Equivalent asthma control and systemic safety of inhaled budesonide delivered via HFA-134a or CFC propellant in a broad range of doses

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Summary
The aim of the present study was to demonstrate an equivalent asthma control and safety of inhaled budesonide 200 μg unit-dose via a spacer device (Jet® Spacer, Chiesi Farmaceutici S.p.A.) given with an HFA-134a or CFC propellant in stable patients treated with inhaled corticosteroids. A total number of 270 patients, 134 in the HFA-134a group and 136 in the CFC group, completed a 2-week run-in period and were then randomised to receive a daily dose of inhaled budesonide (low dose: 400 μg, medium dose: 800 μg, high dose: 1200 or 1600 μg), defined on the basis of the dose of previous inhaled steroids given twice daily for 12 weeks. Morning and evening PEFR, intake of rescue salbutamol, number of day-time and night-time asthma attacks, number of night-time awakenings due to asthma and clinical symptoms were recorded daily by patients on diary cards. Pulmonary function tests (FEV₁, FVC, PEFR and MEF₅₀) and vital signs were measured at the clinics at study entry, at the start of treatment and after 2, 4, 8 and 12 weeks thereafter. Morning serum cortisol (8.00–10.00 AM) was measured at baseline and in the final visit. Adverse events and vital signs were recorded throughout the total study period.

Small increases vs. baseline for lung function (more markedly in the high-dose subsets) and significant decreases of symptoms and use of rescue salbutamol were similarly observed in both groups. Equivalence was demonstrated for the primary endpoint morning PEFR (difference between means = -1.51 l/min; 95% CI: -9.40–6.37 l/min; pre-defined limits: ±42.16 l/min, i.e. ±10% of the reference LSM) as well as for evening PEFR and FEV₁, both in the ITT population or on a per-protocol basis. No statistically significant differences between groups were observed in any of the other efficacy variables.

A similar proportion of drug-related adverse events was observed in the two groups, without drug-related serious events in either group. No evidence of adrenal depletion was also noted with both propellants.

In conclusion, the budesonide HFA-134a formulation given with a spacer device provided an equivalent asthma control with that of a corresponding CFC product.
when administered in stable patients treated with inhaled corticosteroids in a broad range of daily doses. The use of the new propellant did not modify the safety profile of inhaled budesonide.

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Introduction

The pressurised metered dose inhaler (pMDI) is currently the device of choice for asthma inhalation therapy, being a well-established safe and reliable delivery system and the device most widely used by adults with asthma. Pressurised MDIs have been approved for the administration of virtually all inhaled drugs used in the treatment of reversible obstructive airways disease. Since the prevalence of this disease is increasing both in adults and children, there is a rising need for inhaled therapies in the near future, with national and international guidelines recommending use of corticosteroids and bronchodilators for the treatment of asthma and chronic airways’ obstruction.

Due to the growing awareness that traditional chlorofluorocarbons (CFCs) contributes to the depletion of stratospheric ozone through the specific action of their chloride radicals, hydrofluoroalkane (HFA)-134a (1,1,1,2-tetrafluoroethane or norflurane) has been developed as a replacement propellant for use in MDIs since it is chemically inert, non-flammable and of low toxicity. HFA-134a has been found to be a suitable alternative to CFCs used in the formulation of inhaled drugs, and this has been born out by the subsequent development of re-formulated anti-asthma medicines containing this propellant, mainly inhaled glucocorticosteroids.

Among the currently available inhaled glucocorticosteroids, budesonide has a high ratio of topical to systemic activity compared with other reference steroids, such as beclometasone dipropionate, which allows inhalation of therapeutic doses with minimal systemic exposure. Recent in vivo data and human pharmacokinetic/pharmacodynamic studies have shown that the formation of budesonide esters may increase the topical selectivity of budesonide, which, in addition to its prolonged effects, accounts for a once daily administration. The availability of a CFC-free formulation of budesonide is therefore expected to allow a transition from the current pMDI product.

A new HFA-134a formulation of budesonide has now been developed by Chiesi Farmaceutici S.p.A. aimed at maintaining a dose per dose equivalence with respect to the CFC formulation. The present study has been therefore designed to investigate whether the new budesonide HFA-134a, delivered via pMDI with the addition of a spacer, can provide an equivalent asthma control and systemic safety to that of a marketed CFC-formulated budesonide in a broad range of daily doses administered in adult patients.

Patients and methods

Patients

Participating subjects were selected in 13 centres, seven of them were located in Poland, five in Spain and one in Austria. They had to satisfy all of the following entry criteria: age \( \geq 18 \) and \( \leq 70 \) (inclusive); clinical diagnosis of mild to severe stable persistent asthma, well-controlled with inhaled steroids taken from at least 8 weeks (at a daily dose equivalent to inhaled budesonide \( \leq 1600 \) mg); responsive to inhaled \( \beta_2 \)-agonists; ability to correctly use a pMDI and complete diary cards; written informed consent. Subjects with evidence of asthma exacerbation or upper airways infection in the previous 8 weeks, history of clinically significant cardiac, renal, neurologic, hepatic or endocrine disease; intake of oral steroids in the previous 8 weeks, or of inhaled corticosteroids at a daily dose exceeding a corresponding dose of \( 1600 \) mg inhaled budesonide, pregnancy or risk of pregnancy, heavy smoking habits (defined as \( \geq 20 \) cigarettes/day over a 20-year period) or hypersensitivity to inhaled corticosteroids were excluded from the participation in the study.

Intake of inhaled salbutamol was permitted at any time. Long acting \( \beta_2 \)-agonists, inhaled or oral sodium cromoglycate or nedocromil sodium, theophyllines and leukotriene antagonists were permitted at a constant dose throughout the study period only if taken at study entry. Inhaled corticosteroids could continue being taken 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 double blind, randomised, multinational, multicentre, parallel-group design study. Patients were divided into three treatment/dose subsets (low, medium and high dose) based on the daily dose of inhaled corticosteroids taken at study entry, once taken into account the following ratios between the doses of other steroids and budesonide, irrespectively of the formulations (i.e. pMDI or powder) used: fluticasone propionate: budesonide = 1:2; beclometasone dipropionate: budesonide = 5:4. Patients treated at a low dose (≤400 μg/day budesonide equivalent) were assigned to 400 μg/day, those treated at a medium dose (>400 and <800 μg/day budesonide equivalent) were assigned to 800 μg/day and those treated at a high dose (>800 μg/day budesonide equivalent) were assigned to 1200 or 1600 μg/day. If the calculated dose was not exactly corresponding to the four scheduled dose levels of the test treatments (for example a dose of 600 μg/day beclometasone dipropionate) the assigned dose was the next higher (800 μg/day in this case).

Eligible patients entered a 2-week run-in period and were then randomised to start the 12-week treatment with budesonide 200 μg/unit dose twice daily via pMDI plus a spacer (Jet® Spacer, Chiesi Farmaceutici S.p.A, Italy, Fig. 1) using the HFA-134a or the CFC (Ribujet®, Chiesi España, Spain) propellant.

Thereafter the visits to the clinics took place after 2, 4, 8 and 12 weeks. At each visit the following pulmonary function (PF) tests were performed: forced expiratory volume in one second (FEV1, l), forced vital capacity (FVC, l), peak expiratory flow rate (PEFR, l/min), mid expiratory flow at 50% vital capacity (MEF50, l/s) and the FEV1/FVC ratio. Three consecutive tests were performed and the highest FEV1 reading was recorded. If salbutamol or long-acting β2-agonists had been used at home, a minimum of 6 and 12 h, respectively, had to have elapsed between inhalation and PF measurement. Measuring conditions, equipment and daily calibration of the instrument were standardised as recommended by the European Respiratory Society Guidelines.10 Patients also measured their PEFR (l/min) twice daily (morning and evening at 08.00 AM and 08.00 PM, respectively) using a portable peak flow meter (Mini-Wright®, Markos, Italy); the best of three consecutive flows was recorded. Daily PEFR variability was also calculated using the following formula:11 [PEFR evening – PEFR morning/1/2 (PEFR evening + PEFR morning)] × 100.

Intake of rescue salbutamol (number of puffs/day) was recorded daily by patients in a diary card, as well as the number of day-time and night-time asthma attacks and the number of night-time awakenings caused by asthma. Clinical symptoms (dyspnoea, tachypnoea, wheezing and cough) were also measured daily using a 4-point rating scale (where 0 = none; 1 = mild; 2 = moderate; 3 = severe) to obtain a global sum of scores. The percentages of salbutamol-free days and symptoms-free days were also evaluated.

A blood sample was taken from an antecubital vein between 08.00 and 10.00 AM at the start and at the end of treatment phase for the measurement of morning serum cortisol levels. Assays were centralised at Interlab, Heidelberg, Germany, and were done using luminescence enzyme immunoassay (ACS: 180 Cortisol, Chiron Diagnostics, Germany): the range of normal values was set at 5–25 μg/100 ml.

Pulse and blood pressure were measured at each visit. Patients reported adverse events at each clinic visit, together with their severity, outcome and correlation with the study treatments. Compliance was evaluated with the use of diary card recordings of the administered doses; the proportion of the administered drug was then calculated with a limit for a satisfactory compliance set at 75% of scheduled.

Ethics

The study protocol, patient information leaflet and informed consent document were reviewed and approved by the Independent Ethics Committees of each participating centre prior to the start of the study.
Statistics

The sample size was calculated on the criteria of the equivalence efficacy between the two test treatments: it was based on an expected mean morning PEFR final value (last 2-week period) of 400 l/min and a standard deviation (SD) of 95 l/min in the CFC group, a power equal to 80% and type I error $\alpha = 0.025$. The sample size was therefore set at 120 evaluable patients per group.\(^\text{12}\) Equivalence was proven if the bilateral 95% confidence interval (CI) for the difference between treatment means fell within the range of $\pm 10\%$ of the adjusted least-squares means (LSMs) of the BDP CFC group, obtained from an ANCOVA model using baseline values as covariate. Equivalence test between the two treatments was to be done for morning and evening PEFR, as well as for FEV\(_1\), 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.

Baseline data was that derived from the mean values of the 2-week run-in period for variables recorded on the diary cards and data measured at the 2nd clinic visit. Two-weekly means were also calculated for the variables recorded in the diary cards.

All randomised patients with post-baseline data were included in the intention-to-treat (ITT) analysis; patients with major protocol violations were excluded from the per-protocol (PP) population. The last observation carried forward (LOCF) method was used to deal with missing data.

Results

Patients’ disposition and baseline data

A total number of 280 patients were recruited into the study: 10 (3.6%) of them were withdrawn during run-in and 270 were randomised to receive study medication, 134 in the HFA-134a group and 136 in the CFC group. Only one patient in the CFC group did not have post-baseline data and was therefore excluded from the ITT population. The number of patients completing the 12-week study period was 127 (94.8%) in the HFA-134a group and 131 (96.3%) in the CFC group.

Major protocol violations were reported in 28 patients in total, 10 (7.5%) in the HFA-134a group and 18 (13.3%) in the CFC group, and mainly consisted of poor compliance (intake of less than 75% of scheduled drug) and treatment with a daily dose of inhaled corticosteroids at study entry exceeding the permitted limit (i.e. fluticasone 1000 $\mu$g/day, corresponding to budesonide 2000 $\mu$g/day, above the maximum 1600 $\mu$g/day scheduled dose). The per-protocol population was therefore made of 124 patients in the HFA group and of 117 in the CFC group.

The distribution of patients in the three dose subsets was well matched in the two groups: in the HFA-134a group, 47 patients (35.1%) were assigned to the low dose, 47 (35.1%) to the medium dose and 40 (29.8%) to the high dose; in the CFC group, 43 patients (31.8%) were assigned to the low dose, 48 (35.6%) to the medium dose and 44 (32.6%) to the high dose.

All patients were treated at study entry and during run-in with their own routine inhaled corticosteroids: the majority of patients were taking budesonide, 104 (77.6%) in the HFA-134a and 92 (68.1%) in the CFC group, while the remaining took fluticasone (10.4% in the HFA-134a and 19.3% in the CFC group) or beclometasone dipropionate (11.9% in the HFA-134a and 12.6% in the CFC group). In addition, most patients were taking long acting $\beta_2$-agonists (70.9% in the HFA-134a group and 75.6% in the CFC group), which were continued at constant doses during the 12-week treatment period.

The baseline details are presented in Table 1. The two groups were well matched with respect to demographic and other baseline characteristics, including the duration of asthma. The mean FEV\(_1\) predicted normal values (%) at screening in the HFA-134a group were 81.1$\pm$16.0, 86.0$\pm$11.8, 81.8$\pm$16.8 and 74.5$\pm$17.6 in the total population, low, medium and high dose subsets, respectively, whereas the corresponding values in the CFC group were 83.2$\pm$18.9, 89.5$\pm$20.4, 83.9$\pm$15.7 and 76.2$\pm$18.7.

Efficacy

The results of the primary variable mean morning PEFR, and of evening PEFR recorded daily by patients and FEV\(_1\) are presented in Figs. 2, 3 and 4 respectively, both as total population and in the three dose subsets (ITT population).

The LSMs for morning PEFR (AM PEFR in the last 2 weeks) in the total population were 420.0 l/min in the HFA-134a group and 421.6 l/min in the CFC group, with a difference of $-1.51$ l/min. Statistical analysis showed that budesonide HFA-134a was...
equivalent to CFC: the bilateral 95% CI for the treatment difference was $-9.40$ to $6.37$ l/min, well within the pre-defined equivalence limit of $7.42$ l/min (10% of the reference LSM). Small dose-related increases of morning PEFR in the final 2-week period were reported in both groups (Fig. 2): the comparison between subsets did not show statistically significant differences (low dose, $P = 0.291$, intermediate dose, $P = 0.436$, high dose, $P = 0.313$).

Results of evening PEFR (Fig. 3) were similar to that obtained in the morning: the LSMs in the total population were $429.7$ l/min for Budesonide HFA-134a and $430.5$ l/min for CFC, with a difference of $-0.76$ l/min; the bilateral 95% CI for the treatment difference was $-8.62$ to $7.10$ l/min, within the equivalence interval of $-43.05$ l/min. The comparison between subsets did not show statistically significant differences (low dose, $P = 0.588$, intermediate dose, $P = 0.483$, high dose, $P = 0.430$).

As regards to FEV$_1$, increases over baseline were also more marked in the two high-dose subsets: the LSMs in the total population were $2.73$ l in both groups, and the bilateral 95% CI for the treatment

### Table 1 Characteristics of the patients’ population at study entry (ITT population).

<table>
<thead>
<tr>
<th></th>
<th>HFA-134a ($n = 134$)</th>
<th>CFC ($n = 135$)</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males ($n$)</td>
<td>55 (41.0%)</td>
<td>56 (41.5%)</td>
</tr>
<tr>
<td>Females ($n$)</td>
<td>79 (59.0%)</td>
<td>79 (58.5%)</td>
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<tr>
<td><strong>Age, years (mean ± SD)</strong></td>
<td>42.1 ± 13.4</td>
<td>42.3 ± 14.3</td>
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<tr>
<td><strong>Height, cm (mean ± SD)</strong></td>
<td>167.3 ± 9.1</td>
<td>166.7 ± 10.3</td>
</tr>
<tr>
<td><strong>Weight, kg (mean ± SD)</strong></td>
<td>72.9 ± 14.6</td>
<td>73.6 ± 14.5</td>
</tr>
<tr>
<td><strong>Duration of asthma, years (mean ± SD)</strong></td>
<td>13.1 ± 10.0</td>
<td>13.8 ± 10.4</td>
</tr>
<tr>
<td><strong>Morning PEFR, l/min (mean ± SD)</strong></td>
<td>413.7 ± 94.7</td>
<td>418.9 ± 112.6</td>
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<tr>
<td><strong>Evening PEFR, l/min (mean ± SD)</strong></td>
<td>422.1 ± 89.9</td>
<td>427.4 ± 111.4</td>
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<tr>
<td><strong>FEV$_1$ predicted, % (mean ± SD)</strong></td>
<td>81.1 ± 16.0</td>
<td>83.2 ± 18.9</td>
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<tr>
<td><strong>Assigned dose of treatment test</strong></td>
<td></td>
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<tr>
<td>**Low dose ($n$)</td>
<td>47 (35.1%)</td>
<td>43 (31.8%)</td>
</tr>
<tr>
<td>**Medium dose ($n$)</td>
<td>47 (35.1%)</td>
<td>48 (35.6%)</td>
</tr>
<tr>
<td>**High dose ($n$)</td>
<td>40 (29.8%)</td>
<td>44 (32.6%)</td>
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</table>

Figure 2 Morning PEFR (l/min) expressed as 2 weekly means (●, HFA-134a; ○, CFC), ITT population.
difference was 0.08 to 0.08 l, again well within the ±0.27l equivalence interval. The comparison between subsets did not show statistically significant differences (low dose, \( P = 0.459 \), intermediate dose, \( P = 0.874 \), high dose, \( P = 0.756 \)).

Results obtained in the PP population (data not shown) for the above variables were consistent with those observed in the ITT analysis.

Other PF tests (FVC, PEFR and MEF\(_{50}\)) were measured at clinic visits. Statistically significant
increases over baseline for all parameters were observed from week 8 onwards in both groups, without significant differences between them. No substantial changes in both groups were also reported for daily PEFR variability and in the FEV1/FVC ratio (data not shown).

Results of rescue salbutamol intake, asthma attacks and awakenings, and symptoms' scores are shown in Table 2.

A progressive and statistically significant improvement over time of asthma control (symptoms' scores, symptom-free days, day-time and night-time asthma attacks, asthma-induced nocturnal awakenings) was similarly observed in both groups. The daily use of rescue salbutamol and the number of days without salbutamol intake was therefore significantly reduced over time in both groups. The comparison between groups did not show any significant difference for any of the above parameters.

Safety

The individual data of morning serum cortisol in patients with both baseline and final sample are shown in Fig. 5. The overall mean values in the total population showed a small decrease in both groups (−0.46 μg/100 ml in the HFA-134a and −0.19 μg/100 ml in the CFC group), without significant differences between groups (P = 0.248). The mean change from baseline in the low-dose subset showed a small increase in the HFA-134a group (+ 0.43 μg/100 ml) and a small decrease in the CFC group (−0.72 μg/100 ml); a small increase in both groups was observed in the medium-dose (−0.60 μg/100 ml in the HFA-134a and −0.53 μg/100 ml in the CFC group), whereas a decrease in the HFA-134a group (−1.33 μg/100 ml) and an increase in the CFC group (+ 0.77 μg/100 ml) were noted in the high-dose subset. In the HFA-134a group, six patients had a decrease of normal baseline levels below the lower limit of normal range, whereas 11 patients had a normalisation of low baseline levels; in the CFC group, the corresponding figures were of two and eight patients, respectively.

A total of 28 drug-related (with definite, probable, possible or doubtful relationship to study medication) adverse events were reported during the study, with 17 in the HFA-134a group and 11 in the CFC group, and they occurred in 27 patients in total, 16 (11.9%) and 11 (8.1%) in the two groups, respectively. The most commonly affected body system was the respiratory tract; other drug-related events included local effects (hoarseness or disphonia/aphonia, but without cases of mycosis), changes of serum cortisol levels, cardiovascular effects (tachycardia, blood pressure elevation) and unpleasant taste (in two patients treated with HFA-134a). A total of four patients (1.5%), two in each group, discontinued the study due to adverse events: critical elevation of blood pressure and dysphonia in the HFA-134a group and aphonias in the CFC group. Only one serious AE was reported in one patient in the HFA-134a group (high blood pressure), which was of a moderate severity and was considered as not related with the study drug.

No clinically significant changes occurred in vital signs (heart rate and blood pressure). The compliance profile was excellent in both groups: the mean reported intake was 96.3% in the HFA-134a group and 94.4% in the CFC group.

Discussion

The budesonide HFA-134a formulation used in the present study has been developed by adding glycerol as low solvent to the standard ethanol excipient and acting on the actuator’s orifice diameter, with the aim to obtain a particle size distribution similar to that of the CFC-formulated budesonide, thereby allowing a dose per dose transition from the existing product. In fact, the earliest inhaled corticosteroids formulated with CFC-free propellants (e.g. beclometasone dipropionate) were developed as ultrafine aerosol with a halved dose, whereas it has been shown that fluticasone propionate HFA-134a pMDI is comparable to the corresponding CFC at a microgram equivalent dose.

The objective of the present study was therefore to demonstrate equivalent asthma control and safety between budesonide using a HFA-134a and a CFC propellant, both drugs being administered via the Jet spacer, in a broad range of doses. The two treatment groups were equally divided in three randomised subsets, treated with a low (400 μg/day), medium (800 μg/day) or high (1200 or 1600 μg/day) dose, based on the dose of inhaled corticosteroids taken at study entry and during run-in. To exclude any potential carry-over effect due to the previous corticosteroids, the main comparisons were done with outcome measures collected at the end of the 12-week treatment period. The two groups and the three subsets were well matched for asthma severity (FEV1% predicted) and baseline values of all efficacy and safety parameters; the severity of asthma was also dose-related.
<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical parameters daily recorded on diary cards (ITT population).</th>
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<tr>
<td></td>
<td>Treatment</td>
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<tr>
<td>Clinical symptom score</td>
<td>HFA-134a</td>
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<td></td>
<td>CFC</td>
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<tr>
<td>Symptoms-free days (%)</td>
<td>HFA-134a</td>
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<td>CFC</td>
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<tr>
<td>Salbutamol consumption (number of puffs)</td>
<td>HFA-134a</td>
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<td>CFC</td>
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<tr>
<td>Day-time asthma attacks (number)</td>
<td>HFA-134a</td>
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<td></td>
<td>CFC</td>
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<tr>
<td>Night-time asthma attacks (number)</td>
<td>HFA-134a</td>
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<td></td>
<td>CFC</td>
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<tr>
<td>Night-time awakenings (number)</td>
<td>HFA-134a</td>
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<td>CFC</td>
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Values of pulmonary function tests (both measured daily by patients and at clinic visits) showed an overall small improvement from baseline to final in both groups, without differences between them. This improvement may be explained on the basis of a small increase of dose in patients where the daily dose of the previous corticosteroid was not exactly reproducible with the 200 μg unit dose, and on the basis of a maximal adherence to the assigned therapy. For the primary efficacy measure mean morning PEFR during the last 2-week period, the adjusted means were similar for HFA-134a and for CFC, and the calculated 95% CI for the difference between the LSMs was well within the pre-defined limit of ±10% of the reference drug. This equivalence limit is also well contained within narrower ranges (i.e. 30, 25 or 15 l/min), as used in similar comparative trials.17–19 This was also the case for all the other endpoints that were used to test the equivalence, mean evening PEFR and FEV1. Obviously, the study was powered to show equivalence in the total population and not in each dose subset; however, data obtained in the three dose ranges were comparable in the two groups. The estimated treatment differences in the total population were also negligible for the other pulmonary function and no significant differences between groups were observed. Symptoms (number of day-time and night-time asthma attacks, number of nocturnal awakenings, global asthma symptoms’ scores) and use of rescue salbutamol (daily number of puffs and percentage of salbutamol’s free days) showed a similar significant improvement in both groups.

A small non-significant decrease of morning cortisol levels was observed in both groups; notably, in both groups the number of patients with a decrease of final values below the lower limit of normal range (six in the HFA-134a group and two in the CFC group) was lower than the number of patients with baseline values below the normal limit and restored to normal final values (11 and eight in the two groups, respectively). The proportion of patients who reported drug-related adverse events was low in the two groups, with 16 patients (11.9%) in the budesonide HFA group and 11 (8.1%) in the CFC-budesonide group; the minimal difference between groups is mainly caused by two cases of taste dislike, which is a well-known mild and transient event in the switching from CFC to HFA,20 and by a few cases of cardiovascular events (blood pressure elevation and tachycardia), which are more likely to be due to the concomitant use of β2-agonists than to the inhaled corticosteroid.

The results of the present study have therefore shown that inhaled budesonide given with the HFA-134a propellant provides an equivalent asthma control and similar systemic effects to that of the CFC formulation. However, it is actually preferred that in equivalence trials treatments are compared in the steep part of the dose–response curve;21 therefore, these results should be confirmed in a sample of patients with a wider room for improvement to that of the present study, which included subjects with well controlled asthma on their inhaled steroids dosage. Furthermore, the use of the Jet Spacer, which is a small-size device with proven advantages in terms of topical to systemic effects ratio, may have reduced the possibility to observe potential differences on the effects on the hypophysis–pituitary–adrenal axis;22 it would be therefore advised that the results of the present trial are confirmed when budesonide HFA-134 is administered via pMDI only.

We can conclude that the preliminary findings of the present study show that budesonide HFA-134 is equivalent to the CFC formulation in a broad range of doses, when delivered with a spacer device in adult patients with stable asthma controlled with inhaled corticosteroids.
List of participating investigators and study centres

The study was conducted throughout the following investigators and centres:

**Poland:** Grzelewiska-Rzymowska I. (study Coordinator), Clinic of Phtisipneumonology, Medical University of Lodz; Droszcz W., Clinic of Pneumology and Allergology A.M, Warszawa; Malolepszy J., Clinic of Internal Diseases and Allergology, Wroclaw; Palcynski C., Institute of Occupational Medicine, Clinic of Occupational Disease, Lodz; Sladek K., II Clinic of Internal Diseases, "Kolegium Medicus UJ", Krakow; Szmidt M., Clinic of Tuberculosis and Lung Diseases, Lodz; Siergiejko Z., Department of Allergology and Internal Diseases, University Medical School, Bialystok; Austria: Zar- kovic J., Ambulance for Pediatrics and Pneumology, Wien; Spain: Barbeta E., "Servicio de Neumología, Hospital General de Granollers", Granollers, Barcelona; Lloberes P., "Servicio de Neumología, Hospital Vall d’Hebron de Barcelona", Barcelona; de Molina M., "Servicio de Alergia, Consorci Sanitari Creu Roja a Catalunya", Barcelona; Morera J., "Servicio de Neumología, Hospital Germans Trias i Pujol", Barcelona; Picado C., "Servicio de Neumología, Hospital Clinic de Barcelona", Barcelona.

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