Respiratory Medicine (2003) **(Supplement D)**, S20–S28

ELSEVIER

respiratoryMEDICINE

Efficacy and safety of inhaled budesonide delivered once or twice daily via HFA-134a in mild to moderate persistent asthma in adult patients. Comparison with budesonide CFC

E. Vastagh[a], P. Kuna[b], P. Calistru[c], M.A. Bogdan[d], Efficacy on behalf of the budesonide HFA MDI study group[1]

[a]*Sote Tùdogyogyszati Klinica, Budapest, Hungary*
[b]*Klinica Pulmonologii i Alergologii, Lodz, Poland*
[c]*Spitalul Clinic Victor Babes, Bucharest, Romania*
[d]*Institutul National de Pneumologie Marius Nasta, Bucharest, Romania*

KEYWORDS
Hydrofluoroalkane (HFA)-134a;
Budesonide;
MDI;
Once daily;
Twice daily

Summary This study was undertaken to investigate whether budesonide 400 μg twice daily (Chiesi Farmaceutici S.p.A.) given with the HFA-134a propellant is equivalent in efficacy and safety to the same dose regimen delivered with the marketed CFC product in adult asthmatics with mild to moderate persistent asthma; the effects of budesonide HFA 800 μg once daily were also studied. After a 2-week run-in, a total number of 98, 103 and 97 patients were assigned to the 12-week treatment with budesonide given with HFA or CFC twice daily (morning and evening), or HFA once daily (morning), respectively. The main outcome variable morning PEFR, as well as evening PEFR and clinical symptoms (day-time and night-time asthma attacks, number of asthma-induced night-time awakenings and overall symptoms' scores) were measured daily by patients. Other standard pulmonary function testing were measured at clinic visits. A blood sample for morning serum dosing (8.00–10.00 AM) was taken at baseline and at endpoint. Adverse events and vital signs were also recorded.

Significant improvements at endpoint in morning and evening PEFR, as well as in clinic PEFR and MEF_{50}, were observed in both the twice daily groups only. An exact proof of equivalence between HFA and CFC given twice daily was demonstrated for the primary parameters, morning PEFR (equivalence pre-defined limits were ±40.27 l/min, difference between means = 4.0 l/min and 95% CI −6.9–14.9) and secondary parameters as evening PEFR: (limits ±40.19 l/min, difference between means = 2.1 l/min and 95% Confidence interval (CI) −9.4–13.5) and FEV_1 (limits ±0.27 l, difference between means = 0.0 l and 95% CI −0.11–0.10). Less evident (but within limits) proofs of equivalence were shown in the comparisons with the once daily group. No substantial differences between the three groups were observed for the other efficacy variables, including symptoms and use of rescue salbutamol, which significantly improved over the run-in values in all groups.

Minimal and non-significant decreases over pre-treatment values were observed in the three groups for morning serum cortisol levels: the analysis of individual data has shown a better outcome in the HFA twice daily regimen, compared with the other two groups. Again, a similar amount of patients in both the twice daily groups reported drug-related adverse events, which were more frequent in the once daily HFA group.

[1]*E-mail address*: a.monicipreti@chiesigroup.com (A. Monici Preti)

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2003.10.001

Therefore, the results of this study have shown that inhaled budesonide given with new HFA-134a propellant can replace microgram-equivalent doses of the corresponding marketed CFC product when given twice daily. An overall maintainment and an unchanged risk-benefit ratio has emerged for budesonide HFA given once daily, which was however slightly inferior compared with the standard twice daily regimens.

Introduction

The pressurised metered dose inhaler (pMDI) is still the device of choice for asthma inhalation therapy[1] and is an essential therapeutic option for the estimated more than 300 million people worldwide who suffer from asthma and the many millions more affected by a variety of other respiratory diseases.

Chlorofluorocarbons (CFCs) are still currently available in Europe and elsewhere for the manufacture of MDIs in their essential use exemption. However, beside the evidence that CFCs (such as the freons) contained as propellants in MDIs have a proven damaging effect on the atmospheric ozone layer,[2] an international conference held in Montreal in 1987[3] led to a commitment by participating countries to cease production of these compounds, and the European Community has set a target date of 2003 for a no further use of CFC-containing aerosols.[4]

In order to provide prescribers, in compliance with the European guidelines, a variety of pMDIs-delivered products, mainly bronchodilators and inhaled glucocorticosteroiods, containing hydrofluoroalkane (HFA)-134a as an alternative CFC-free propellant has been developed. Different approaches have been used in the development of non-CFC formulated glucocorticosteroids: the transition from the fluticasone propionate CFC to HFA-134a has been possible at a microgram equivalent dose, as shown in a variety of clinical trials,[5–7] while the increased deposition of beclometasone dipropionate in the lungs has permitted an halved dosage of the current HFA-marketed product (QVAR®, 3M Healthcare), relative to the CFC formulation.[8]

Budesonide is an established and widely used topically active synthetic glucocorticosteroid. Its systemic absorption is generally low, and may vary from 10% to 30% depending on the device and user technique. The bioavailability of orally administered budesonide is about 10% due to extensive pre-systemic metabolism.[9] These favorable properties have evidenced the need of a safe replacement of freon-delivered budesonide as a part of CFCs phasing out: the main objective of the development program for the HFA-134a-delivered budesonide used in this study was to produce solution formulations of the active drug that are equivalent in terms of efficacy, safety and dose per actuation to the currently marketed budesonide CFC-containing products. This objective has been implemented by applying Chiesi's proprietary technology (Modulite®), which includes glycerol as a low volatile co-solvent, in order to obtain a particle size distribution which mimics that of the CFC -product to be replaced.

The objective of the present study was to compare the efficacy and safety of budesonide 800 μg/day propelled with either the HFA-134a or the marketed CFC in adult patients with mild to moderate persistent asthma. In view of the evidence supporting a once daily administration of inhaled budesonide,[10] a third arm with the HFA-delivered formulation has been included in this study.

Patients and methods

Patients

This study was carried out in 21 centres across four European countries (France, Hungary, Poland and Rumania). Patients aged between 18 and 70 years, with mild to moderate persistent asthma reversible to beta$_2$-agonists and with a FEV$_1$ between 60% and 90% of predicted normal were eligible to take part in the study. Patients satisfying any of the following criteria were excluded from the participation in the study: evidence of asthma exacerbation or upper respiratory tract infection in the previous 8 weeks; medical history of clinically significant diseases; intake of oral steroids in the previous 8 weeks; intake of inhaled corticosteroids at a dose exceeding a corresponding dose of 800 μg/day inhaled budesonide; inability to abstain from the non-permitted concomitant medications; pregnancy or risk of pregnancy, heavy smoking habits (defined as $\geq$20 cigarettes/day over a 20-year period); hypersensitivity to inhaled corticosteroids. In addition,

patients were admitted to the treatment phase provided that their FEV_1 did not change ($\pm$15% vs. screening) at the end of the 2-week run-in period.

Intake of inhaled rescue salbutamol was permitted at any time (at minimum 6 h from pulmonary function testing). Long acting $beta_2$-agonists (at minimum 12 h from pulmonary function testing), inhaled or oral sodium cromoglycate or nedocromil sodium, theophyllines and leukotriene antagonists, if taken at study entry, were permitted at a constant dose throughout the study period. Inhaled corticosteroids could continue at constant daily dose during the run-in period, whereas anticholinergics, oral corticosteroids, and antihistamines were not permitted at any time.

Study design, treatment and outcome measures

This was a 12-week, double blind, double dummy (the group treated with budesonide HFA given in a once daily dose was an open control group), randomised, multinational, multicentre, parallel-group design study.

After a 2-week run-in period, eligible patients were randomised to one of the following three treatment arms: budesonide HFA, or budesonide CFC (Pulmicort®, AstraZeneca), both given at a dose of 400 μg twice daily (08.00 AM and 08.00 PM), or budesonide HFA given at a dose of 800 μg once daily (08.00 AM). To keep blinding, patients assigned to the 2 twice daily regimens also received the alternative placebo.

At each visit, done at study entry, baseline (end of run-in), and after 2, 4, 8 and 12 weeks of treatment, the following pulmonary function (PF) tests were measured according with standard guidelines:[11] forced expiratory volume in 1 s (FEV_1, l), forced vital capacity (FVC, l), peak expiratory flow rate (PEFR, l/min) and mid expiratory flow at 50% vital capacity (MEF_{50}, l/s). Three consecutive tests were performed and the best (that with highest FEV_1 reading) was recorded. Patients also used a portable peak flow meter (Mini-Wright®, Markos, Italy) to measure their peak flow (l/min) twice daily (at 08.00 AM and at 08.00 PM); the best of three readings was used for data analysis, together with the calculation of daily peak flow variability using the following formula:[12] [PEFR evening−PEFR morning/1/2 (PEFR evening + PEFR morning)] × 100.

Patients recorded daily the number of puffs of inhaled salbutamol taken on demand, as well as a daily symptoms' score, which was obtained by a 4-point rating-scale measurement of dyspnoea, tachypnoea, wheezing and cough (0 = none; 1 = mild; 2 = moderate; 3 = severe). The frequencies of salbutamol-free days and symptoms-free days were also calculated.

A blood sample was taken at baseline and at week 12, between 08.00 and 10.00 AM, to measure serum cortisol levels. Assessment was done using direct radio-immunologic assay (RIA), and was centralised at MDS Pharma Services Central Lab (Baillet en France, France), the provided range of normal value was 250–700 nmol/l.

Adverse events were questioned at each visit and described in terms of date of onset, date of end, severity, outcome and correlation with the study treatment. Vital signs (pulse rate and blood pressure) were also measured at each clinic visit.

Patients had to record daily on a diary card the number of administered puffs; a limit for a satisfactory compliance was set at 75% of scheduled drug.

Ethics

The study protocol was submitted to and approved by the Independent Ethics Committees of each participating centre prior to any study-related procedure was started. In addition, all patients were fully informed in writing of the objectives and implications of the trial and their written informed consent was obtained before they were enrolled.

Statistics

Once defined the final (weeks 11–12) mean value of morning PEFR as the primary outcome variable, the sample size calculation was aimed to satisfy a criteria of equivalent efficacy between both twice daily groups.[13] The limit for equivalence was set at a 10% of the mean morning PEFR value (460 l/min) observed in a sample, drawn from a similar population, treated with the CFC propellant. Being a clinical equivalence trial, the test was based on the calculation of the bilateral confidence interval (1-2α) of the two means difference. Type I error was fixed at $\alpha = 0.025$ and type II error was set at 0.2 in order to ensure a 80% power to verify the hypothesis of equivalence. With an expected difference between the two formulations equal to zero and the common standard deviation equal to 90 l/min, each group had to contain 82 patients (246 in total).

Morning PEFR values were analysed within treatment by calculating, after 4 weeks of treatment and at the end of study periods, the 95% confidence interval (CI) for the mean change from baseline; a

minimum of 10 measurements was required in each 2-week period.

Two by two comparisons between treatment groups were made using an analysis of covariance (ANCOVA) model for morning PEFR values recorded on the last 2-week period. The ANCOVA model included terms for investigator and treatment effects and baseline value as a covariate. A preliminary test for the centre-by treatment interaction was performed at 0.10 significance level.

The equivalence between the three test treatments was evaluated by calculating the bilateral 95% CIs for the difference between the least-squares means (LSMs), from ANCOVA, in the two-by-two comparisons. The two twice daily test treatments were defined as equivalent if the confidence limits for the difference fall within the $\pm 10\%$ of the LSM of the budesonide group using the CFC propellant, which was also used as reference drug in the comparison with the once daily group. When comparing the two HFA groups, the once daily regimen was used as reference drug.

Other than morning PEFR, evening PEFR and FEV_1 were also tested for equivalence whereas the other PF tests, daily PEFR variability, salbutamol daily use, days without use of salbutamol, asthma attacks, clinical symptoms, symptoms-free days, morning serum cortisol and vital signs were analysed by calculating the 95% CI for the mean change from baseline; an ANCOVA model was used for between-group comparisons.

Mean values of the run-in period for variables recorded daily by patients and values measured at the 2nd clinic visit were the baseline data; 2-weekly means were also calculated for the daily recorded variables. Study populations were as follows: intention-to-treat (ITT), defined as all randomised patients with post-baseline data; per-protocol (PP), made of patients in the ITT without major protocol violations; safety population (SP), entered by patients having taken at least one dose of study drug. Missing data were managed using the last observation carried forward (LOCF) method.

Results

Patients' disposition and baseline data

Three hundred and thirteen (313) patients in total were included in the study, 298 (95.2%) of them were randomised, while 15 (4.8%) were withdrawn during run-in. Among the 298 randomised patients, 98 (32.9%) patients were assigned to treatment with HFA twice daily, 103 (34.6%) to CFC and 97 (32.6%) to HFA once daily. Three patients, all in the CFC group, did not have post-baseline data and were excluded from ITT population. A total number of 284 patients (94, 96 and 94 in the three groups, respectively) completed the 12-week period: the main reasons of the 14 withdrawals consisted of adverse events or poor co-operation.

A total of 13 patients had at least one major protocol violation during the study (poor compliance in eight patients, incorrect use of anti-asthma medications in four and FEV_1 outside the required range in another) and were therefore excluded from the PP analysis.

The number of patients taking inhaled corticosteroids at study entry and during run-in period was similar in the three groups: 82 (83.7%) patients in the HFA twice daily group, 74 (74.0%) in the CFC group and 78 (80.4%) in the HFA once daily. The amount of patients taking long-acting β_2-agonists for the total study period was 43.9%, 39.0% and 47.4% in the three groups, respectively, while fewer patients took xanthine derivatives, leukotriene antagonists or sodium cromoglycate.

Baseline data (Table 1) were well matched among the three groups with respect to demo-

Table 1 Baseline characteristics of the ITT population.

	HFA twice daily($n = 98$)	CFC twice daily($n = 100$)	HFA once daily($n = 97$)
Sex			
Males (*n*)	49 (50.0%)	38 (38.0%)	39 (40.2%)
Females (*n*)	49 (50.0%)	62 (62.0%)	58 (59.8%)
Age, years (mean $\pm$ SD)	42.2 $\pm$ 13.8	43.0 $\pm$ 14.3	43.8 $\pm$ 13.9
Height, cm (mean $\pm$ SD)	169.5 $\pm$ 10.2	166.7 $\pm$ 8.9	167.4 $\pm$ 10.3
Weight, kg (mean $\pm$ SD)	74.0 $\pm$ 13.6	70.6 $\pm$ 13.6	75.8 $\pm$ 12.1
Morning PEFR, l/min (mean $\pm$ SD)	404.1 $\pm$ 105.7	386.0 $\pm$ 104.2	393.8 $\pm$ 96.5
Evening PEFR, l/min (mean $\pm$ SD)	412.2 $\pm$ 106.2	391.9 $\pm$ 104.8	397.4 $\pm$ 95.2
FEV_1 predicted, % (mean $\pm$ SD)	77.6 $\pm$ 8.2	77.3 $\pm$ 9.0	77.8 $\pm$ 8.3

N.S between groups for all variables.

graphics, pulmonary function, symptoms, time from first asthma diagnosis and morning serum cortisol levels. The mean FEV_1% predicted normal values at study entry were 77.6±8.2 in the HFA twice daily, 77.3±9.0 in the CFC group and 77.8±8.3 in the HFA once daily group.

Efficacy

Results of the primary variable morning PEFR show an increase over baseline that was reported from weeks 1–2 onwards in both the twice daily groups only (Fig. 1). No statistically significant differences between groups were reported in the ANCOVA model in the total population ($P = 0.153$), as well as in the steroid-naive subset ($P = 0.227$). Values of LSMs were 406.7 l/min in the HFA twice daily group, 402.7 l/min in the CFC group and 396.0 l/min in the HFA once daily group. The 95% bilateral CI of the estimate difference between the LSM (4.0 l/min) of the two twice daily groups in the ANCOVA model was −6.9 to 14.9, which was well within the ±10% of the adjusted mean of budesonide CFC group (±40.27 l/min) thus showing that both the twice daily groups were equivalent. The comparisons between both the twice daily regimens with the HFA once daily also satisfied an hypothesis of equivalence: 95% CI for the difference between CFC and HFA (−6.7 l/min) once daily was −17.6 to 4.2 and in the comparison of the two HFA regimens (10.7 l/min) was −0.3 to 21.7.

The analysis of equivalence in the PP population was consistent with that obtained in the ITT analysis: the 95% CI for the difference between HFA twice daily and CFC (4.7 l/min) was −6.4 to 15.9 (limits: ±40.10 l/min), values for the difference between CFC and HFA once daily (−5.7 l/min) were −16.8 to 5.5 and that in the comparison between the two HFA groups (10.4 l/min) were −0.8 to 21.5 (limits: ±39.54 l/min).

Results of evening PEFR (Fig. 2) were similar to that obtained in the morning: the 95% CI for the difference between the LSMs of HFA twice daily and CFC (2.1 l/min) was −9.4 to 13.5, within the ±10% of value of CFC group (±40.87 l/min), that between LSMs of HFA once daily and CFC (−6.8 l/min) was −18.3 to 4.7, and that between the two HFA regimens (8.9 l/min) was −2.7 to 20.4 (adjusted mean of HFA once daily group, ±40.19 l/min).

With regards to FEV_1 (Table 2), a statistically significant increase over baseline was reported from week 2 onwards in each treatment group, without significant differences between them in the total population ($P = 0.615$), as well as in the steroid-naive subgroup ($P = 0.374$).

Values of LSMs were 2.66 l in both the twice daily groups and 2.62 in the HFA once daily group; the 95% CI for the differences was −0.11 to 0.10 in the comparison between the twice daily groups, −0.15 to 0.06 between CFC and HFA once daily and −0.06 to 0.15 between the two HFA groups, thus showing an evident proof of equivalence between the three groups. Results of evening PEFR and FEV_1 obtained in the PP analysis were similar to those of ITT population (data not shown).

Results of the other PF tests (FVC, PEFR and MEF_{50}) measured at clinic visits are shown in Table 2: improvements were evident in all the three treatment groups, but significant increases over baseline at end-point were obtained in all variables in both the twice daily groups, whereas the HFA once daily regimen produced significant increases only for FVC (Table 2). However, no statistically

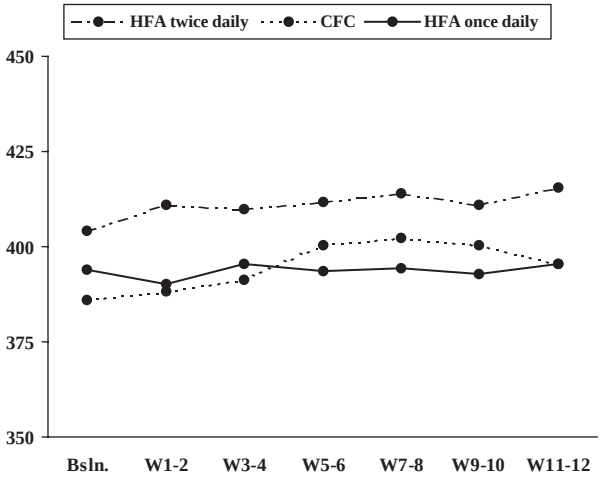

Figure 1 Morning PEFR (l/min) expressed as two weekly means.

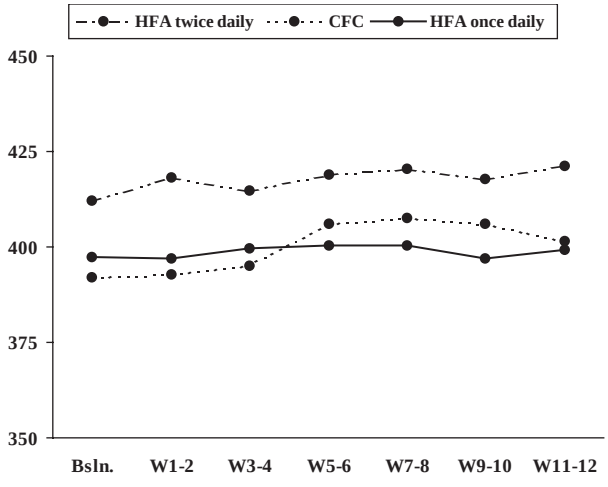

Figure 2 Evening PEFR (l/min) expressed as two weekly means.

Table 2 Pulmonary function tests during the study (ITT population).

	Group	Baseline (mean ± SD)	Week 2 (mean ± SD)	Week 4 (mean ± SD)	Week 8 (mean ± SD)	Week 12 (mean ± SD)
FEV_1 (l)	HFA twice daily	2.63 ± 0.67	2.70 ± 0.78*	2.74 ± 0.78*	2.74 ± 0.82*	2.77 ± 0.80*
	CFC twice daily	2.46 ± 0.69	2.53 ± 0.81*	2.61 ± 0.79*	2.63 ± 0.85*	2.63 ± 0.83*
	HFA once daily	2.44 ± 0.68	2.56 ± 0.76*	2.53 ± 0.78*	2.54 ± 0.79*	2.54 ± 0.77*
FVC (l)	HFA twice daily	3.54 ± 0.97	3.59 ± 1.08	3.63 ± 1.05*	3.62 ± 1.04*	3.65 ± 1.05*
	CFC twice daily	3.28 ± 0.91	3.35 ± 0.96*	3.40 ± 0.93*	3.44 ± 1.00*	3.46 ± 0.97*
	HFA once daily	3.26 ± 0.97	3.38 ± 1.00*	3.33 ± 0.99	3.36 ± 0.99*	3.39 ± 1.00*
PEFR (l/min)	HFA twice daily	364.6 ± 111.5	388.0 ± 121.4*	381.2 ± 117.5*	388.9 ± 125.5*	397.5 ± 133.1*
	CFC twice daily	336.8 ± 110.7	358.6 ± 114.6*	369.3 ± 114.3*	374.9 ± 124.9*	370.6 ± 118.3*
	HFA once daily	352.6 ± 110.6	376.0 ± 124.2*	367.1 ± 122.0	364.9 ± 115.9	364.2 ± 120.9
MEF_{50} (l/s)	HFA twice daily	2.70 ± 1.06	2.83 ± 1.21	2.90 ± 1.18*	2.87 ± 1.25*	2.91 ± 1.24*
	CFC twice daily	2.53 ± 1.16	2.73 ± 1.37*	2.81 ± 1.34*	2.83 ± 1.40*	2.78 ± 1.35*
	HFA once daily	2.55 ± 1.12	2.67 ± 1.12	2.69 ± 1.21	2.65 ± 1.25	2.60 ± 1.21

*$P < 0.05$ vs. baseline.

significant differences between groups were reported in the ANCOVA model ($P = 0.879$ for FVC, $P = 0.153$ for PEFR and $P = 0.211$ for MEF_{50}).

Table 3 shows the results obtained in the daily measurements of symptoms and intake of rescue salbutamol.

A progressive and statistically significant improvement over time of symptoms' scores and percentage of symptom-free days was similarly observed in the three groups (N.S. between groups for both variables). A statistically significant decrease over baseline in the use of rescue salbutamol was also observed at any time point in the two twice daily groups and from weeks 3–4 onwards in the HFA once daily group ($P = 0.707$ between groups).

Safety

Small and non-significant declines were observed in mean values of morning serum cortisol in all the three treatment groups: in the HFA twice daily group mean baseline values were 399.0 ± 277.6 nmol/l and mean values at week 12 were 382.0 ± 166.0 nmol/l; in the CFC group baseline and final means were 394.3 ± 137.6 nmol/l and 377.9 ± 158.2 nmol/l, respectively; corresponding values in the HFA once daily group were 363.5 ± 155.5 nmol/l and 354.5 ± 161.0 nmol/l, respectively. The comparison between groups of change from baseline did not show statistically significant differences ($P = 0.960$). Individual data are as follows: nine patients in the HFA twice daily group, 15 in the CFC group and 18 in the HFA once daily group had baseline values within the normal range which declined below the lower limit at the end of treatment. Conversely, the amount of patients with low baseline values which entered the normal range at week 12 was 15, 6 and 13 in the three groups, respectively.

A total number of 63 adverse drug reactions (defined as those adverse events with definite, probable, possible or doubtful relationship to study medication), with 15 (in 11 patients, 11.2%) in the HFA twice daily, 20 (in 11 patients, 10.8%) reported in the CFC group and 28 (in 20 patients, 20.6%) reported in the HFA once daily group. The comparison between groups of the distribution of drug-related adverse events did not show statistically significant differences between groups ($P = 0.113$). Most of these events consisted of local effects (i.e. cough, dysphonia, pharyngo-laryngitis, rhinitis and oral mycosis), which occurred in eight patients in the HFA twice daily group, in seven in the CFC group and in 12 in the HFA once daily group. In addition, a taste dislike was reported by three (3.1%), five (4.9%) and eight (8.2%) patients in the three groups, respectively, as a probable result of HFA-134a intake (with active or placebo) propellant. Only two patients reported serious adverse events (hospitalisation), both of which were not related with study drug.

No clinically significant changes over baseline were observed in vital signs (pulse rate and blood pressure). An excellent proof of compliance was observed in the three groups: the mean percentages (± SD) of administered drug in respect of that

Table 3 Clinical parameters daily recorded on diary cards (ITT population).

	Group	Baseline (mean ± SD)	Weeks 1–2 (mean ± SD)	Weeks 3–4 (mean ± SD)	Weeks 5–6 (mean ± SD)	Weeks 7–8 (mean ± SD)	Weeks 9–10 (mean ± SD)	Weeks 11–12 (mean ± SD)
Clinical symptoms' score	HFA twice daily	2.0 ± 1.8	1.7 ± 1.8	1.5 ± 1.7*	1.6 ± 1.7*	1.4 ± 1.6*	1.4 ± 1.7*	1.4 ± 1.7*
	CFC twice daily	2.1 ± 2.0	1.8 ± 1.8	1.6 ± 1.8*	1.2 ± 1.4*	1.3 ± 1.5*	1.3 ± 1.5*	1.4 ± 1.6*
	HFA once daily	2.1 ± 2.0	2.0 ± 2.0*	1.8 ± 1.9*	1.8 ± 2.0	1.7 ± 2.0*	1.5 ± 1.8*	1.6 ± 1.8*
Symptoms-free days (%)	HFA twice daily	31.8 ± 39.3	39.8 ± 40.1*	44.0 ± 39.6*	41.3 ± 39.2*	45.2 ± 39.8*	48.1 ± 40.2*	46.5 ± 41.7*
	CFC twice daily	33.5 ± 39.8	37.9 ± 38.7	41.1 ± 40.2*	50.5 ± 42.1*	50.2 ± 41.9*	48.1 ± 40.7*	46.3 ± 40.7*
	HFA once daily	31.2 ± 37.5	35.2 ± 38.7	37.2 ± 39.3	36.8 ± 40.7	38.8 ± 41.4*	40.3 ± 39.6*	40.3 ± 40.4*
Salbutamol intake (daily number of puffs)	HFA twice daily	1.4 ± 1.6	1.0 ± 1.3*	0.9 ± 1.2*	0.9 ± 1.1*	0.9 ± 1.1*	0.8 ± 1.1*	0.9 ± 1.3*
	CFC twice daily	1.3 ± 1.4	1.0 ± 1.2*	1.0 ± 1.2*	0.8 ± 1.1*	0.9 ± 1.3*	0.8 ± 1.2*	0.9 ± 1.2*
	HFA once daily	1.6 ± 2.1	1.4 ± 2.1	1.4 ± 1.9	1.2 ± 1.4*	1.2 ± 1.4*	1.1 ± 1.4*	1.1 ± 1.4*

$P < 0.05$ vs. baseline values.

scheduled on the basis of the extent of exposure were 97.4 ± 9.3 in the HFA twice daily group, 97.6 ± 5.8 in the CFC and 97.9 ± 5.1 in the HFA once daily group.

Discussion

The results of the present study have demonstrated an exact proof of clinical and statistical equivalence in the comparison of budesonide HFA and CFC given in the twice daily regimen both in the pulmonary function and in the symptoms scoring, thus showing that the administration of inhaled budesonide with the HFA-134a propellant does not modify the efficacy in respect with a similar budesonide CFC dosing. The primary outcome variable morning PEFR showed significant improvements in both the twice daily groups, with mean increases in the final period of 11.4 l/min in the budesonide HFA group and of 9.5 l/min in the budesonide CFC group, being the 95% CI for the differences between groups (−6.9 to 14.9) comprised in a very narrow range, well within the pre-defined limit of 10% of the reference LSM. Improvements observed in the HFA once daily group (1.8 l/min in the final period), despite satisfying the pre-defined limit for equivalence, were not significant and were lower to that obtained in the other groups.

The results obtained in evening PEFR, as well as for PEFR or MEF_{50} measured at clinic visits, were consistent with those of the primary variable, as both the twice daily regimens produced more relevant increases than the once daily group, although differences in the two-by-two comparisons were not significant. The results of FEV_1 (and that of FVC) showed statistically significant improvements over baseline in all the three groups at all visits and FEV_1 final values increased of 0.14 l in the two twice daily groups, and of 0.09 l in the HFA once daily group. The analysis of equivalence showed that the 95% CIs were comprised in a very narrow interval in the comparison between the two twice daily groups (−0.11 to 0.10 l) and well within the pre-defined limit in the comparisons with the once daily dosing. Also, the results of symptoms and use of rescue salbutamol showed an overall and significant similar improvement in the three groups, without significant differences between them in any of the considered variables.

Importantly, the three groups were well matched for asthma severity and baseline values of all efficacy and safety parameters; the overall FEV_1% predicted at study entry was 77.6, with similar

values in the three groups, thereby showing a satisfactory room for improvement and a potential sensitivity to detect differences between them. To establish true clinical equivalence, it is essential that the compared drugs show a real improvement from baseline to end-point[14]; the small improvements obtained in the once daily group in the primary and in some of the secondary efficacy variables, compared with both the twice daily groups, confirm that this study met this requirement. However, it should be also noted that, according with actual trend in prescription and with international guidelines,[15] an overall proportion of patients in this trial (more than 40%) were using long-acting $beta_2$-agonists at study entry and this treatment could not have been discontinued during the treatment phase. This proportion is higher than that reported in similar studies previously done,[5,6] and this evidence could explain the moderate improvements in lung function obtained in the two twice daily groups.

Minimal and similar decreases of mean values of morning serum cortisol (-17 nmol/l in the HFA twice daily group, -16.4 nmol/l in the CFC group and -9.0 nmol/l in the HFA once daily group) were reported in the three groups, without statistically significant differences between them. The analysis of patients whose baseline level decreased below the lower limit of normal range and whose low baseline was restored at the end of treatment gave better results in the HFA twice daily group (nine and 15 patients, respectively), compared with the CFC (15 and six) and the HFA once daily group (18 and 13). Considering that a proportion of approximately 20% of patients were not treated with inhaled corticosteroids at study entry and during run-in, and that in any case the dose of previous inhaled corticosteroids was not decreased with the study treatment, the individual values show a lack of any detrimental effect of budesonide given twice daily via the HFA-134a, in terms of possible adrenal suppression.

The proportion of patients who experienced adverse drug reactions was low in both the twice daily groups, accounting for 11 patients (11.2%) in the HFA and 11 (10.8%) in the CFC group, whereas the frequency of adverse drug reactions was almost doubled in the HFA once daily group, as they occurred in 20 patients (20.6%) and mainly consisted of typical local effects of inhaled glucocorticosteroids. Among the reported adverse drug reactions, a sensation of unpleasant taste, which is a well recognised effect when a HFA-containing inhaled drug is started[16,17] and generally requires an initial adaptation, was described by three patients in the HFA twice daily, five in the CFC (probably due to the alternative HFA placebo) and eight in the HFA once daily group. The results obtained in the once daily group, either obtained in the general safety profile or relative to taste dislike, might be due to a double number of puffs of active drug given simultaneously.

A variety of studies has shown that inhaled budesonide given once daily is as effective as the same amount of drug given in divided doses. However, most of these studies were done with budesonide pMDI delivered in patients already receiving inhaled corticosteroids[18] or using the conventional dry powder inhaler (i.e. the Turbuhaler®) in stable[19] or mild asthmatics;[20] in addition, results obtained in relatively short terms were not confirmed in another study of a 12-month duration.[21] The results of the present study have indicated that the presumed equivalence between different dose regimens of inhaled glucocorticosteroids is to be interpreted with caution. When given in patients with a satisfactory room for improvement, budesonide given once daily with the HFA propellant produced an overall improvement and a favourable risk-benefit ratio, which was however slightly inferior compared to the standard twice daily regimen; it remains a convenient therapeutical option in patients with mild asthma or sub-optimal compliance.

We can therefore conclude that the results of the present study have provided evidence of equivalent efficacy of inhaled budesonide given with the HFA-134a or the conventional CFC propellants, when given twice daily at a microgram-equivalent dose. The administration of budesonide via the HFA propellant is also at least as safe as the marketed CFC-containing product.

List of participating investigators and study centres

The study was conducted throughout the following investigators and centres:

Hungary: Vastagh E. (study Co-ordinator), ''Sote Tudogygogyaszati Klinica'', Budapest; Devai A., ''Favarosi Onkormanyzat, Uzsoki Korhaz Tudosztaly'', Budapest; Herjavecz I., ''Orszagos Koranyi TBC Intezet Pulmonologia'', Budapest; Lukacs J., ''Szent-Janos Korhaz Tudosztaly'', Budapest; Petho L., ''Budai MAV Korhaz I. Pulmonologia'', Budapest; *Poland*: Adamek-Guzik T.; ''Poradnia Alergologiczna, Szpital Specjalistyczny'', Krakow; Kuna P., ''Klinika Pulmonologii i Alergologii'', Lodz; Skucha W., ''SPZOZ w Proszowicach Oddzial Chorób Pluc i Gruzlicy'', Proszowice; Nalepa P.,

''V Wojskowy Szpital Kliniczny Samodzielny Publiczny Zaklad Opieki Zdrowotnej Oddzial ch. Pluc'', Krakow; Szafranski W., ''Oddzial Pulmonologiczny Wojewódzki Szpital Specjalistyczny'', Radom; *Romania*: Bogdan M.A., ''Institutul National de Pneumologie Marius Nasta'', Bucharest; Calistru P., ''Spitalul Clinic Victor Babes'', Bucharest; Isacoff D., ''Spitalul Clinic Coltea'', Bucharest; Poposcu E., ''Saint Maria Hospital'', Bucharest; Radu J.R., ''Spitalul Clinic Nicolae Malaxa'', Bucharest; *France*: Courtois L., Rueil Malmaison; Delsaux M.C., Gournay sur Marne; Douillet C., Monterau; Martinat Y., ''Centre Médical Parot'', Lyon; Ortolan D., Villejuif; Pigearias B., Nice; Schwender D., Dijon.

References

1. Woodcock A. CFCs and inhalers. *Lancet* 1994;**344**:182–3.
2. Noakes TJ. CFCs, their replacements, and the ozone-layer. *J Aerosol Med* 1995;**8**(Suppl. 1):3–7.
3. Montreal Protocol on substances that deplete the ozone layer, Final Act (Nairobi: UNEP, 1987). *Federal Register* 1994;**59**:56276–98.
4. Strategy for the phase out of CFCs in metered dose inhalers. Commission of the European Communities, 23.10.98, COM (1998) 603 Final.
5. Tonnel AB, Bons J, Legendre M, Prud'Homme A, Bugnas B, Evano-Celli I, Stuart AM. Clinical efficacy and safety of fluticasone propionate 250 μg twice daily administered via a HFA 134a pressurized metered dose inhaler to patients with mild to moderate asthma. *Respir Med* 2000;**94**(Suppl. B):S29–34.
6. Perruchoud AP, Lundback B, Yigla M, Sykes P. Clinical efficacy and safety of fluticasone propionate 1 mg per day administered via a HFA-134a pressurized metered dose inhaler to patients with moderate to severe asthma. *Respir Med* 2000;**94**(Suppl. B):S35–41.
7. Ayres JG, Millar AB, Sykes AP. 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. *Respir Med* 2000;**94**(Suppl. B):S42–50.
8. Van der Burgt JA, Busse WW, Martin RJ, Szefler SJ, Donnell D. Efficacy and safety overview of a new inhaled corticosteroid, QVAR (hydrofluoroalkane—beclomethasone extrafine inhalation aerosol), in asthma. *J Allergy Clin Immunol* 2000;**105**:1210–26.
9. Donnelly R, Seale JP. Clinical pharmacokinetics of inhaled budesonide. *Clin Pharmacokinetics* 2001;**40**(6): 427–40.
10. Campbell ML. Once-daily inhaled corticosteroids in mild to moderate asthma. *Drugs* 1999;**58**(Suppl 4):25–33.
11. Quanjer PhH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. *Eur Respir J* 1993;**6**(16):5–40.
12. Quackenboss JJ, Lebowitz MD, Krzyzanowski M. The normal range of diurnal changes in peak expiratory flow rates. *Am Rev Respir Dis* 1991;**143**:323–30.
13. Jones B, Jarvis P, Lewis JA. Trials to assess equivalence: the importance of rigorous methods. *BMJ* 1996;**313**:36–9.
14. Ebbutt AF, Frith L. Practical issues in equivalence trials. *Stat Med* 1998;**17**:1691–701.
15. USA National Institute of Health. National Heart, Lung and Blood Institute. *NHLBI/WHO Workshop Report: Global strategy for Asthma Management and Prevention*. Report No. 02-3659, issued January 1995, revised 2002.
16. Huchon G, Hofbauer P, Cannizzaro G, Iacono P, Wald F. Comparison on the safety of drug delivery via HFA- and CFC- metered dose inhalers in CAO. *Eur Respir J* 2000;**15**: 663–9.
17. Anderson PB, Langley SJ, Mooney P, Jones J, Addlestone R, Rossetti A, Cantini L. Equivalent efficacy and safety of a new HFA-134a formulation of BDP compared with the conventional CFC in adult asthmatics. *J Invest Allergy Clin Immunol* 2002;**12**(2):107–13.
18. Stiksa G, Glennow C. Once daily inhalation of budesonide in the treatment of chronic asthma: a clinical comparison. *Ann Allergy* 1985;**55**:49–51.
19. Gunn SD, Choudhury M, Au K. Inhaled steroid treatment reduction in stable asthmatics: a comparison of beclomethasone/budesonide metered dose inhaler with half dose treatment using budesonide turbuhaler®, given once or twice daily. *Br J Clin Res* 1997;**8**:67–80.
20. Chisholm SL, Dekker FW, Knuistingh Neven A, Petri H. Once-daily budesonide in mild asthma. *Respir Med* 1998;**92**: 421–5.
21. Weiner P, Weiner M, Azgad Y. Long term clinical comparison of single versus twice daily administration of inhaled budesonide in moderate asthma. *Thorax* 1995;**50**:1270–3.