^{-1} via a chlorofluorocarbon (CFC) pMDI or the same dose of FP via a CFC pMDI followed by an HFA 134a pMDI at (a) week 6 and (b) weeks 3–6.

imbalance was also evident in other diary card variables and clinic FEV_1.

Mean morning PEF improved throughout the 6-week treatment period in all patients. In the HFA 134a→CFC pMDI sequence group, morning PEF at baseline was 334 l min^{-1} and mean value at weeks 3–6 during the HFA 134a pMDI treatment period was 355 l min^{-1}. In the CFC→HFA 134a pMDI sequence group, baseline PEF was 297 l min^{-1} and mean morning PEF during weeks 3–6 of the HFA 134a pMDI treatment period was 333 l min^{-1} (Table 2; Fig. 1).

Combined analysis of the data from both sequence groups showed that the differences between treatments (HFA 134a–CFC pMDI) for mean adjusted morning PEF were 2 and 0 l min^{-1}, respectively, at weeks 3–6 and week 6. The 90% CI for the differences were within the predefined ±15 l min^{-1} criterion set for equivalence (weeks 3–6: −3, 6 l min^{-1}; week 6: −7, 6 l min^{-1}). Data for evening PEF showed statistical equivalence between the two treatment groups, although the clinical improvements were small (Table 3).

There was no significant difference between the two treatment groups with respect to the other diary card parameters, including daytime and night-time symptom scores and use of additional salbutamol (Table 4). Large volume spacer devices were used by 77% of the total population and their use was not associated with any difference in diary card parameters.

CLINIC LUNG FUNCTION

Mean FEV_1 at baseline was 1·821 for all patients. Mean FEV_1 (±SE) increased to 1·97±0·021 (n=106) and

TABLE 3. Diary card evening peak expiratory flow (l min^{-1}) based on overall treatment groups

Mean evening PEF (l min^{-1})	FP HFA 134a pMDI	FP CFC pMDI	Treatment difference (±SE)	90% CI
Baseline ±SD	356±92	321±99		
(*n*)*	(60)	(58)		
Adjusted† mean±SE				
over weeks 3–6	356±2	353±2	4±2	0, 7
(*n*)	(106)	(106)		
at week 6	358±2	357±2	1±3	−5, 6
(*n*)	(97)	(97)		

*Number of patients who provided data.
†Adjusted for treatment, period and patient; data presented for all patients.
CFC, chlorofluorocarbon; CI, confidence interval; FP, fluticasone propionate; HFA, hydrofluoroalkane; pMDI, pressurized metered dose inhaler; PEF, peak expiratory flow; SD, standard deviation; SE, standard error.

TABLE 4. Symptom scores and use of additional inhaled bronchodilator (based on overall treatment groups)

	Baseline*	FP HFA 134a pMDI	FP CFC pMDI
Symptom scores			
Number of patients who provided data	117	105	105
Median % days with symptom score <2	100	89	88
Median % symptom-free nights	93	89	86
Median daytime symptom score	1	0	1
Median night-time symptom score	0	0	0
Additional bronchodilator			
Number of patients who provided data	118	106	106
Median % days with no additional bronchodilator	0	10	4
Median % nights with no additional bronchodilator	86	82	82
Median daytime additional bronchodilator (puffs day^{-1})	2	2	2
Median night-time additional bronchodilator (puffs day^{-1})	0	0	0

*Overall mean of baseline data for both sequence groups.
CFC, chlorofluorocarbon; FP, fluticasone propionate; HFA, hydrofluoroalkane; pMDI, pressurized metered dose inhaler.

2·02±0·02 l (*n*=102), respectively, after 3 and 6 weeks of treatment with the HFA 134a pMDI. In the CFC pMDI group, the respective values were 2·00±0·02 l (*n*=106) and 1·98±0·02 l (*n*=102). The treatment differences between the two groups (HFA 134a–CFC pMDI) for adjusted mean FEV_1 were −0·02 l (90% CI: −0·07, 0·03 l) during weeks 3–6 and 0·04 l (90% CI: −0·01, 0·08 l) at week 6.

Mean baseline clinic visit PEF was 338 l min^{-1} for all patients. During treatment with the HFA 134a pMDI, mean clinic visit PEF (±SE) was 366±4 l min^{-1} after 3 weeks (*n*=103) and 369±3 l min^{-1} after 6 weeks (*n*=100). For the CFC pMDI, the respective values were 365±4 l min^{-1} (*n*=103) and 369±3 l min^{-1} (*n*=100). The treatment differences between the two groups (HFA 134a–CFC pMDI) for adjusted mean clinic PEF were 2 l min^{-1} (90% CI: −8, 11 l min^{-1}) over weeks 3–6 and 0 l min^{-1} (90% CI: −8, 7 l min^{-1}) at week 6.

FIRST-DOSE EFFECT

The frequency distribution of the percentage change in PEF from baseline 5 min after administration of the first dose of study medication was comparable in the HFA 134a and CFC pMDI groups (Fig. 2). A clinically relevant reduction in PEF was considered to be greater than 20% of baseline.

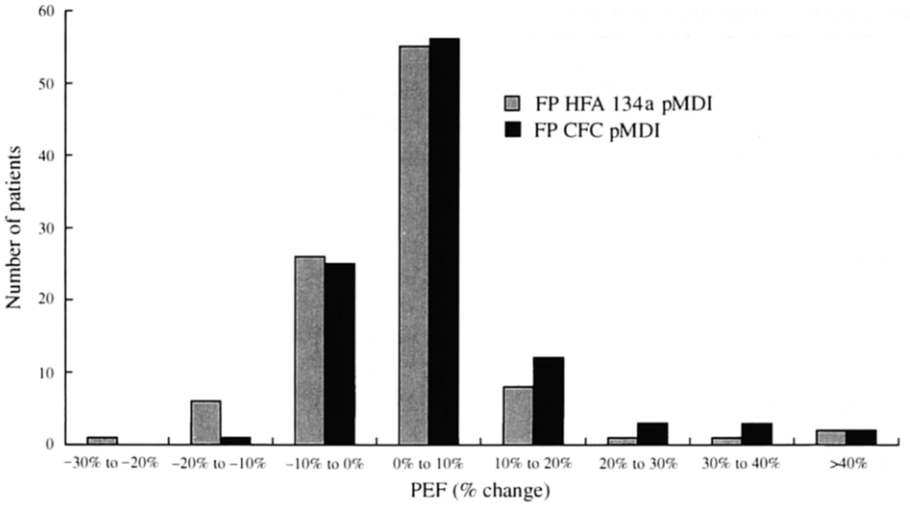

FIG. 2. Frequency distribution of the percentage change in peak expiratory flow (PEF) 5 min post-inhalation of fluticasone propionate (FP) medication either via a hydrofluroalkane (HFA 134a) pressurized metered dose inhaler (pMDI) or via a chlorofluorocarbon (CFC) pMDI.

TABLE 5. Most common (incidence ≥10%) and predictable adverse events

	FP HFA134a pMDI	FP CFC pMDI
Total number of patients who received treatment	114	115
Number of patients reporting an adverse event	88 (77%)	86 (75%)
Asthma and related events	23 (20%)	24 (21%)
Headache	18 (16%)	14 (12%)
Upper respiratory tract infection	18 (16%)	12 (10%)
Respiratory infection	13 (11%)	19 (17%)
Sore throat	11 (10%)	7 (6%)
Predictable adverse events		
Hoarseness	17 (15%)	7 (6%)
Candidiasis: mouth	4 (4%)	11 (10%)
Rash/skin eruption	1 (<1%)	4 (3%)
Allergic skin reactions	1 (<1%)	0

CFC, chlorofluorocarbon; FP, fluticasone propionate; HFA, hydrofluoroalkane; pMDI, pressurized metered dose inhaler

One patient was reported with a reduction in PEF of this magnitude but there were no reports of paradoxical bronchoconstriction or adverse events immediately after dosing.

SAFETY

A comparable number of patients in the HFA 134a and CFC pMDI groups reported adverse events: 88 patients (77%) receiving fluticasone propionate via the HFA 134a pMDI and 86 patients (75%) receiving fluticasone propionate via the CFC pMDI. The most commonly reported adverse events during treatment, experienced by ≥10% of patients in each group, are presented in Table 5 together with the incidence of commonly occuring adverse events typically associated with inhaled corticosteroids.

Of the predictable adverse events, hoarseness was more common in the HFA 134a than in the CFC pMDI group (17 *vs.* seven reports; $P=0{\cdot}032$), but conversely, the incidence of oral candidiasis was greater in the CFC pMDI group (11 *vs.* four reports; $P=0{\cdot}106$), although not statistically significant. The incidence of dysphonia was comparable in both groups at week 3 (11 *vs.* 12% in the HFA 134a and CFC pMDI group, respectively) and although higher in the HFA 134a pMDI group at week 6 this was not statistically significantly different (7% difference; 90% CI: −2, 15).

TABLE 6. Serum and urinary cortisol measurements

	All Patients	FP HFA 134a pMDI	FP CFC pMDI	Adjusted* geometric ratio† (90% CI)
Serum cortisol (nmol l^{-1})				
Baseline				
geometric mean (CV)	227 (0·56)			
(*n*)	107			
After 6 weeks‡				
geometric mean (CV)		250 (0·61)	213 (0·66)	
(*n*)		(93)	(97)	
Adjusted geometric mean* (CV)		259 (0·42)	227 (0·42)	1·14 (1·03–1·27)§
(*n*)		(83)	(83)	
Urinary cortisol (nmol l^{-1})				
Baseline				
geometric mean (CV)	5·36 (1·16)			
(*n*)	(109)			
After 6 weeks‡				
geometric mean (CV)		6·05 (2·01)	6·14 (2·75)	
(*n*)		(99)	(94)	

*Adjusted for patient, period, treatment.
†Ratio of mean HFA 134a pMDI to CFC pMDI value.
‡Patients with data for that week in both periods.
§$P=0·035$.
CFC, chlorofluorocarbon; CI, confidence interval; CV, coefficient of variation; FP, fluticasone propionate; HFA, hydrofluoroalkane; pMDI, pressurized metered dose inhaler.

Mean serum cortisol levels were higher after treatment with fluticasone propionate administered via the HFA 134a pMDI than via the CFC pMDI (ratio of geometric means: 1·14; $P=0·035$) (Table 6). This difference reflected an increase in mean serum cortisol from baseline with the HFA 134a formulation compared with no change or a slight reduction with the CFC formulation. Therefore, there was no evidence of cortisol suppression with the HFA 134a product. The distribution of individual serum cortisol values was also similar with both treatments. In all, two patients on either treatment had values below the normal range. In contrast, urinary cortisol levels were raised compared with baseline on both treatments and were comparable in the two groups (Table 6).

Discussion

These findings demonstrate that the efficacy and tolerability of FP 2 mg day^{-1} in patients with severe asthma is comparable whether administered via an HFA 134a or CFC pMDI providing 250 μg of drug per actuation. As shown previously, these two products are similar with respect to particle size distribution and fine particle mass (13) and the present study provides clinical evidence that the two products behave similarly *in vivo*. These results also concur with those of other published studies investigating HFA 134a; when used to replace the CFC propellants 11 and 12 in salbutamol pMDIs and fluticasone propionate pMDIs of various strengths, HFA 134a did not compromise the efficacy or tolerability of either therapeutic agent (14–17).

The degree of asthma severity in the patients enrolled in this study precluded the use of a formal washout period. In an effort to overcome this, data from the first 2 weeks of each treatment period were not used in the analyses. Furthermore, patients had to demonstrate 'room for improvement' (based on their ability to demonstrate a $\geq$15% reversibility to salbutamol 400 μg) to minimize the risk of dosing at the top of the dose–response curve (7).

There were differences between the patients in the two sequence groups at baseline; by chance, patients randomized to the HFA 134a pMDI in the first 6-week treatment period had higher baseline values for all parameters than those patients randomized to initial treatment with the CFC pMDI. Nonetheless, there was a trend towards a similar improvement in the efficacy parameters in both groups compared to baseline.

The present study was powered ($\geq$80%) to show clinical equivalence. This was defined by the 90% CI for the treatment difference in the primary efficacy parameter, mean morning PEF, using limits of $\pm$15 l min^{-1}, if at least 150 evaluable patients were enrolled in this study. The lower number of patients recruited was, however, balanced by the smaller residual standard deviation so the power of the study was increased from that planned. This was supported by a more restrictive analysis (based on 95% CIs) which demonstrated equivalence at the specified level ($\pm$15 l min^{-1}). In this study, the increases in mean morning

PEF from baseline at the end of treatment were similar to that reported in another study evaluating fluticasone propionate 2 mg day^{-1} for 6 weeks (24 l min^{-1}) (18) and smaller than that reported in a longer 16-week study using the same dose of fluticasone propionate (83 l min^{-1}) (5).

Inhaled corticosteroids are well tolerated but the likelihood of systemic side-effects tends to increase as the dosage is increased, particularly hypothalamic pituitary adrenal (HPA) axis suppression (19). The safety profile of fluticasone propionate in this respect is good, having low systemic absorption after oral administration (20) and being as effective at half the dose of other currently used inhaled corticosteroids (21). In this study, fluticasone propionate administered via an HFA 134a pMDI resulted in a modest increase in serum cortisol levels at the end of the 6-week treatment period but this was neither of clinical or statistical significance. In previous studies, mean serum cortisol levels remained within the normal range during treatment with a wide range of fluticasone propionate dosages (21,22), although small decreases have been observed in two studies (5,18).

Safety monitoring showed that both formulations of fluticasone propionate were well tolerated and associated with a similar incidence of adverse events. The incidence and type of adverse events was not unexpected in a population of patients with severe asthma receiving high-dose inhaled corticosteroid therapy. During the analysis of adverse events, only the incidence of hoarseness differed significantly between the two groups. This result may have been due to the fact that multiple tests were performed on the same subjects, although a true effect cannot be ruled out.

In conclusion, the results of this study demonstrate that at a microgram equivalent dose the efficacy and tolerability of fluticasone propionate when propelled by a non-CFC propellant, HFA 134, are comparable with those of fluticasone propionate propelled by the CFC propellants 11 and 12.

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