

# A comparison of the efficacy and tolerability of single doses of HFA 134a albuterol and CFC albuterol in mild-to-moderate asthmatic patients

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**Background:** After the signing of the Montreal Protocol in 1987, new propellants for use in pressurized metered-dose inhalers that are non-ozone-depleting have been developed.

**Objective:** This study was designed to compare the efficacy and tolerability of single doses of albuterol/HFA 134a with albuterol/CFC and to demonstrate a dose-response among the different doses of both formulations.

**Methods:** A single-center, randomized, double-blind, placebo-controlled, crossover study. Sixty-three adolescent and adult asthmatic patients were randomized to receive at separate treatment visits single doses via a pressurized metered-dose inhaler of either placebo/hydrofluoroalkane (HFA) 134a; 100  $\mu$ g, 200  $\mu$ g, or 400  $\mu$ g albuterol/HFA 134a; 100  $\mu$ g or 200  $\mu$ g albuterol/chlorofluorocarbon (CFC). Triplicate measurements of forced expiratory volume in 1 second (FEV<sub>1</sub>) were made immediately before dosing and 15 minutes, 30 minutes, 1, 2, 3, 4, 5, and 6 hours postdose. The primary efficacy variables were area under the entire 6-hour FEV<sub>1</sub> curve, relative to baseline subtracted from the area above baseline (AUC<sub>(0-6)</sub>) and peak effect (derived from serial FEV<sub>1</sub> measurements).

**Results:** Analysis of AUC<sub>(0-6)</sub> and peak effect showed that all doses of albuterol had a significantly greater effect than placebo (HFA 134a propellant). Comparisons of the two formulations at 100  $\mu$ g and 200  $\mu$ g showed no difference in AUC<sub>(0-6)</sub> (100  $\mu$ g, -0.23 Lhr,  $P = 0.114$  and 200  $\mu$ g -0.08 Lhr,  $P = 0.590$ ) or in peak effect, percentage of baseline (100  $\mu$ g, -1.3%,  $P = 0.354$  and 200  $\mu$ g, 0.17%,  $P = 0.902$ ). There were no differences seen among formulations in the incidence of adverse events or with any of the other safety parameters, including electrocardiogram, vital signs, clinical laboratory assessments, and asthma exacerbations.

**Conclusions:** The study demonstrated comparability in terms of efficacy and safety between albuterol/HFA 134a and albuterol/CFC.

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## INTRODUCTION

The destruction of the ozone layer by chlorofluorocarbons (CFCs) was first suggested in 1974.<sup>1</sup> Although the con-

tribution to ozone depletion from medicinal aerosols has been minimal, the pharmaceutical industry, consistent with environmental legislation,<sup>2</sup> has been searching for an alternative, environmentally friendly replacement propellant that is safe in patients. Historically, CFCs 11 and 12 have been used routinely as propellants in the pressurized metered-dose inhaler (pMDI) since the late 1950s. After screening thousands of potential compounds, the hydrofluoroalkane (HFA) 134a has been selected by several pharmaceutical companies as one of the preferred propellants with which to

reformulate the pMDI products. HFAs have ideal properties for a propellant suitable for human use and have a similar pharmaceutical dose delivery to CFCs.<sup>3</sup> Although HFAs have zero ozone-depleting potential, they do have a global warming potential, but this is a fraction (one-tenth) of that of CFCs 11 and 12.<sup>4</sup>

Inhaled  $\beta_2$ -agonists are the bronchodilators of choice for asthma. Albuterol delivered via a pMDI is an established reliever medication. Although dry powder devices are also available for delivery of albuterol, they are not always suitable in some patient populations, and there is a need for the continued availability of albuterol delivered via a pMDI.<sup>5</sup> A full evaluation of the efficacy and tolerability profile when delivered via HFA 134a in comparison with the CFC propellants (propellants 11 and 12) is therefore required. This study was designed to compare the bronchodilator effect of single, clinically relevant doses of the albuterol/HFA 134a pMDI with the albuterol/CFC pMDI and to investigate the dose-response effect of the albuterol/HFA 134a product.

## METHODS

### Patients

Patients were male or female aged 12 years or over with a documented clinical history of asthma and a forced expiratory volume in 1 second (FEV<sub>1</sub>) of 50 to 85% of predicted at screening, who could demonstrate an improvement in FEV<sub>1</sub> of at least 15% after inhaling 200  $\mu$ g albuterol/CFC. Patients had a smoking history of no more than 10 cigarette pack years. Patients had not suffered from upper re-

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spiratory tract infections in the 6 weeks before screening or asthma exacerbations in the previous 4 weeks. Each subject provided written informed consent to participate in the study which was approved by the South Manchester Medical Research Ethics Committee.

### Study Design

The study was of a single-center, randomized, double-blind, placebo-controlled, six-way crossover design. There was a screening visit, a 4- to 14-day run-in period, followed by six treatment visits (each separated by 1 to 14 days), and a followup visit 7 to 14 days after the last study treatment visit. At each treatment visit, if the highest 30-minute predose FEV<sub>1</sub> value varied by 15% or more when compared with the highest baseline FEV<sub>1</sub> value at screening, the treatment visit was rescheduled to at least 1 day and not more than 14 days later. Patients were required to attend each of the study days within 1 hour of the time they attended the screening visit (which was between 8:00 AM and 12:00 PM), having refrained from smoking or consuming caffeine-containing food and drinks for the previous 6 hours, and vigorous exercise for the previous 24 hours. Short-acting  $\beta_2$ -agonists were withheld for 8 hours, long-acting  $\beta_2$ -agonists for 48 hours, oral  $\beta_2$ -agonists for 12 hours, oral sustained-release  $\beta_2$ -agonists for 24 hours, inhaled anticholinergics for 24 hours, and antihistamines for 8 hours before each study visit. Patients were randomized to receive each of the following six treatments in any order and in a double-blind manner: 1) placebo/HFA 134a; 2) 100  $\mu\text{g}$  albuterol/HFA 134a; 3) 200  $\mu\text{g}$  albuterol/HFA 134a; 4) 400  $\mu\text{g}$  albuterol/HFA 134a; 5) 100  $\mu\text{g}$  albuterol/CFC; and 6) 200  $\mu\text{g}$  albuterol/CFC. The doses of study medication are ex-valve doses. At each visit patients took one inhalation from four inhalers so that blinding was maintained.

### Study Measures

Triplicate measurements of FEV<sub>1</sub> were made immediately before dosing and then 15 minutes, 30 minutes, 1, 2, 3, 4, 5, and 6 hours postdose on a dry roll-

ing seal spirometer (PK Morgan, Gillingham, UK) attached to an Apple Macintosh using the MacSpiro software (P. Altounyan, Leicester, UK). At each time point, the highest FEV<sub>1</sub> maneuver was recorded. Vital sign measurements were made before dosing and serially over a 6-hour period postdosing on each of the study days. Electrocardiograms (including QTc intervals) were recorded and clinical laboratory tests (hematology and biochemistry) were performed 30 minutes pre- and 45 minutes postdosing, on each study day.

### Statistical Analysis

The primary endpoints were the FEV<sub>1</sub> area under the curve (AUC) above baseline and the peak effect on FEV<sub>1</sub>. The AUC was calculated as the area under the entire 6-hour FEV<sub>1</sub> curve, relative to baseline, with the area below the baseline subtracted from the area above baseline (AUC<sub>(0-6)</sub>). The peak effect was calculated by finding the maximum postdosing FEV<sub>1</sub> measurement for that subject at that treatment visit. Both variables were analyzed using analysis of covariance (ANCOVA) appropriate for a crossover model. The SAS general linear model procedure (SAS Institute, Cary, NC) was used. Terms for subject, period, and treatment were fitted, using this procedure. FEV<sub>1</sub> was also included as the covariate, and taken to be the single FEV<sub>1</sub> measurement recorded immediately before dosing at each treatment visit. The treatment by period interaction term was investigated in the ANCOVA. A test for first-order carryover effects was carried out in the context of a model, also containing the effects for subject, period, and treatment. SAS type I sums of squares were used to evaluate the contribution of each factor entered into the model. Three sets of pairwise comparisons were tested: 1) placebo versus active treatments; 2) propellant comparisons: 100  $\mu\text{g}$  albuterol/CFC versus 100  $\mu\text{g}$  albuterol/HFA 134a, 200  $\mu\text{g}$  albuterol/CFC versus 200  $\mu\text{g}$  albuterol/HFA 134a; and 3) dose comparisons: 100  $\mu\text{g}$  versus 200  $\mu\text{g}$  albuterol/CFC; 100

$\mu\text{g}$  versus 200  $\mu\text{g}$ , 100  $\mu\text{g}$  versus 400  $\mu\text{g}$ , 200  $\mu\text{g}$  versus 400  $\mu\text{g}$  albuterol/HFA 134a.

Treatment differences and 90% confidence intervals (CI) for treatment differences were calculated from the initial main effects model, without interaction terms. The CIs of 90% (rather than 95%) were selected, as this was the accepted practice at the time the study was performed.

There was some evidence of nonhomogeneous variances for peak effect for different treatments. In addition, investigation of the residuals for peak effect indicated that ANCOVA may not be an appropriate model. Therefore, a nonparametric analysis was also performed on peak effect, to confirm the results of the ANCOVA. Wilcoxon signed rank tests were performed on the pairwise treatment differences specified above.

Clinical laboratory assessments, vital signs, and electrocardiograms were evaluated for postdose changes from baseline, where baseline was the predose measurement at each study visit.

## RESULTS

From a total of 85 patients screened, 63 patients were randomized to treatment (intent-to-treat population). Thirty-one (49%) were male and the majority of patients (97%) were Caucasian/white. Six patients withdrew after randomization; 3 patients had a 30-minute predose FEV<sub>1</sub> value falling outside the 15% variability criterion when compared with the highest baseline FEV<sub>1</sub> at the screening visit; 2 patients suffered adverse events; and 1 subject withdrew from the study for personal reasons. The characteristics of the intent-to-treat population are shown in Table 1.

### Pulmonary Function

Table 2 summarizes the AUC<sub>(0-6)</sub> for the intent-to-treat population and shows the adjusted means and their standard errors. The adjusted means are the estimates of population means obtained after adjusting sample means for baseline, subject, and period via the ANCOVA model. As the AUC is adjusted for baseline, a value

Table 1. Demographic Details of Intent-to-Treat Population

	Number of patients (%)
Number of patients	63
Sex	
Males	31 (49%)
Females	32 (51%)
Age (years)	
Mean	36
Range	13-63
FEV <sub>1</sub> at baseline (L)	
Mean	2.33
Range	1.1-3.9
FEV <sub>1</sub> % predicted at baseline	
Mean	69.2
Range	50-85
Concurrent asthma	
Medication at screening	
Short-acting $\beta_2$ -agonists	63 (100%)
Inhaled corticosteroids	47 (75%)
Long-acting $\beta_2$ -agonists	7 (11%)
Other	4 (6%)
Ethnic origin	
Caucasian (white)	61 (97%)
Asian	2 (3%)
Tobacco use	
Current	14 (22%)
Ex-smoker	14 (22%)
Life-long non-smoker	35 (56%)

greater than zero shows an overall increase in FEV<sub>1</sub> compared with the baseline FEV<sub>1</sub> (immediately before dosing with study medication). The adjusted mean for the placebo/HFA 134a propellant group of 0.24 Lhr was significantly lower than every active treatment ( $P < 0.001$  for every pairwise comparison between placebo and active treatments). The increase in AUC<sub>(0-6)</sub> with increase in dose of study medication for both propellants are indicative of a dose-response relationship. The difference between 100  $\mu$ g and 200  $\mu$ g albuterol/HFA 134a was 0.42 Lhr which was significant ( $P = 0.005$ ; 90% CI of 0.18 to 0.66 Lhr).

Significance levels for the pairwise comparisons of interest are shown in

Table 3. Albuterol/HFA 134a was comparable with albuterol/CFC in terms of effect. For the 100- $\mu$ g dose, the difference was -0.23 Lhr ( $P = 0.114$ ; 90% CI of -0.48 to 0.01 Lhr), and was -0.08 Lhr ( $P = 0.590$ ; 90% CI of -0.32 to 0.16 Lhr) for the 200- $\mu$ g dose.

The results for the adjusted mean peak effect are summarized in Table 2 and the mean serial FEV<sub>1</sub>s for each treatment are presented in Figure 1. The increase in peak effect with increase in dose of study medication for both propellants is also indicative of a dose relationship. There was also comparability between propellants when pairwise comparisons were made (Table 3). There was, however, a signifi-

cant treatment by baseline interaction ( $P = 0.001$ ). The residual plots also showed some evidence that the model did not fit well. The treatment by baseline interaction was investigated further. The interaction showed that the effect of active treatment compared with placebo was more marked for patients with a very low baseline FEV<sub>1</sub>, compared with patients with a higher baseline. However, the effect of active treatment was still well summarized by the adjusted means from the model without the treatment by baseline interaction term. A nonparametric analysis was also performed, the results of which were very similar to the parametric model results, and therefore, the results from this main effects parametric model have been reported.

#### Safety

Adverse events are summarized in Table 4. There were no clinically relevant differences between the CFC and the non-CFC formulations in the incidence of events, and no apparent dose relationship. The most common adverse events reported during treatment were asthma and headaches. There were no reports of other predictable adverse events including palpitations, muscle cramp, tachycardia, and paradoxical bronchospasm, although there was one report of tremor during treatment with 400  $\mu$ g albuterol/HFA 134. Two subjects were withdrawn because of adverse events during the study, both of which were evaluated as not drug related. There were no reports of adverse events which were defined as serious. One subject was noted to have a prolonged QTc value of 485 milliseconds which increased by 42 milliseconds from the predosing baseline, after receiving the 400- $\mu$ g albuterol/HFA 134a formulation. This was considered

Table 2. The Adjusted Means and Standard Error for the AUC<sub>(0-6)</sub> (Lhr) and Peak Effect (% of Baseline FEV<sub>1</sub>)

	Placebo/ HFA 134a	100 $\mu$ g Albuterol/ HFA 134a	200 $\mu$ g Albuterol/ HFA 134a	400 $\mu$ g Albuterol/ HFA 134a	100 $\mu$ g Albuterol/ CFC	200 $\mu$ g Albuterol/ CFC
AUC <sub>(0-6)</sub> Lhr Adj. means (s.e.)	0.24 (0.11)	1.27 (0.11)	1.69 (0.10)	1.97 (0.11)	1.50 (0.11)	1.77 (0.11)
Peak effect; (% of baseline FEV <sub>1</sub> ) Adj. means (s.e.)	108.8 (1.01)	119.9 (1.01)	123.2 (0.99)	125.5 (1.02)	121.2 (1.01)	123.0 (1.00)

Table 3. Statistical Analysis for the Pairwise Comparisons of Interest for AUC<sub>(0-6)</sub> (Lhr) and Peak Effect (% of the Baseline FEV<sub>1</sub>)

Comparison	AUC <sub>(0-6)</sub>	Peak effect
100 µg Albuterol/HFA 134a vs. 100 µg Albuterol/CFC	Difference -0.23 90% CI -0.48,0.01 P value 0.114	Difference -1.30 90% CI -3.60,1.01 P value 0.354
200 µg Albuterol/HFA 134a vs. 200 µg Albuterol/CFC	Difference -0.08 90% CI -0.32,0.16 P value 0.590	Difference 0.17 90% CI -2.14,2.48 P value 0.902
200 µg Albuterol/HFA 134a vs. 100 µg Albuterol/HFA 134a	Difference 0.42 90% CI 0.18,0.66 P value 0.005	Difference 3.25 90% CI 0.94,5.55 P value 0.021
400 µg Albuterol/HFA 134a vs. 100 µg Albuterol/HFA 134a	Difference 0.71 90% CI 0.46,0.95 P value <0.001	Difference 5.59 90% CI 3.27,7.92 P value <0.001
400 µg Albuterol/HFA 134a vs. 200 µg Albuterol/HFA 134a	Difference 0.28 90% CI 0.04,0.53 P value 0.055	Difference 2.35 90% CI 0.03,4.66 P value 0.095
200 µg Albuterol/HFA 134a vs. 200 µg Albuterol/CFC	Difference 0.27 90% CI 0.02,0.51 P value 0.071	Difference 1.78 90% CI -0.53,4.08 P value 0.205

All active treatments were superior to placebo for AUC<sub>(0-6)</sub> and peak effect ( $P < 0.001$ ).

to be of no clinical relevance. This subject also had raised QTc interval above 440 milliseconds before dosing with placebo/HFA 134a and pre-dosing and postdosing with 100 µg albuterol/CFC.

The mean pulse rate and systolic blood pressure was similar between all treatment groups and showed no marked change over the 6 hours after dosing with study medication. The mean diastolic blood pressure was similar among all treatment groups although the mean in the 400-µg albuterol/HFA 134a and the 100-µg and 200-µg albuterol/CFC groups showed a small but consistent fall over the 6 hours in comparison to the baseline value and in comparison to the other three treatments.

The number of patients experiencing an exacerbation on or after any particular treatment was similar across all treatment groups; 3 patients in the placebo/HFA 134a and 200-µg albuterol/CFC groups, 2 patients in each of the 200-µg albuterol/HFA 134a and 100-µg albuterol/CFC group, and 1 each in the 100-µg and 400-µg albuterol/HFA 134a groups. None of the exacerbations required hospitalization and only one patient was

withdrawn because of exacerbation of their asthma.

There was no notable difference between the formulations for clinical laboratory values. The number of patients who had a change in hematologic or biochemical parameter postdose compared with predose was low and com-

parable among the groups, with no changes reported as an adverse event.

## DISCUSSION

pMDIs are the most frequently prescribed inhalation device, and their use is expected to continue as many patients prefer this type of inhaler and they are relatively inexpensive. They have also been proven to have efficient efficacy in emergencies when used in conjunction with a large volume spacer and in some studies are superior to a nebulizer.<sup>6,7</sup> Also, the introduction of spacers for preschool children<sup>8</sup> has resulted in the pMDI being the formulation of choice for this age group. The continued availability of pMDIs depends on the production of safe alternatives to formulations containing CFC propellants.

The objectives of this study were to evaluate the comparability in terms of efficacy and tolerability of the bronchodilator effect between single doses of albuterol/HFA 134a and albuterol/CFC, and to establish whether a dose-response existed within formulation as evaluated by serial FEV<sub>1</sub> measurements for 6 hours after dosing. We wanted to demonstrate a dose-response

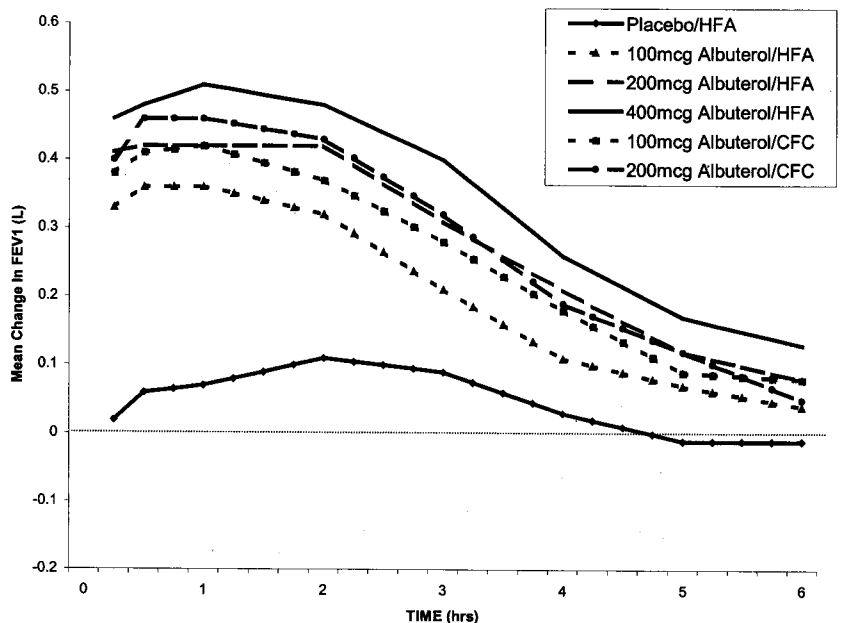


Figure 1. Mean change in FEV<sub>1</sub> by time and treatment.

Table 4. Total Number of Adverse Events Per Treatment Group and Incidence of the Most Common and Pharmacologically Predictable Events during Treatment

	Placebo/ HFA 134a	100 µg Albuterol/ HFA 134a	200 µg Albuterol/ HFA 134a	400 µg Albuterol/ HFA 134a	100 µg Albuterol/ CFC	200 µg Albuterol/ CFC
No. of patients with adverse event	7 (12%)	2 (3%)	4 (7%)	5 (9%)	2 (3%)	4 (7%)
Asthma	3 (5%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)	2 (3%)
Headache	2 (3%)	1 (2%)	1 (2%)	2 (3%)	0	1 (2%)
Tremors	0	0	0	1 (2%)	0	0

Most commonly defined as a total of 2 or more patients experiencing an adverse event from any treatment group.

relationship to confirm that the doses chosen were not on the plateau of the dose-response curve for the primary efficacy variables. Studies conducted on the plateau of the curve can result in apparently similar results among formulations that might not truly exist.

Analysis of the primary efficacy variables of FEV<sub>1</sub>, AUC<sub>(0-6)</sub> and peak effect demonstrated that all doses of albuterol/HFA 134a and albuterol/CFC produced statistically significant improvements when compared with placebo. Pairwise comparisons of the 100-µg and 200-µg doses of both albuterol formulations showed that the clinical effect was comparable for the AUC<sub>(0-6)</sub> and peak effect. Further pairwise comparisons of the different doses of albuterol showed a dose-response for both albuterol formulations, although only the comparisons between 100 µg and 200 µg and 100 µg and 400 µg albuterol/HFA 134a were statistically significant. The FEV<sub>1</sub> peak effect for all doses of albuterol/HFA 134a and albuterol/CFC formulations were superior to placebo.

Previous studies have shown HFA-formulated albuterol to be an effective drug equivalent to existing CFC formulations in terms of its bronchodilator effect<sup>9-12</sup> and its bronchoprotective effects against inhaled histamine in both adults<sup>13</sup> and children,<sup>14</sup> and exercise-induced asthma both in adults<sup>15</sup> and children.<sup>16</sup> This study provides further evidence of efficacy by comparing the bronchodilator effects of different doses. The safety of HFA 134a formulations has been evaluated in studies where patients were treated for up to 12 months,<sup>17</sup> showing tolerability that

is comparable with the CFC formulation. Further, a large epidemiologic study has recently shown that there is no clinically relevant increase in adverse event rates in patients changing from their albuterol CFC-containing pMDI to the HFA 134a product.<sup>18</sup>

In our single-dose study, albuterol/HFA 134a was well tolerated with no significant difference in the incidence of any adverse events compared with the CFC formulation. Also, there did not seem to be any dose-related events in the HFA 134a group. In our study, electrocardiograms were recorded pre- and postdosing. One subject was noted to have a raised QTc (of 485 milliseconds) which increased by 42 milliseconds from the predose baseline after the albuterol/HFA 134a 400-µg dose, which was thought to be possibly drug-related. However, this patient was also noted to have a QTc above 440 milliseconds before dosing on the placebo/HFA 134a study day and pre- and postdosing on the 100-µg albuterol/CFC study day. In previous studies evaluating the cardiac safety of HFA 134a albuterol,<sup>10,19</sup> no clinically relevant QTc changes were seen in doses up to 200 µg when compared with the CFC formulation. Safety in our study was also evaluated by vital signs, urinalysis, and biochemistry and hematology measurements. No significant differences among treatment groups were seen in any parameter measured. Bronchospasm is a feature sometimes associated with administration from a pMDI. However, there was no evidence that the HFA formulation was associated with an increased incidence of acute bronchospasm compared with

the CFC formulation, although they were a preselected group of patients with a demonstrated reversibility to albuterol. Although patients were not specifically questioned about taste of the study treatments and sensation in the mouth, no adverse events relating to these symptoms were reported. Similar results have been reported from two postmarketing surveillance studies where the same product was surveyed.<sup>18,20</sup>

Albuterol has been successfully reformulated as a suspension of micronized drug in the liquefied propellant HFA 134a without the use of excipients, and has been designed to be similar in terms of appearance and performance to the CFC product.<sup>3</sup> The dosing performance of the CFC product and the HFA product has been compared, and in terms of the fine particle mass and the particle size distribution, the products are pharmaceutically equivalent.<sup>3</sup> Other manufacturers have developed ethanol-based solution formulations for drugs such as albuterol and beclomethasone dipropionate, which contain a smaller particle size of drug from the CFC suspension formulation. For drugs such as beclomethasone dipropionate, this results in substantially greater quantities delivered to the lung.<sup>21</sup>

This study demonstrated clinical equivalence at the same microgram dose between the albuterol HFA and CFC products. This result may help minimize the issues needing to be addressed with the healthcare team when converting a patient from CFC to HFA products. Patient education and education of the healthcare professional is vital during the transition period to en-

sure patients that their new medication is safe and effective. All members of the healthcare team (including nurses, pharmacists, physicians) and the pharmaceutical industry have a role to play in ensuring accurate and understandable information is available to patients.<sup>22</sup>

## CONCLUSION

The results of our study demonstrate that single doses of albuterol formulated with HFA 134a and albuterol formulated with CFC propellants 11 and 12 showed comparable clinical efficacy at the same dose in adolescent and adult asthmatic patients with mild to moderate asthma, and that this effect was dose-dependent. No notable difference in safety between albuterol/HFA 134a and albuterol/CFC was seen in this population of subjects.

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