

# Clinical Comparability of Ventolin Formulated With Hydrofluoroalkane or Conventional Chlorofluorocarbon Propellants in Children With Asthma

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**Background:** Aerosolized asthma medications with chlorofluorocarbon (CFC) propellants are being phased out because of environmental concerns about the ozone layer. Medications are being reformulated with non-ozone-depleting propellants.

**Objective:** To evaluate the clinical comparability of albuterol sulfate formulated in a new hydrofluoroalkane-134a (HFA) propellant (Ventolin HFA Inhalation Aerosol), and conventional CFC-containing albuterol (Ventolin Inhalation Aerosol) in children with asthma.

**Design:** Randomized, double-blind, placebo-controlled 2-week clinical trial with a 1- to 2-week run-in period. During the run-in, patients took Ventolin CFC as needed. Patients (n=135) aged 4 to 11 years with asthma then were assigned randomly to treatment with Ventolin HFA, Ventolin CFC, or placebo administered 4 times daily via metered-dose inhaler for 2 weeks. All patients were allowed rescue albuterol use in matching propellant as needed for relief of breakthrough symptoms. The main outcome measure was the mean per-

centage of predicted peak expiratory flow (PEF) after the morning dose of study drug on day 1 and after 2 weeks as assessed by results of 6-hour serial tests.

**Results:** At day 1, the mean ( $\pm$  SE) percentage of predicted PEF increased postdose by 14% ( $\pm$  1%) in the Ventolin HFA group and 13% ( $\pm$  1%) in the Ventolin CFC group compared with 6% ( $\pm$  2%) in the placebo group ( $P \leq .006$ ). At week 2, mean postdose increases were 11% ( $\pm$  1%) in the Ventolin HFA and CFC groups compared with 5% ( $\pm$  1%) in the placebo group ( $P < .001$ ). There were no significant differences between the Ventolin HFA and CFC groups in postdose increases in pulmonary function, time to onset of response, duration of response, or peak effects. Safety profiles were similar among the 3 groups.

**Conclusion:** Ventolin HFA is clinically comparable to Ventolin formulated with the conventional CFC-containing propellant when administered to children with asthma.

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**A**LIBUTEROL delivered via metered-dose inhaler (MDI) has been used safely and effectively in the treatment and prevention of bronchospasm for 30 years. However, the propellants used in albuterol MDIs and most other aerosolized asthma medications are chlorofluorocarbons (CFCs). Chlorofluorocarbons have been implicated in contributing to the damage of the ozone layer and are to be phased out when adequate non-CFC substitution products become available.<sup>1,2</sup> Before physicians could begin prescribing the new non-CFC formulations of asthma medications, clinical trials had to be conducted to demonstrate the safety and efficacy of these new formulations.

Ventolin in the propellant hydrofluoroalkane-134a (Ventolin HFA; Glaxo Well-

come Inc, Research Triangle Park, NC) is a non-CFC formulation of albuterol sulfate that has been developed recently for the treatment and prevention of bronchospasm in asthma and for the prevention of exercise-induced bronchospasm in patients aged 4 years and older. One puff of Ventolin HFA contains 108  $\mu$ g of albuterol sulfate, which is equivalent to 90  $\mu$ g of albuterol base (1 puff of conventional Ventolin in CFC). Ventolin HFA, unlike other non-CFC albuterol preparations, contains no surfactants or cosolvents such as ethanol. Ventolin HFA has been approved for use in at least 50 countries worldwide, and MDI-delivered Ventolin with CFC propellant has been phased out in at least 12 countries. Ventolin HFA is under review by the Food and Drug Administration, Washington, DC, for use in the United States.

## PATIENTS, MATERIALS, AND METHODS

### PATIENT SELECTION

Boys and premenarchal girls aged 4 to 11 years were enrolled if they had asthma<sup>6</sup> requiring physician-prescribed chronic pharmacotherapy for at least 6 months and had no other significant pulmonary disease or serious chronic disease. Patients were required to have a baseline peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV<sub>1</sub>) of 50% to 80% of predicted values. Predicted FEV<sub>1</sub> and PEF values were based on standards of Polgar and Promadhat<sup>7</sup> for sex and height, with standard corrections for African American patients.<sup>8</sup> At least 15% reversibility of diminished lung function was required. Patients were excluded from the study if they had life-threatening asthma. To evaluate the effect of Ventolin HFA on cardiovascular end points, including data collected from Holter monitors, patients were not allowed to take medications with a potential impact on these analyses (eg, methylphenidate hydrochloride [Ritalin Hydrochloride]).

### STUDY DESIGN

This randomized, double-blind, parallel-group, placebo-controlled study (study No. SALA3006) was conducted at 11 clinical sites in the United States and Puerto Rico. Institutional review board approval and a written informed consent form for each patient signed by a parent or legal guardian were obtained before the start of the study. The study consisted of a 1- to 2-week run-in period and a 2-week treatment period. At the beginning of the run-in, patients stopped all short-acting  $\beta_2$ -agonist therapy except as-needed albuterol (CFC-containing formulation of Ventolin Inhalation Aerosol, 90  $\mu$ g per puff, 2 puffs). Patients also stopped taking long-acting  $\beta_2$ -agonists, all forms of theophylline, and ipratropium bromide; patients taking oral corticosteroids during the previous month were not enrolled. Patients were allowed to continue inhaled corticosteroid or cromolyn sodium therapy during the study and to use antihistamines and decongestants as needed, although these medications were withheld before each clinic visit. Patients showing signs of unstable asthma, defined as using 12 or more puffs of rescue albuterol on more than 2 days during the 7 preceding days, were not randomized. The population was stratified by age (4-8 and 9-11 years).

After the run-in, eligible patients were assigned randomly to 1 of the following 3 treatments administered via MDI every 4 to 6 hours for 2 weeks: 2 puffs of Ventolin

HFA (Ventolin HFA group), conventional Ventolin CFC (Ventolin CFC group), or HFA propellant only (placebo group). During the treatment period, each patient was given a canister of rescue albuterol (Ventolin in either HFA or CFC propellant to match their randomized treatment) to use as needed for breakthrough symptoms.

### MEASUREMENTS

Mean percentage of predicted PEF during 6-hour serial tests was a primary measure of efficacy for all patients. Mean percentage of predicted FEV<sub>1</sub> during serial tests was a second primary efficacy measure for patients aged 6 to 11 years and those aged 4 and 5 years who were capable of performing spirometry. Functions of serial pulmonary function tests (eg, time to onset of response, duration of response, and peak effect) also were assessed. On day 1 and after 2 weeks, pulmonary function tests (PEF and FEV<sub>1</sub>; highest of 2 attempts) were conducted 30 minutes before the morning dose of study drug, immediately before dosing, and at the following postdose time points: 5, 15, and 30 minutes and 1, 2, 3, 4, 5, and 6 hours. If patients had taken study drug or rescue albuterol within 8 hours, the visit was rescheduled.

Additional measures of efficacy included daily patient-conducted determinations of morning and evening PEF, guardian- or patient-rated asthma symptoms, percentage of nights with awakenings due to asthma requiring albuterol treatment, use of rescue albuterol, and the frequency of asthma exacerbations. Symptoms during the previous 24 hours were assessed daily before measuring morning PEF; patients rated the most severe of 4 possible symptoms (chest tightness, shortness of breath, wheezing, and coughing) on a scale from 1 (no symptoms) to 4 (annoying symptoms occurring even at rest). All patients and parents or guardians were instructed on the proper technique for using an MDI and the peak flow meter (Mini Wright Peak Flow Meter; Clement Clarke Inc, Columbus, Ohio). Patients and parents or guardians were instructed to measure morning and evening PEF before administering the morning and evening doses of study medication (or before administering rescue albuterol). Patients, parents, or guardians recorded PEF, symptom ratings, nighttime awakenings, and albuterol use on daily diary cards.

An *exacerbation* was defined as asthma requiring treatment with medications other than study drug qid, rescue albuterol, or allowed concomitant medications. During serial testing, if patients experienced a single episode of breakthrough symptoms, they were treated first with rescue albuterol and then nebulized albuterol if necessary.

Previous studies conducted in adults have demonstrated the comparability of conventional CFC-containing Ventolin with Ventolin HFA<sup>3</sup> and with other brands of non-CFC albuterol (Proventil HFA; Schering Corporation, Kenilworth, NJ).<sup>4,5</sup> However, to our knowledge, this is the first report of a study designed to compare the efficacy and safety of an HFA-containing albuterol formulation with conventional CFC-containing albuterol in children. As with the adult studies, a 4-times-daily (qid) regimen was used to meet regulatory requirements. A placebo control arm, in which patients re-

ceived only HFA propellant qid and as-needed Ventolin HFA, was included.

## RESULTS

### STUDY POPULATION

One hundred thirty-five patients aged 4 to 11 years completed the 1- to 2-week run-in and were randomly assigned to treatment; 118 patients (87%) completed the 2-week treatment period. The most common reason re-

Although the serial spirometry was terminated, patients remained at the clinic for the scheduled 6 hours and vital signs were taken hourly. Patients experiencing 2 episodes of breakthrough symptoms requiring treatment during serial spirometry and patients for whom nebulized albuterol failed to provide adequate relief (necessitating administration of subsequent drugs) were discontinued from the study. Patients receiving treatment for an exacerbation outside the clinic other than study drug qid, rescue albuterol, or allowed concomitant medications also were discontinued from the study.

Safety assessments at each visit included adverse event monitoring, vital signs, 12-lead electrocardiograms (ECGs) with standard lead II rhythm strips (predose and approximately 45 minutes postdose), and Holter monitoring in a subset of patients. *Abnormal ECG findings* were, as a minimum, defined as a 12-lead tracing consistent with ischemic changes, ventricular hypertrophy, clinically significant intraventricular conduction abnormalities (eg, left bundle-branch block, Wolff-Parkinson-White syndrome), or clinically significant arrhythmias (eg, atrial fibrillation, ventricular tachycardia). Holter monitoring was conducted at 6 study centers using established methods.<sup>9</sup> A baseline 24-hour Holter recording was performed during screening. Results of the recording were analyzed and reviewed before randomization to study medication at treatment day 1. Only patients with normal or clinically insignificant abnormal recordings were randomized. Eight-hour Holter monitoring was conducted at each treatment visit approximately 1 hour before dosing and for a full 6 hours postdose. Routine clinical laboratory tests and physical examinations were conducted at the screening visit and at week 2. Laboratory tests were performed before the start of serial testing at week 2.

#### DATA ANALYSIS

Enrollment was planned for 90 evaluable patients (30 completed patients per treatment group). A sample size of 30 patients per treatment group provided at least 80% power to detect a difference of 10% in percentage of predicted FEV<sub>1</sub> between any 2 treatment groups by means of an analysis of variance (ANOVA) F test (significance level of .05) and assuming an SD of 12% as indicated by previous studies. All statistical tests were 2-sided, and treatment differences were considered statistically significant at  $P \leq .05$ . Pairwise treatment comparisons were only interpreted when the overall treatment comparison was significant. The intent-to-treat population (all patients exposed to study drug) was

used for all safety and efficacy analyses. Statistical software (SAS version 6.09; SAS Institute, Cary, NC) was used for summary and inferential statistics.

Treatment groups were compared for demographic and other characteristics at baseline. Treatment comparisons for sex, ethnic origin, inhaled corticosteroid use, and cromolyn use were based on the Cochran-Mantel-Haenszel test, a  $\chi^2$  test controlling for investigator. Treatment comparisons for age and pulmonary function test results were based on ANOVA F tests controlling for investigator. Treatment comparisons for diary card assessments were based on the van Elteren test.<sup>10</sup>

Serial pulmonary function was analyzed as the percentage of predicted PEF or FEV<sub>1</sub>. Baseline was the average of the -30- and 0-minute measurements at each treatment visit. Treatment groups were compared by means of a repeated-measures analysis of covariance F test controlling for investigator and using baseline percentage of the predicted value as the covariate. For each 6-hour serial measurement, the last postdose observed value before use of rescue albuterol (if any) was carried forward as the value for each postintervention observation time. A response to treatment was defined as at least a 15% improvement above baseline measurements within 30 minutes of inhalation of study drug. Times of onset and offset of response were calculated for each patient by means of linear interpolation. For those patients who failed to respond, onset and offset of response were set to 6 hours, and duration was set to 0 hours. *Peak effect* was defined as the maximum increase above baseline (expressed as a percentage) achieved at any time during the 6-hour serial day. Time to onset, duration, and time to peak effect were analyzed by means of a van Elteren test controlling for investigator. Peak effect was analyzed by means of an ANOVA F test. Induction of tolerance to the bronchodilator effect was assessed by the change in PEF, expressed as a percentage of the predicted value, between test day 1 and week 2.

Patient-recorded daily morning and evening PEF, patient-rated symptom scores, rescue albuterol use, and nighttime awakenings were averaged for the 7 days before randomization (baseline) and for the 2-week treatment period (or the period before discontinuation from the study). Patient-recorded PEF values were tested for treatment differences in the change from baseline for the overall treatment period (average of weeks 1 and 2) by means of ANOVA. Treatment group differences in changes from baseline for all other diary card variables were analyzed using a van Elteren test. Missing diary card values were not imputed; last observations were not carried forward.

corded for study withdrawal was "other," eg, protocol violations and noncompliance (2 to 5 patients in each group). Mean compliance with scheduled study drug administration, as reported by the 133 patients (or parents or guardians) who returned diary cards, was 88% to 90% across the 3 treatment groups. Treatment groups were comparable for demographic and other characteristics at baseline with a few exceptions. Fifty percent of patients (23 patients) in the Ventolin HFA group were receiving inhaled corticosteroids compared with 28% (13 patients) in the Ventolin CFC group and 30% (13 pa-

tients) in the placebo group. Patients in the Ventolin HFA group reported fewer symptom-free days and higher symptom scores during the screening period compared with the placebo group (**Table 1**).

#### EFFICACY

##### Six-Hour Serial Pulmonary Function Tests

The Ventolin HFA and CFC formulations produced comparable bronchodilation as assessed by the mean in-

**Table 1. Demographics and Other Characteristics of Patients at Baseline\***

	Treatment Group		
	Ventolin HFA	Ventolin CFC	Placebo
No. of patients enrolled	46	46	43
No. (%) receiving inhaled corticosteroids	23 (50)	13 (28)†	13 (30)†
No. (%) receiving inhaled cromolyn sodium	14 (30)	12 (26)	11 (26)
Median age, y	9.0	8.5	9.0
Male, % of total population	54	72	53
PEF, L/min	187 ± 10	201 ± 11	191 ± 9
PEF, % predicted	72 ± 2	71 ± 2	70 ± 2
FEV <sub>1</sub> , ‡	1.37 ± 0.07	1.51 ± 0.07	1.38 ± 0.06
FEV <sub>1</sub> % predicted	69 ± 2	71 ± 1	67 ± 2
Rescue albuterol use, puffs per day	3.1 ± 0.3	3.0 ± 0.4	2.6 ± 0.4
Days with no rescue albuterol use, %	28.1 ± 5.3	30.5 ± 5.7	42.6 ± 6.8
Asthma symptom score§	2.05 ± 0.09	1.84 ± 0.09	1.76 ± 0.09
Days symptom free, %	25.2 ± 5.1	35.5 ± 5.5	44.7 ± 6.0
Nights with no awakenings, %	88 ± 3	91 ± 2	86 ± 4

\* Treatment groups are described in the "Study Design" subsection of the "Patients, Materials, and Methods" section. HFA indicates hydrofluoroalkane-134a propellant; CFC, chlorofluorocarbon propellant; PEF, peak expiratory flow; and FEV<sub>1</sub>, forced expiratory volume in 1 second. Unless otherwise indicated, data are given as mean ± SE. For pulmonary function measures, baseline is the average of the -30- and 0-minute (predose) measurements at treatment day 1. For diary card measures, baseline is the average of data collected from the 7 days immediately before treatment day 1.

†P ≤ .05 compared with the Ventolin HFA group.

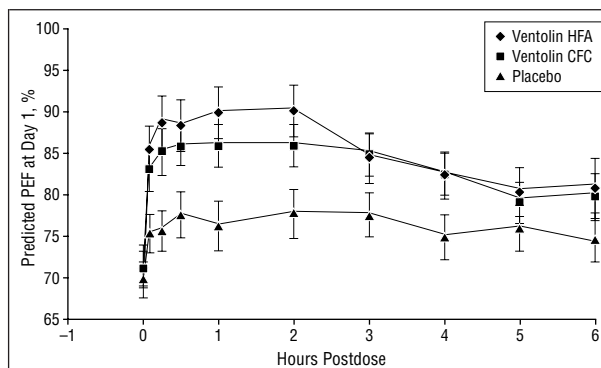
‡Performed for all patients aged 6 to 11 years and for patients younger than 6 years if able to perform procedure (n = 41 for the Ventolin HFA group, n = 40 for the Ventolin CFC group, and n = 39 for the placebo group).

§For asthma symptom score, 1 indicates none; 2, mild; 3, moderate; and 4, severe.

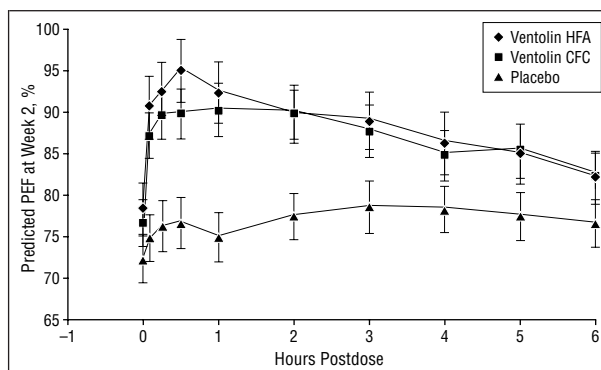
||P ≤ .01 compared with placebo group.

crease in percentage of predicted PEF (**Figure 1** and **Figure 2**). The Ventolin HFA and CFC groups were similar in the mean increase in percentage of predicted PEF at both clinic visits; increases in the Ventolin HFA and CFC groups ranged from 11% to 14% compared with 4% to 6% of predicted PEF in the placebo group (**Table 2**; P ≤ .006 vs placebo). Predose PEF rates at week 2 were higher than at day 1 for all groups, with increases ranging from 5% in the placebo group to 9% in the Ventolin HFA group. The Ventolin HFA and CFC groups were similar for serial PEF functions (Table 2). The median times to onset of response were within 5 to 12 minutes for the Ventolin HFA and CFC groups (P ≤ .02 vs placebo).

One hundred twenty patients, 39 to 41 in each group, also underwent assessment using spirometry. Results were similar to those of the PEF evaluations. Increases in mean (± SE) percentage of predicted FEV<sub>1</sub> for day 1 and week 2 were 14% (± 1%) and 10% (± 1%), respectively, in the Ventolin HFA group; 11% (± 1%) and 9% (± 1%), respectively, in the Ventolin CFC group; and 5% (± 1%) and 4% (± 1%), respectively, in the placebo group (P ≤ .003 for Ventolin HFA and CFC vs placebo). There were no significant differences between the Ventolin HFA and CFC groups in mean increases. Serial FEV<sub>1</sub> functions gener-



**Figure 1.** Percentage of predicted serial peak expiratory flow (PEF) (measured in liters per minute) at day 1 (P ≤ .006 for change from baseline during the 6-hour serial testing for the groups treated with Ventolin containing propellant hydrofluoroalkane-134a [Ventolin HFA group] or chlorofluorocarbons [Ventolin CFC group] compared with the placebo group). Treatment groups are described in the "Study Design" subsection of the "Patients, Materials, and Methods" section. Ventolin is the proprietary name for albuterol sulfate marketed by Glaxo Wellcome Inc, Research Triangle Park, NC.



**Figure 2.** Percentage of predicted serial peak expiratory flow (PEF) (measured in liters per minute) at week 2 (P < .001 for change from baseline during the 6-hour serial testing for the groups treated with Ventolin containing propellant hydrofluoroalkane-134a [Ventolin HFA group] or chlorofluorocarbons [Ventolin CFC group] compared with the placebo group). Treatment groups are described in the "Study Design" subsection of the "Patients, Materials, and Methods" section. Ventolin is the proprietary name for albuterol sulfate marketed by Glaxo Wellcome Inc, Research Triangle Park, NC.

ally were similar to those calculated for PEF. Predose FEV<sub>1</sub> rates at week 2 were higher than at day 1 for all groups.

### Daily Assessments Recorded on Diary Cards

At baseline, patients in the 3 groups were taking an average of 2 to 3 puffs of albuterol daily as needed (Table 1). During the treatment period, patients receiving 2 puffs of active treatment qid also took a mean of 1.3 (Ventolin HFA) and 1.1 (Ventolin CFC) puffs per day of rescue albuterol (mean total daily doses of 9.3 and 9.1 puffs, respectively). The placebo group (as-needed albuterol use only) took a mean of 1.9 puffs daily. These values represent decreases of as-needed albuterol use by 1.8 and 2.0 puffs in the Ventolin HFA and CFC groups, respectively, compared with a decrease of 0.8 puffs in the placebo group (**Table 3**; P ≤ .03). There was a 36% (Ventolin HFA) and 40% (Ventolin CFC) increase in the percentage of days with no rescue albuterol compared with an increase of 12% for the placebo group (P ≤ .009).

**Table 2. Six-hour Serial Peak Expiratory Flow\***

	Treatment Groups					
	Ventolin HFA		Ventolin CFC		Placebo	
	Day 1 (n = 46†)	Week 2 (n = 41)	Day 1 (n = 46)	Week 2 (n = 41)	Day 1 (n = 43†)	Week 2 (n = 36)
Baseline PEF, % predicted	71.5 ± 2.4	78.5 ± 3.1	71.0 ± 2.2	76.7 ± 2.8	69.7 ± 2.1	72.3 ± 2.8
Change from baseline in PEF, % predicted	13.9‡ ± 1.4	10.8‡ ± 1.4	12.6‡ ± 1.4	10.8‡ ± 1.4	6.3 ± 1.7	4.5 ± 0.9
Mean peak PEF, % predicted	95.4 ± 3.2	98.8 ± 3.9	91.8 ± 2.6	95.8 ± 3.2	84.4 ± 2.9	85.2 ± 2.9
Median time to onset of response, min§	4.8‡	4.6‡	12.0‡	11.4‡	360	360
Median duration of response, h§	2.6‡	1.6‡	1.1	1.9‡	NA	NA
Mean peak effect, % change from baseline	35.8‡ ± 3.5	28.0‡ ± 3.3	31.5‡ ± 3.1	26.6‡ ± 2.7	21.9 ± 2.7	19.7 ± 2.7
Median time to peak response, h	1	1‡	2	2‡	3	3

\*NA indicates not applicable. Treatment groups and other abbreviations are described in the first footnote to Table 1. Unless otherwise indicated, data are given as mean ± SE.

†The first postdose measurement was missing for 1 of the 46 patients in the Ventolin HFA group and 1 of the 43 patients in the placebo HFA group on day 1; data from these patients were excluded from all day-1 PEF analyses except the baseline analysis.

‡P < .03 compared with the placebo group. Change from baseline (expressed as percentage of predicted value) has been averaged during 6-hour postdose serial testing.

§Response was defined as an increase in PEF of at least 15% above same-day predose value within 30 minutes postdose. For patients who did not respond, time to onset was set to 6 hours; duration was not applicable.

There was no significant difference between albuterol treatment groups in rescue albuterol use.

There were small increases in patient-collected pre-dose morning and evening PEF values compared with the prerandomization baseline value in each group, with the greatest increases occurring in the Ventolin HFA group (Table 3;  $P \leq .01$  vs placebo). Similarly, there were small improvements in asthma symptom scores in the Ventolin HFA and CFC groups (decreases of 0.1 to 0.3), with the greatest improvement observed in the Ventolin HFA group ( $P < .01$  vs placebo). Although symptoms were mild for all groups and changes were small, the Ventolin HFA and CFC groups decreased mean symptom scores (indicating improved symptoms), and the placebo group increased the mean symptom score. During run-in, patients had few nighttime awakenings due to asthma; changes from baseline were not statistically significant among treatment groups.

### Asthma Exacerbations

Serial pulmonary function testing was terminated for patients experiencing an asthma exacerbation during a clinic visit. On day 1, 1 patient in the placebo group and 1 patient in the Ventolin HFA group had an exacerbation. Both patients and 3 additional patients in the placebo group had an exacerbation at the week-2 clinic visit. No patient had a second episode of breakthrough symptoms during serial testing. During the period between clinic visits, 2 patients in the placebo group and 3 patients in the Ventolin CFC group had an exacerbation requiring treatment other than rescue albuterol and were discontinued from the study.

### SAFETY

The Ventolin HFA formulation was comparable in safety to Ventolin CFC and similar in most assessments to placebo. There were few adverse events in this study; 30% of patients in the Ventolin HFA group (14 patients) and

**Table 3. Mean Change From Baseline in Diary Card Variables\***

	Treatment Group		
	Ventolin HFA (n = 46)	Ventolin CFC (n = 46)	Placebo (n = 41)†
Morning PEF, L/min	17 ± 4‡	9 ± 4	2 ± 3
Evening PEF, L/min	15 ± 3‡	11 ± 4	3 ± 3
Rescue albuterol use, mean puffs per day	-1.8 ± 0.4‡	-2.0 ± 0.4‡	-0.8 ± 0.4
Days with no rescue albuterol use, %	36.4 ± 6.1‡	39.5 ± 5.6‡	11.5 ± 6.2
Asthma symptom score	-0.3 ± 0.1‡	-0.1 ± 0.1	0.1 ± 0.1
Days symptom free, %	15.6 ± 4.2	7.1 ± 4.0	0.9 ± 5.9
Nights with no awakenings, %	1 ± 4	4 ± 2	5 ± 4

\*Treatment groups, abbreviations, and asthma symptom scores are described in the first footnote to Table 1. Data are given as mean ± SE. For diary card measures, baseline is the average of data collected from the 7 days immediately before treatment day 1. Mean change is the average of data collected during treatment weeks 1 and 2.

†Two patients in the placebo group did not return diary cards.

‡P < .03 compared with the placebo group.

35% of patients in the Ventolin CFC and placebo groups (16 and 15 patients, respectively) had at least 1 adverse event. The most common adverse events were headache (4 patients in the Ventolin HFA group, 3 patients in the Ventolin CFC group, and 4 patients in the placebo group) and upper respiratory tract infection (1 patient in the Ventolin HFA group, 5 patients in the Ventolin CFC group, and 2 patients in the placebo group). Five patients had an adverse event considered potentially related to study drug. In the Ventolin HFA group, potentially drug-related events included throat irritation (1 patient), epistaxis (1 patient), and throat spasm with oropharyngeal edema several hours later (1 patient). All of these events were resolved, and the use of study drug was continued without recurrence of events on subsequent days. Other potentially drug-related events were hyperactivity in the

Ventolin CFC group (1 patient) and headaches in the placebo group (1 patient). The only adverse event leading to discontinuation of study drug and the only serious adverse event during the treatment phase was asthma exacerbation secondary to an upper respiratory tract infection in 1 patient in the Ventolin CFC group. There were no treatment-related trends in clinical laboratory evaluations or physical examinations.

Vital signs and cardiovascular evaluations revealed no statistically significant or clinically significant findings. Mean changes in pulse and blood pressure in the 6 hours after study drug administration at weeks 1 and 2 were small. Mean pulse rate for the Ventolin HFA group increased by 2 to 4 beats/min more than that of the placebo group at each visit, and mean pulse rate for the Ventolin CFC group differed from that of the placebo group by less than 2 beats/min at each visit. The numbers of patients who experienced changes in systolic or diastolic blood pressure were comparable among groups. No clinically or statistically significant changes from baseline were observed in 12-lead ECG findings or with Holter monitors (subset of 76 patients; 26 from the Ventolin HFA group, 27 from the Ventolin CFC group, and 23 from the placebo group). Mean changes in QTc interval were minimal ( $\leq 4.8$  milliseconds) for each treatment group at day 1 and week 2. Mean minimum and maximum cardiac rates were comparable across treatment groups at each visit. The median number of ventricular ectopic events was 0, and only single ventricular ectopic events occurred during the 6-hour postdose treatment visits. Similarly, the median number of supraventricular ectopic events was very low, ranging from 0 to 1; 75% of the patients had no more than 3 supraventricular ectopic events. No statistically significant differences were observed among treatment groups with respect to the number of patients with either event.

#### COMMENT

The results of this placebo-controlled study in children with asthma demonstrate that Ventolin reformulated with the new HFA propellant produces bronchodilation that is clinically comparable to the effects of inhaled Ventolin using the conventional CFC propellant. During 6-hour serial pulmonary function tests (PEF and FEV<sub>1</sub>), the Ventolin HFA and CFC formulations produced significant increases in bronchodilation compared with placebo (HFA propellant only), and no statistically significant differences between the Ventolin HFA and CFC groups were observed.

The safety profiles were similar among the 3 groups. Our results showed Ventolin HFA to have comparable safety to the Ventolin CFC formulation and to be similar to placebo in most assessments. Clinical investigators considered very few adverse events to be potentially drug related. Data collected from 12-lead ECGs in all patients and from 6-hour Holter monitors in a large subset of patients showed no clinically significant cardiovascular effects. These results are consistent with previously reported studies in adult patients with asthma demonstrating that albuterol reformulated with the HFA

propellant produces a safety and efficacy profile comparable to that of the original product.<sup>3-5</sup>

To meet regulatory requirements, a regularly scheduled qid dosing regimen was used in this study. Although this study was of limited duration, the mean peak PEF expressed as a percentage of predicted values were similar at day 1 and at week 2, suggesting no reduction in the bronchodilatory response over time. Other studies evaluating the use of regularly scheduled bronchodilator therapy in adults have shown mixed results.<sup>11-13</sup> Drazen et al<sup>13</sup> found neither deleterious nor beneficial effects with the regular use of inhaled albuterol compared with as-needed use in adult patients with mild asthma. Current guidelines of the National Institutes of Health for the diagnosis and management of asthma include as-needed dosing of a short-acting  $\beta_2$ -agonist for all patients regardless of age and asthma severity. For any patient with asthma, increasing amounts of daily albuterol use should be evaluated as a worsening of asthma, and additional pharmacotherapy may be warranted. Current guidelines indicate that children older than 5 years who are using short-acting  $\beta_2$ -agonists more than 2 times weekly have persistent asthma and require anti-inflammatory therapy (inhaled corticosteroids or cromolyn) for long-term control of their persistent asthma, in addition to the quick relief provided by inhaled short-acting  $\beta_2$ -agonists.<sup>14</sup> In addition, although the current registration study conducted to support the safety and efficacy of Ventolin HFA delivered via MDI in children did not include the use of spacers, asthma guidelines recommend that a spacer be used with the MDI for maximum efficacy and minimum side effects.

It is interesting to note that, although changes were small, there were statistically significant differences in patient-rated symptoms and rescue albuterol use between the Ventolin groups and the placebo group. The placebo group's mean symptom score increased slightly, whereas the Ventolin HFA and CFC groups showed an improvement in symptoms. As expected, rescue albuterol use significantly decreased in the Ventolin HFA and CFC groups, and there was a significant increase in the percentage of days with no rescue albuterol use. What was unexpected was the finding that rescue albuterol use decreased by almost 1 puff per day in the placebo group, although asthma symptoms remained unchanged or increased slightly. Our findings may be related to study design or may suggest that those children receiving placebo treatment qid and as-needed albuterol, or their caretakers (ie, parents, teachers, day care providers), may not have recognized subtle signs of worsening asthma to increase albuterol use or perhaps did not have easy access to an inhaler at school or day care.

Although 1 non-CFC albuterol product is already on the US market, few pediatric studies have been conducted with this product, and the currently marketed product has not obtained a pediatric indication in the United States. Studies such as the one reported here that evaluate newly formulated non-CFC asthma medications in the pediatric population and demonstrate comparable safety and efficacy to the conventional CFC-containing formulations will help the transition from CFC to non-CFC asthma medications. In addition, non-CFC medications such as this albuterol formulation, which

maintains the same dosages as corresponding CFC medications, will assist in a smooth transition. Similarity of the non-CFC and CFC inhalers, in terms of taste and feel of the aerosol plume, will help minimize patient perception issues in this transition. No patients in this study or in the other Ventolin HFA registration studies<sup>3,15</sup> reported any adverse event related to taste sensation with the HFA product.

As the United States begins the transition to non-CFC asthma medications, already occurring in other countries, data demonstrating comparability of old and new formulations specifically in children are needed for each chemical moiety. Although medications such as albuterol are available in a dry-powder inhaler, the MDI remains one of the most widely used delivery devices. It is important for patients and physicians to maintain their options in the process of individualizing asthma management plans, and thus, non-CFC aerosols for the different classes of asthma medications are being developed. Multiple treatment options and asthma management plans individualized to patient needs and preferences are important factors in increasing adherence to prescribed asthma medication and in reducing costly asthma exacerbations.

## CONCLUSIONS

This study has demonstrated the efficacy and safety of qid dosing with Ventolin HFA (2 puffs, 90 µg/puff) in children aged 4 to 11 years with persistent asthma. These data also show that Ventolin HFA is clinically comparable to Ventolin delivered in the conventional CFC-containing propellant.

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## REFERENCES

1. United Nations Environment Programme. *Handbook for the Montreal Protocol on Substances That Deplete the Ozone Layer*. 3rd ed. Nairobi, Kenya: United Nations Environmental Programme, Ozone Secretariat; 1993:8.
2. United Nations Environment Programme. *Report of the Technology and Economic Assessment Panel: Montreal Protocol on Substances That Deplete the Ozone Layer*. Nairobi, Kenya: United Nations Environmental Programme, Ozone Secretariat; 1995:89-99.
3. Lumry W, Noveck R, Weinstein S, et al. Switching from Ventolin (CFC) to Ventolin HFA is well tolerated and effective in patients with asthma. *Ann Allergy*. In press.
4. Bleeker ER, Tinkelman DG, Ramdsdell J, et al. Proventil HFA provides bronchodilation comparable to Ventolin over 12 weeks of regular use in asthmatics. *Chest*. 1998;113:283-289.
5. Tinkelman DG, Bleeker ER, Ramdsdell J, et al. Proventil HFA and Ventolin have similar safety profiles during regular use. *Chest*. 1998;113:290-296.
6. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis*. 1987;136:225-244.
7. Polgar G, Promadhat V. *Pulmonary Function Testing in Children: Techniques and Standards*. Philadelphia, Pa: WB Saunders Co; 1971:12-17.
8. Position Statement of the American Thoracic Society. Lung function testing: selection of reference values and interpretable strategies. *Am Rev Respir Dis*. 1991;144:1202-1218.
9. Morganroth J. Ambulatory Holter electrocardiography: choice of technologies and clinical uses. *Ann Intern Med*. 1985;102:73-81.
10. van Elteren PH. On the combination of independent two sample tests of Wilcoxon. *Bull Inst Intern Stat*. 1958;37:351-361.
11. Sears MR, Taylor DR, Print CG, et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet*. 1990;336:1391-1396.
12. Chapman KR, Kesten S, Szali JP. Regular vs as-needed inhaled salbutamol in asthma control. *Lancet*. 1994;343:1379-1382.
13. Drazen JM, Israel E, Houshey HA, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. *N Engl J Med*. 1996;335:841-847.
14. Highlights of the Expert Panel Report 2. *Guidelines for the Diagnosis and Management of Asthma*. Bethesda, Md: National Heart, Lung, and Blood Institute, National Institutes of Health; May 1997. NIH publication 97-4051A.
15. Peden DB, Vicherat LV, DeGraff AC, et al. Ventolin HFA administered via the MDI is safe for the long-term treatment of adolescent and adult subjects with asthma [abstract]. *J Allergy Clin Immunol*. 1999;103(suppl 1, pt 2):S128.