Fluticasone propionate 100 µg bid using a non-CFC propellant, HFA 134a, in asthmatic children

Brian Lyttle MD[1], John Gilles MBChB[2], Maarja Panov MD[3], Andrzej Emeryk nMed[4], Claire Wixon BSc[5]
on behalf of an international study group

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BACKGROUND: Secondary to phasing out chlorofluorocarbons (CFCs), the fluticasone propionate (FP) pressurized metered-dose inhaler has been formulated in a nonozone-depleting propellant, hydrofluoralkane (HFA) 134a.
OBJECTIVES: To demonstrate equivalent efficacy and safety of FP 200 µg daily propelled by HFA 134a to FP 200 µg daily propelled by CFCs 11 and 12 over a four-week treatment period in pediatric asthmatic patients.
METHODS: The study was multinational, randomized, double blind and of parallel group design. Eligible patients aged 16 years and younger were steroid naive or receiving 500 µg/day or less of beclomethasone dipropionate, budesonide or flunisolide, or 250 µg/day or less of inhaled FP. The primary efficacy variable was mean morning peak expiratory flow with equivalence determined if the 90% CIs for the treatment differences between groups were within ±15 L/min.
RESULTS: Three hundred fifteen patients (mean age 9.3±2.8 years) were randomly assigned; 158 patients received FP HFA 134a and 157 patients received FP CFC. Over the four-week treatment period, mean morning peak expiratory flow increased from baseline in both groups (14 L/min and 17 L/min, respectively), with a mean treatment difference of –2 L/min. Equivalence was demonstrated between the groups (90% CI –6 to +3 L/min; P=0.589). Both formulations were well tolerated with no serious drug-related events.
CONCLUSIONS: FP propelled by HFA 134a has equivalent efficacy and comparable safety to FP propelled by CFC propellants at a microgram equivalent dose in pediatric asthmatic patients.

Key Words: *Asthma; Fluticasone propionate; Hydrofluoralkane 134a; Pediatrics*

100 µg de propionate de fluticasone bid au moyen d'un propulseur sans CFC, le HFA 134a, chez les enfants asthmatiques

HISTORIQUE : Après la suppression progressive du chlorofluorocarbure (CFC), les aérosols doseurs pressurisés au propionate de fluticasone (PF) ont été formulés de manière à contenir un propulseur ne détruisant pas la couche d'ozone, l'hydrofluoralcane (HFA) 134a.
OBJECTIFS : Démontrer l'efficacité et l'innocuité équivalente d'une dose quotidienne de 200 µg de PF propulsée par HFA 134a par rapport à une dose quotidienne de 200 µg propulsée par CFC 11 et 12 pendant une période de traitement de quatre semaines chez des enfants asthmatiques.
MÉTHODOLOGIE : L'étude aléatoire à double insu en contrôle parallèle était d'envergure multinationale. Les patients admissibles de 16 ans ou moins n'avaient jamais pris de stéroïdes ou avaient reçu une dose quotidienne maximale de 500 µg de dipropionate de béclométhasone, de budésonide ou de flunisolide, ou de 250 µg de PF en aérosol. La principale variable d'efficacité était le débit expiratoire de pointe moyen pendant l'avant-midi, l'équivalence étant déterminée si 90 % des IC pour ce qui est des différences de traitement entre les groupes correspondaient à une marge de ±15 L/min.
RÉSULTATS : Trois cent quinze patients (âge moyen de 9,3±2,8 ans) ont été répartis au hasard; 158 ont reçu du PF par HFA 134a, et 157, du PF par CFC. Au cours de la période de traitement de quatre semaines, le débit expiratoire de pointe moyen pendant l'avant-midi a augmenté dans les deux groupes par rapport à la base de référence (14 L/min et 17 L/min, respectivement), la différence moyenne de traitement équivalant à –2 L/min. L'équivalence était démontrée entre les groupes (90 % IC –6 L/min à +3 L/min, P=0,589). Les deux préparations étaient bien tolérées et ne provoquaient aucune réaction néfaste importante reliée aux médicaments.
CONCLUSIONS : Le PF propulsé par HFA 134a a une efficacité équivalente et une innocuité comparable au PF propulsé par CFC à une dose à un microgramme près chez les enfants asthmatiques.

The pressurized metered-dose inhaler (pMDI) is the most commonly prescribed asthma medication device and is a key therapeutic option for the large number of patients who suffer from asthma (1). Although pediatric patients do experience some difficulties in using the pMDI, this can be overcome by the use of a spacer device, which also reduces the potential for local side effects such as candida and hoarseness. Chlorofluorocarbons (CFCs) 11 and 12 have been used as the propellants in pMDIs for more than 40 years (2). However, CFCs have been shown to contribute to the depletion of stratospheric ozone (3), and although the contribution of medicinal aerosols has been minimal, a search for an alternative propellant has been made. Alternative propellants have been extensively researched by the pharmaceutical industry to

[1]*Department of Paediatrics, Children's Hospital of Western Ontario, London, Ontario;* [2]*Anglesea Clinic, Hamilton, New Zealand;* [3]*Department of Paediatrics, Tartu University Children's Hospital, Tartu, Estonia;* [4]*Department of Paediatrics, Szpital Dzieciecy, Lublin, Poland;*
[5]*Respiratory Clinical Development and Product Strategy, GlaxoSmithKline Research and Development, Greenford, Middlesex, United Kingdom*
Correspondence and reprints: Claire Wixon, Respiratory Clinical Development and Product Strategy, GlaxoSmithKline Research and Development, Greenford, Middlesex UB6 OHE, United Kingdom. Telephone +011-44-020-8966-5196, fax +011-44-020-8996-5199, e-mail cw48080@gsk.com

provide a replacement that has similar chemical properties and, most important, that is acceptable to patients in terms of delivery of medication, taste and smell (4). Hydrofluoroalkane (HFA) 134a (1,1,1,2-tetrafluoroethane) has been identified as one such replacement. Preclinical and clinical studies have shown it to be inert with a similar safety profile to CFC propellants (5-7).

Fluticasone propionate (FP), a topically active corticosteroid that shows little or no systemic activity after oral administration, is indicated for the prophylactic management of asthma of all severities. It is licensed as a CFC pMDI formulation for use in children with asthma, and data from clinical studies extending for up to one year have shown that it is effective and well tolerated in this population at doses of up to 200 μg/day (8,9). FP has been successfully reformulated in pMDIs with HFA 134a without the use of excipients and has been shown to have similar pharmaceutical characteristics to its CFC counterpart (6). The FP HFA 134a pMDI contains a suspension of micronized FP in the liquefied propellant HFA 134a.

This study has been conducted to evaluate the 50 μg strength HFA formulation of FP and to demonstrate that it is clinically equivalent to the 50 μg strength CFC formulation in children with asthma when administered at a daily dose of 200 μg.

PATIENTS AND METHODS

Study subjects

Patients aged four to 16 years inclusive with a documented history of reversible airways obstruction and who were either steroid naive or receiving inhaled corticosteroids (500 μg/day or less of inhaled beclomethasone dipropionate, budesonide or flunisolide, or 250 μg/day or less of inhaled FP) were eligible for the study. Patients who had required a change in their regular asthma medication, or who had required antibiotics or hospitalization for a respiratory tract infection in the four weeks before entry were excluded. Patients were required to be able to use a pMDI correctly, and to understand and complete a daily record card (DRC) and measure their peak expiratory flow (PEF) using a mini-Wright peak flow meter (Clement Clarke International Ltd, United Kingdom). Parental or guardian assistance for younger patients was permitted. At the end of the run-in period, patients were required to meet the additional criteria outlined below to demonstrate that they still had scope for improvement in their asthma control.

- Patients were required to have a forced expiratory volume in 1 s (FEV_1) or PEF value between 70% and 100% of their predicted normal value (10).
- Patients had their PEF measured in the clinic following administration of salbutamol (maximum 800 μg) via a pMDI. The mean morning PEF during the last seven days of the run-in, calculated from the DRC, had to be 90% or less of that recorded following inhalation of salbutamol.

The following Polgar formulas (10) were used to calculate the predicted FEV_1:

$$\text{Predicted } FEV_1 = 2.098 \times 10^{-6} \times \text{height}^{2.7986}$$

$$\text{Predicted PEF} = -425.5714 + 5.2428 \times \text{height}$$

The percentage predicted values were calculated using the following formula:

$$\text{Percentage predicted} = \text{observed/predicted} \times 100$$

Study design

This was a multinational, multicentre, randomized, double-blind, parallel group study over a treatment period of four weeks. The study was performed in 32 centres in 12 countries. Written approval for the study was obtained from the appropriate regulatory authorities and local ethics committees for each centre. Patients attended the clinic on four occasions. Patients who satisfied the above criteria entered a 10- to 14-day run-in period, during which they continued to take their existing asthma medications.

At the end of the run-in period, eligible patients were randomly assigned to treatment by allocating the next sequential treatment number from a predefined list generated by Patient Allocation for Clinical Trials (PACT) software (GlaxoSmithKline, United Kingdom) and were given the treatment corresponding to that treatment number. Patients were randomly assigned to receive either FP 100 μg bid propelled by HFA 134a (n=158) or FP 100 μg bid propelled by CFCs (n=157), both given twice daily as 50 μg/actuation in the morning or evening. The study treatment was administered with a large volume spacer (Volumatic, Betts, United Kingdom) if required. Other inhaled corticosteroids were discontinued when the study drug was initiated. All inhaled short-acting bronchodilators were withdrawn, and salbutamol CFC pMDIs were provided for rescue relief as required. Other asthma medication could be continued throughout the study provided that the dose remained constant.

Methods

At the screening visit, after written informed consent was obtained from the child, parent or guardian, DRCs were issued to each patient to record the following information: the highest of three morning and evening PEF readings, the number of pMDI actuations administered for symptomatic relief, daytime symptom score on a six point scale (0 = no symptoms; 5 = symptoms so severe that patients were unable to go to school or perform normal daily activities) and nighttime symptom score on a five-point scale (0 = no symptoms; 4 = symptoms so severe that the patient did not sleep at all). Patients used a mini-Wright peak flow meter to record their PEF and were instructed to measure their PEF before taking any rescue or study medication. Spirometry was measured at clinic visits. If a patient was unable to perform an FEV_1 manoeuvre, clinic PEF was measured instead. Patients were asked to bring their PEF meter with them to the clinic for measurement of clinic visit PEF.

Safety was monitored by recording adverse events at each clinic visit. In addition, blood samples were collected at the beginning and end of the four-week treatment period, between 8:00 and 10:00, to measure serum cortisol levels, and routine biochemical and hematology parameters. Hematological and biochemical parameters were analyzed by a single central laboratory. An oropharyngeal examination took place at all clinic visits, and swabs were taken if candidiasis was suspected. Heart rate and blood pressure were measured at each clinic visit.

Analysis

The primary assessment of equivalence was based on the mean morning PEF recorded on the DRC in the intent to treat (ITT)

TABLE 1
Patient characteristics (randomly assigned population) in a study examining fluticasone propionate (FP) 100 µg bid using a nonchlorofluorocarbon (non-CFC) propellant, hydrofluoroalkane (HFA) 134a, in asthmatic children

Intent to treat population	FP HFA 134a pMDI	FP CFC pMDI
Patients (n)	158	157
Sex (n)		
Male	103 (65%)	93 (59%)
Female	55 (35%)	64 (41%)
Mean age (years ± SD)	9.3±2.8	9.3±3.0
Patients using a spacer (n)	125 (79%)	127 (81%)
Dose of inhaled corticosteroid on entry (n)		
None	54 (34%)	51 (32%)
<200 µg/day	20 (13%)	26 (17%)
200-500 µg/day	83 (53%)	77 (49%)
>500 µg/day	1 (<1%)	3 (2%)
Patients taking FP on entry to the study (n)	25 (16%)	21 (13%)
Patients taking DSCG during the study (n)	14 (9%)	10 (6%)
Patients taking inhaled long-acting $beta_2$-agonists during the study (n)	5 (3%)	3 (2%)

DSCG Disodium cromoglycate; pMDI Pressurized metered-dose inhaler

population, defined as all randomly assigned patients. Clinical equivalence between FP propelled by HFA 134a and FP propelled by CFCs was established if the 90% CIs for the treatment difference of mean morning PEF were within ±15 L/min (11). The primary variable was also analyzed in the per protocol population, defined as the ITT population excluding major protocol violators. The sample size was based on the mean morning PEF. Assuming a standard deviation of the treatment difference of 35 L/min, which is taken to be an average from previous studies, 120 evaluable patients per treatment group would give the study at least 90% power to demonstrate equivalence (two-sided) between the formulations using 90% CIs (12). The mean morning and evening PEFs over the four-week treatment period were analyzed using analysis of covariance, with terms for baseline, age, sex, centre and treatment. Baseline was calculated as the mean value of the last week of the run-in period. Tests for treatment interactions with previous steroid use and spacer use were performed. Clinic visit FEV_1s and PEFs were analyzed in the same manner, with baseline taken as the value recorded at the randomization visit. The Wilcoxon's rank sum test stratified by centre using the van Elteren method (13) was used to assess treatment differences in percentage of symptom-free days (days with a symptom score below 2), and percentage of days and nights when rescue salbutamol was not required.

Serum cortisol levels measured at the beginning and end of the four-week treatment period were log transformed to satisfy normality assumptions and were analyzed using analysis of covariance as described above.

RESULTS

Patient characteristics

A total of 410 patients were enrolled, of whom 315 were randomly assigned to receive study medication. Ninety-five patients were withdrawn from the study before random assignment, mainly for failure to meet the entry criteria for random assignment because of limited scope for improvement in lung function (75 patients). The demographic characteristics of each treatment group are outlined in Table 1. The treatment groups were well matched for age, the number of patients taking inhaled steroids at the start of the study and other asthma medication throughout the study (Table 1). At random assignment, patients in both treatment groups had a similar capacity for improvement in morning PEF, expressed as a percentage of the maximum clinic visit PEF after taking salbutamol (86% in the HFA group and 85% in the CFC group). There were very few withdrawals during the treatment period – four patients in the FP HFA 134a group and two patients in the FP CFC group. The main reason for these withdrawals in both groups was noncompliance. Seventy patients were excluded from the ITT population to form the per protocol population, mainly due to receiving unpermitted medication (48 patients), with the remaining patients not meeting the entry criteria for lung function. In the per protocol population, 124 patients received FP HFA 134a and 121 patients received FP CFC.

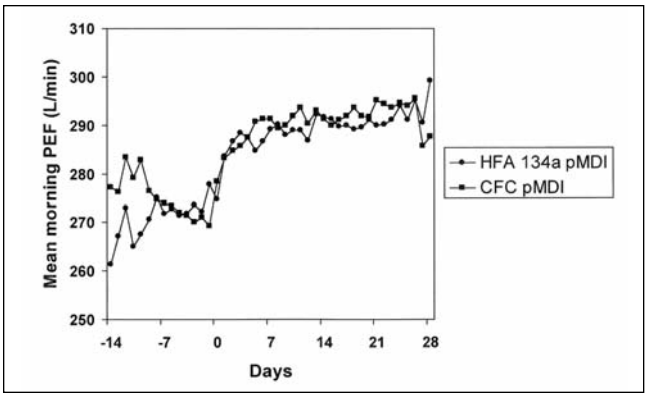

Figure 1) *Mean morning peak expiratory flow (PEF) (L/min) over four weeks of treatment in a study examining fluticasone propionate 100 µg bid using a nonchlorofluorocarbon (non-CFC) propellant, hydrofluoroalkane (HFA) 134a, in asthmatic children. pMDI Pressurized metered-dose inhaler*

DRC data

Baseline morning PEF was similar between the two treatment groups – 274 L/min for the FP HFA 134a group and 272 L/min for the FP CFC group. Mean morning PEF increased in both treatment groups following random assignment to FP (Figure 1). The adjusted mean increase (adjusted for baseline, centre, age and sex) from baseline at the end of four weeks was 14 L/min in the HFA 134a pMDI group and 17 L/min in the CFC pMDI group. The two formulations of FP were shown to be equivalent, with a mean treatment difference of –2 L/min and a 90% CI of –6 to 3L/min, well within the ±15 L/min equivalence limits (Table 2). Over weeks 1 to 4, the mean morning PEF, expressed as a percentage of the maximum clinic visit PEF after treatment with salbutamol, was 91% in both groups. In both treatment groups, the improvement from baseline was seen as early as seven days after starting treatment and continued throughout the four-week treatment period (Figure 1). A similar improvement was seen in the per protocol population, with

TABLE 2
Mean morning peak expiratory flow (PEF) at baseline and after four weeks of treatment with fluticasone propionate (FP) 100 µg twice daily, administered via a hydrofluoroalkane (HFA) 134a or chlorofluorocarbon (CFC) pressurized metered-dose inhaler (pMDI)

PEF variable (L/min)	Population (n)	FP HFA 134a pMDI	FP CFC pMDI	Treatment difference (HFA – CFC)	90% CI	P
Baseline PEF (mean ± SD)	ITT (n=315)	274±86	272±95			
Adjusted mean ± SE PEF at week 4		288±2	289±2	–2±3	–6 to 3	0.589
Baseline PEF (mean ± SD)	Per protocol (n=245)	282±92	263±93			
Adjusted mean ± SE PEF at week 4		288±3	291±3	–3±3	–9 to 2	0.338
Baseline PEF (mean ± SD)	With spacer (ITT) (n=251)	267±88	264±97			
Adjusted mean ± SE PEF at week 4		280±2	278±2	–2±3	–3 to 7	0.424
Baseline PEF (mean ± SD)	No spacer (ITT) (n=63)	302±77	308±83			
Adjusted mean ± SE PEF at week 4		318±7	333±8	–15±8	–29 to 1	0.007

P values are based on analysis of covariance. All values are adjusted for baseline, centre, age and sex. ITT Intent to treat

TABLE 3
Secondary efficacy parameters for the intent to treat population at baseline and after four weeks of treatment with fluticasone propionate (FP) 100 µg twice daily, administered via a hydrofluoroalkane (HFA) 134a or chlorofluorocarbon (CFC) pressurized metered-dose inhaler (pMDI)

Variable	FP HFA 134a pMDI (n=158)	FP CFC pMDI (n=157)	Treatment difference (HFA – CFC)	90% CI	P
Baseline mean ± SD morning % predicted PEF	92±18	91±17			
Adjusted mean ± SE morning % PEF at week 4	97±1	98±1	–1±1	–3 to 1	0.382
Baseline mean ± SD evening % predicted PEF	95±18	94±18			
Adjusted mean ± SE evening % PEF at week 4	98±1	99±1	–1±1	–3 to 0	0.184
Baseline mean ± SD evening PEF (L/min)	282±89	279±99			
Adjusted mean ± SE evening PEF (L/min) at week 4	291±2	294±2	–3±3	–8 to 2	0.277

P values are based on analysis of covariance. All values are adjusted for baseline, centre, age and sex

TABLE 4
Change in symptom-related parameters after four weeks of treatment with fluticasone propionate (FP) 100 µg twice daily, administered via a hydrofluoroalkane (HFA) 134a or chlorofluorocarbon (CFC) pressurized metered-dose inhaler (pMDI)

	FP HFA 134a pMDI (n=158)		FP CFC pMDI (n=157)	
	Run-in	Week 4	Run-in	Week 4
Days with no salbutamol (%)	76	84	76	81
Nights with no salbutamol (%)	87	92	85	92
Days with symptom score <2 (%)	89	94	88	91
Symptom-free nights (%)	79	85	79	85

equivalence demonstrated between the groups (Table 2). Statistical analysis on the morning PEF in the ITT population for previous steroid use did not show a significant interaction. A significant interaction for spacer use, however, was observed. The results indicated that for patients not using a spacer (20% of patients in each group), more improvement was seen in patients in the FP CFC pMDI treatment group than in the FP HFA 134a pMDI group (90% CI –29 to 1 L/min; P=0.007). For patients using a spacer (80% of patients in each group), no significant interaction was observed (Table 2).

The findings for the primary variable were further supported by the results of analysis of the secondary efficacy PEF variables, which showed no difference between the two treatment groups. The treatment difference between the two groups for evening PEF was –3 L/min (90% CI –8 to 2 L/min), and for both the percentage predicted mean morning and predicted mean evening PEF, the difference was –1 L/min (90% CI –3% to 1% and 90% CI –3% to 0%, respectively) (Table 3). An increase from baseline in both days and nights when salbutamol was not required was seen over the four-week treatment period in both groups. The number of days with a symptom score less than 2 and the number of symptom-free nights also improved in both treatment groups (Table 4). There was no significant difference between the two treatment groups for any of these parameters over the four-week treatment period.

A significant interaction for patients not using a spacer was also observed for the evening PEF (Table 5). For all other secondary efficacy variables, no significant interactions with spacer use were observed (Table 5).

Clinic visit data

At baseline, the FP HFA 134a pMDI group had an adjusted mean FEV_1 value of 1.94 L, which increased by 0.10 L at the end of four weeks. Over the same time interval, the FP CFC pMDI group also rose by 0.10 L from an adjusted baseline of 1.97L (Table 6). The per cent predicted FEV_1 at baseline was 88% in both groups, which increased to 93% at week 4 in both groups (90% CI –3 to 1 L). The change from baseline in clinic PEF is shown in Table 6.

TABLE 5
Statistical analysis of Volumatic (Betts, United Kingdom) spacer use for the secondary efficacy variables in a study examining fluticasone propionate (FP) 100 µg bid using a nonchlorofluorocarbon (non-CFC) propellant, hydrofluoroalkane (HFA) 134a, in asthmatic children

Variable	ITT population	Mean change from baseline: FP HFA 134a pMDI (mean ± SE)	FP CFC pMDI (mean ± SE)	Treatment difference (HFA – CFC) (mean ± SE)	95% CI	P
Evening PEF (L/min)	No spacer (n=63)	8±4.6	29±4.8	–20±6.1	–32 to –8	0.001
	With spacer (n=250)	11±2.3	10±2.2	1±3.1	–5 to 7	0.707
Clinic visit PEF (L/min)	No spacer (n=27)	25±10.7	16±13.4	10±15.8	–22 to 41	0.544
	With spacer (n=94)	33±7.3	23±6.5	9±8.5	–7 to 26	0.274
% symptom-free days	No spacer (n=63)	6±2.6	2±2.7	4±3.5	–3 to 11	0.288
	With spacer (n=250)	4±1.3	2±1.3	1±1.7	–2 to 5	0.400
% of days no additional bronchodilator required	No spacer (n=63)	7±4.1	7±4.1	–0±5.4	–11 to 11	0.995
	With spacer (n=248)	10±2.0	5±1.9	4±2.7	–1 to 9	0.128

P values are based on analysis of covariance. All values are adjusted for baseline, centre, age and sex. ITT Intent to treat; PEF Peak expiratory flow; pMDI Pressurized metered-dose inhaler

TABLE 6
Change in clinic forced expiratory volume in 1 s (FEV_1) and peak expiratory flow (PEF) at baseline and after four weeks of treatment with fluticasone propionate (FP) 100 µg twice daily, administered via a hydrofluoroalkane (HFA) 134a or chlorofluorocarbon (CFC) pressurized metred-dose inhaler (pMDI)

Variable	FP HFA 134a pMDI	FP CFC pMDI	Treatment difference (HFA – CFC)	90% CI	P
Baseline FEV_1 (mean ± SD) (L)	1.94±0.63 (n=136)	1.97±0.65 (n=137)			
Adjusted mean FEV_1 (L) at week 4 (mean ± SE)	2.04±0.02	2.07±0.02	–0.03±0.03	–0.08 to 0.02	0.334
Baseline % predicted FEV_1 (mean ± SD)	88±8 (n=136)	88±9 (n=137)			
Adjusted mean % predicted FEV_1 at week 4 (mean ± SE)	93±1	93±1	–1±1	–3 to 1	0.567
Baseline PEF (L/min) (mean ± SD)	245±85 (n=61)	251±92 (n=60)			
Adjusted mean PEF (L/min) at week 4 (mean ± SE)	274±6	265±6	9±7	–3 to 21	0.233

P values are based on analysis of covariance. All values are adjusted for baseline, centre, age and sex

Safety

No patient was withdrawn from treatment due to an adverse event after random assignment. The most commonly reported events during treatment were upper respiratory tract infection (10 patients in each group) and headache (seven patients in the FP HFA 134a group and six patients in the FP CFC pMDI group). The incidence of pharmacologically predictable adverse events expected for inhaled corticosteroids was low and similar between the two groups. Four patients in each group reported throat irritation, three patients in the FP HFA 134a group reported hoarseness (none in the FP CFC group) and one patient had oral candidiasis in the FP CFC group (none in the FP HFA 134a group). There was no evidence to suggest any treatment effect on laboratory data or vital sign parameters for either formulation. The mean serum cortisol levels were similar at baseline and after four weeks of treatment. In the FP HFA 134a pMDI group, the baseline value was 223 nmol/L, which increased to 266 nmol/L at week 4. This compares with corresponding values of 237 nmol/L and 261 nmol/L in the FP CFC pMDI group.

DISCUSSION

This study demonstrated equivalent efficacy and comparable safety of FP 100 µg administered twice daily via either a HFA 134a pMDI or a CFC pMDI in pediatric patients with asthma who had demonstrable room for improvement with their existing therapy. Study design is an important factor when evaluating equivalence between the same dose of steroid at microgram equal doses. Studies should be conducted on the steep part of the dose-response curve for the primary efficacy variable evaluated and ideally should include two dose strengths (14), although this is difficult practically in pediatric asthmatic patients due to the relatively flat dose response of inhaled steroids. This study was designed to ensure that only patients with room for improvement in lung function and who were clearly on the steep part of the dose-response curve were enrolled. It was also designed in accordance with the Committee for Proprietary Medicinal Products guidelines (15) for equivalence testing between CFC and HFA products, which state that to establish efficacy, low strength HFA corticosteroid formulations should be compared with their CFC counterparts for a minimum of a four-week treatment period in a parallel group design.

National and international guidelines have given clear guidance on the use of inhaled corticosteroids in the treatment of childhood asthma (16-18). Although patients in this study had relatively mild symptoms and the majority of patients in each group were taking inhaled steroids on entry to the study, the mean morning PEF was seen to improve in both groups over the four-week treatment period. Clinical equivalence between the two groups was established for the primary vari-

able of daily morning PEF, because the preset limits of an inter-treatment difference with 90% CIs between ±15 L/min was achieved (11). This was supported by the data for the secondary efficacy variables, which demonstrated that there were no clinically meaningful differences between the two treatment groups. The improvement in mean morning PEF was seen after as early as one week, which is consistent with data from previous studies with daily doses of 100 µg and 200 µg in children with mild asthma (19-21). The magnitude of improvement was also comparable with other published data in a study using a daily dose of 200 µg of FP in pediatric patients with mild to moderate asthma (21).

A statistically significant interaction between morning and evening PEF and patients who were not using spacer devices was observed, which suggested that patients in the FP CFC pMDI group improved more than those in the FP HFA 134a pMDI group. However, there were relatively few patients who were not using spacers (approximately 20% in each group), making the clinical relevance of this finding unclear, particularly because recent pharmaceutical data have suggested that the dose delivery characteristics of the FP CFC formulation is similar to the FP HFA formulation, irrespective of spacer use (6). Furthermore, comparable analyses of other efficacy variables, including clinic visit PEF, did not show any evidence of such an interaction, and no such interaction was observed in the adult study investigating this dose of FP (22). In this short term study, the safety profile of the FP HFA 134a formulation was found to be similar to the CFC formulation with respect to the incidence of adverse events and measures of hypothalamic pituitary adrenal axis suppression. The incidence of pharmacologically predictable events, such as oral candidiasis and hoarseness, was low in both treatment groups, possibly because most patients used a spacer, and the frequency of these events was similar to other studies in this patient population (20).

It is recognized, however, that safety is more appropriately assessed in longer term studies, and that systemic exposure is more reliably assessed by measures such as drug concentrations in the blood over time, as well as overnight or 24 h urinary cortisol, rather than morning cortisol, levels (23). However, urinary cortisol measures are dependent on accurate urine volume measurements, which would be difficult in a multicentre, outpatient study in children. A previous study with this dose of FP CFC formulation in children has, however, shown that there was no effect on the mean 24 h urinary cortisol levels following administration for one year (9).

The efficacy and safety of the FP HFA formulation has been established in adults with all severities of asthma over periods of up to one year (24-26). Furthermore, salbutamol and BDP as HFA 134a formulations have also been shown to be effective and well tolerated in children (27,28), and a large epidemiological study has shown that there is no adverse effect in patients changing from their salbutamol CFC-containing pMDI to the HFA product (29). This study, however, provides the first published data showing that the 50 µg/actuation strength of FP administered by HFA 134a is safe and effective in children with mild asthma at a dose of 200 µg/day, and is equivalent on a dose for dose basis to the CFC product.

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