

## Safety and Efficacy of a New Albuterol Hydrofluoroalkane Formulation for Treating Asthma Symptoms in Children Two to Less than Four Years of Age

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### ABSTRACT

Metered dose inhalers (MDIs) are being reformulated with hydrofluoroalkane (HFA) propellants because of the ozone-depleting effects of chlorofluorocarbons. Although currently indicated for children 4 years of age or older, albuterol (Ventolin™; GlaxoSmithKline, Research Triangle Park, NC) HFA is sometimes used to treat younger children. Therefore, its safety in children aged 2 to less than 4 years was determined in this randomized, double-blinded, multicenter parallel-group study. Seventy-seven children with asthma received albuterol HFA 90 or 180  $\mu\text{g}$  or placebo three times daily for 4 weeks via MDI with one of two holding chambers and a face mask. Because of the small sample size, the study was not powered to achieve statistically significant outcomes. Improvements in 24-hour and nighttime asthma symptom scores were not significantly different between groups. Compared to placebo, albuterol HFA groups had greater improvements in daytime asthma symptom scores, rescue albuterol use, nighttime awakenings, percent symptom-free days, and twice daily peak expiratory flow although these differences did not reach statistical significance. Adverse events were less frequent in albuterol HFA 90  $\mu\text{g}$  (35% or 9 subjects) than in albuterol HFA 180  $\mu\text{g}$  (52% or 13 subjects) and placebo (42% or 11 subjects). Frequently reported adverse events included pyrexia (placebo and albuterol HFA 90  $\mu\text{g}$ :8% [2 subjects each]; albuterol HFA 180  $\mu\text{g}$ :4% [1 subject]), vomiting (placebo: 8% [2 subjects]; albuterol HFA 90  $\mu\text{g}$ :4% [1 subject]) and diarrhea (albuterol HFA 90  $\mu\text{g}$ :8% [2 subjects]). QT prolongation occurred in 4 subjects, 3 subjects in the albuterol HFA 180  $\mu\text{g}$  and 1 subject in the albuterol HFA 90  $\mu\text{g}$  group. Mild tremor occurred in 12% (3 subjects in albuterol HFA 90  $\mu\text{g}$ ), 8% (2 subjects in albuterol HFA 180  $\mu\text{g}$ ), and 4% (1 subject in placebo) of patients.

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**Drug-related tachycardia and abnormal blood glucose or serum potassium were not observed. The study demonstrated improved trends in efficacy measures and a safety profile similar to that of controls regarding administration of albuterol HFA to children under 4 years of age. (Pediatr Asthma Allergy Immunol 2006; 19[2]:xx-xx.)**

## INTRODUCTION

**A**STHMA is a major chronic airway inflammatory disorder with a rising prevalence throughout the world. From 1980 to 1994, the asthma prevalence rate in the United States increased by 75%, with the rate among children under the age of 5 increasing by 160%.<sup>1</sup> Data from the National Health Interview Survey indicate that in the United States, asthma affects 7.5% and 14% of children aged 0–4 years and 5–11 years, respectively.<sup>2</sup> Of children with asthma, 50% to 80% develop symptoms of cough, wheeze, chest tightness, or shortness of breath before 5 years of age,<sup>3</sup> indicating the need for early treatment to stabilize this debilitating disease effectively.

Short-acting inhaled  $\beta$ -agonists relax airway smooth muscle, enhance mucociliary clearance, and decrease vascular permeability.<sup>4–6</sup> Guidelines established by the National Asthma Education and Prevention Program<sup>7</sup> and the Global Strategy for Asthma Management and Prevention<sup>8</sup> recommend administration of short-acting bronchodilators in addition to regular daily controller therapy for as-needed asthma symptom control in all children including those less than 5 years of age.

Bronchodilators can be delivered as a solution aerosolized via pressurized metered dose inhalers (MDIs) or a nebulizer. Inhalation is the preferred method of delivery because it dispenses high drug concentrations into the airways, minimizes side effects and produces the most rapid onset of action.<sup>3</sup> In the past, the use of nebulized therapy was more prevalent in the majority of children under 4 years of age. However, recent asthma guidelines have indicated that the use of MDIs with auxiliary devices and face masks is appropriate for children under 5 years of age,<sup>3,9</sup> and many studies have demonstrated the efficacy, cost-effectiveness, and convenience of this device even in such a young population.<sup>10–12</sup>

As mandated by the Montreal Protocol,<sup>13</sup> hydrofluoroalkanes (HFA) are replacing the ozone-depleting chlorofluorocarbon (CFC) propellants in MDIs delivering inhaled bronchodilators and corticosteroids. Although albuterol sulfate (Ventolin™, GlaxoSmithKline, Research Triangle Park, NC) HFA MDI is approved only for children 4 years of age and older, it is acknowledged that physicians prescribe this medication even in younger children. Because clinical data are very limited in this population, this study evaluated the safety and efficacy of Ventolin HFA 90 or 180  $\mu$ g administered three times daily via a MDI with one of two holding chambers and a face mask to children between 2 and less than 4 years old with symptoms of asthma.

## PATIENTS AND METHODS

### *Patients*

Males and females aged 24 to less than 48 months with a documented history of asthma symptoms that required pharmacotherapy at least twice over the 12 months prior to the study, and who had received regular maintenance asthma pharmacotherapy (except systemic corticosteroids) and/or a short-acting  $\beta_2$ -agonist at least 3 times per week over the past 4 weeks, were eligible for the study. Children were excluded from the study if they had life-threatening asthma or other severe concurrent disease, upper or lower respiratory tract, sinus or middle ear infections within the previous 2 weeks, used systemic corticosteroids either short-term over the preceding 14 days or long-term over the preceding 3 months, or had clinically significant laboratory or electrocardiogram (ECG) abnormalities. Patients were allowed to continue their use of leukotriene modifiers, cromolyn, and/or nedocromil, and inhaled corticosteroids during the study if the dosing regimen was started at least 4 weeks prior to screening and remained unchanged during the course of the study. All other asthma medications, including oral and inhaled  $\beta$ -agonists, were discontinued at screening for the duration of the study.

*Study design and treatments*

This randomized, double-blinded, parallel-group, placebo-controlled study was conducted at 37 centers in the United States. All centers obtained Institutional Review Board approval and a signed consent form from a patient's parent or legal guardian before starting the study. The study comprised a 7- to 28-day screening period, followed by a 29-day treatment period during which patients were randomized to receive albuterol (Ventolin™), HFA inhalation aerosol 90 or 180 µg or placebo HFA three times daily. Study medications were administered via a MDI in conjunction with one of two of the most commonly used valved holding chambers, the Aerochamber Plus™ (Monaghan Medical, Plattsburgh, NY) or Optichamber™ (Respironics Healthscan, Cedar Grove, NJ) and attached face masks. In addition, open-label albuterol HFA MDI (90 µg per actuation) or albuterol nebule (2.5 mg per 3 mL) formulations, along with a holding chamber other than the one used for study drug, were provided for rescue use as needed during the study. The manufacturers instructions for administration of the medication were provided with each of the valve-holding chambers. Treatment demonstration kits were provided to study sites and parents/care givers were trained in the use of the study medications and valved holding chambers.

To be eligible for randomization, patients had to demonstrate asthma symptoms and albuterol use recorded in the daily diary on at least 2 of 7 consecutive days during the screening period. Patients experiencing an asthma exacerbation during the screening period were not eligible for randomization. Each patient was dispensed two MDI inhalers containing either albuterol HFA or placebo HFA along with the holding chamber, face mask, and instructions for administration. Each inhaler was "test sprayed" four times before using for the first time and then inserted into the holding chamber. Patients were asked to inhale one puff from each of the two inhalers three times daily, approximately 4 to 6 hours apart. Children capable of performing peak expiratory flow measurements were provided with a peak flow meter at screening.

*Evaluations*

During the screening period, baseline safety evaluations were performed and measures of asthma status were obtained. After randomization patients attended the clinic for safety and efficacy evaluations on treatment days 1, 8, 15, and 29. Patients completed a total of 5 study visits, including the screening visit. Study drug and rescue albuterol were not permitted for at least 4 hours prior to the procedures on days 1 and 29. If rescue albuterol was required, the procedures were rescheduled.

Safety measures included the assessment of adverse events (AEs), signs and symptoms of adrenergic stimulation (assessed by certain questions on the Functional Status II (R) questionnaire (FSII(R))<sup>14</sup> administered at randomization and at all subsequent clinic visits, and on symptoms recorded on the daily diary, as well as by the physician's assessment of tremor measured on a 4-point scale of none to severe), clinical laboratory assessments, ECG measurements (including QTc interval), and physical examination. ECGs were conducted before and 1 hour after albuterol dose at screening visit 1 and visit 5 (treatment week 4). In addition to the initial evaluation of the 12-lead ECG by the study investigator, ECGs were interpreted by an independent electrocardiographer who was blinded to treatment assignments. Results were classified as normal, abnormal—not clinically significant, or abnormal—clinically significant. Criteria for these ECG classifications are presented in Table 1. The cutoff for the QTc interval was chosen as 460 msec based on suggested QTc values of under 440 msec as normal, 440–460 msec as borderline, and 460 msec as prolonged in children aged 1–15 years.<sup>15</sup>

Other safety measures included laboratory samples for serum potassium and glucose drawn 60 minutes postdosing at visit 5. Vital signs and tremor assessments were obtained at all visits except for: (1) visit 2 where both the predose and the 1-hour postdose assessments were performed for both assessments; (2) Visit 5 tremor assessment was conducted both predose and 60 minutes postdose; and (3) visit 5 vital signs were collected 60 minutes postdose.

The primary efficacy measure was the mean change from baseline to end point (average of the 4-week treatment period) in 24-hour daily asthma symptom scores. Asthma symptoms including cough, wheeze, and shortness of breath were rated by the parent or guardian on a scale of 0 (no symptoms) to 3 (symptoms so severe that they restricted normal daily activities or kept patient awake most of the night).

TABLE 1. ELECTROCARDIOGRAM CLASSIFICATIONS

Abnormal, clinically insignificant <sup>a</sup>	
Sinus bradycardia	
Ages 24–35 months	65–79 beats/min
Ages 36–47 months	60–74 beats/min
Ages 48–60 months	60–69 beats/min
Sinus tachycardia	
Ages 24–35 months	140–149 beats/min
Ages 36–47 months	135–149 beats/min
Ages 48–60 months	130–149 beats/min
Abnormal, clinically significant	
Marked sinus bradycardia	
Ages 24–35 months	<65 beats/min
Ages 36–47 months	<60 beats/min
Ages 48–60 months	<60 beats/min
Marked sinus tachycardia (heart rate $\geq$ 150 beats/min)	

<sup>a</sup>Other abnormal clinically insignificant criteria included: minor abnormalities of the QRS, T-wave and/or the ST segment and isolated premature atrial contraction/premature ventricular contraction.

<sup>b</sup>Other abnormal clinically significant criteria included: PR Intervals > 160 msec; QRS intervals > 100 msec; QTc intervals > 460 msec; clinically significant arrhythmias (including supraventricular tachycardia, junctional or idioventricular rhythm and atrial flutter/fibrillation; ventricular ectopy including any premature ventricular complexes; Wolff-Parkinson-White pattern; AV blocks including first degree AV block (PR > 160 msec) and Mobitz 2 second-degree AV block but excluding Wenckebach or Mobitz type 1 AV block.

Secondary measures included the mean percent change from baseline to endpoint in daytime asthma symptom scores, percentage of symptom-free days and rescue albuterol use. Other efficacy parameters included mean percent change from baseline to endpoint in nighttime asthma symptom scores, percentage of nights with no awakenings due to asthma and morning and evening peak expiratory flow for patients capable of performing this maneuver. Patient compliance with study medication was assessed by using the daily diary record.

### *Statistical analysis*

Enrollment was planned for approximately 75 patients (25 per treatment group), so that at least 22 patients per treatment group would complete the study. Literature reviews demonstrate established efficacy and safety data in children 4–11 years of age. There are limited data in children less than 4 years old. Therefore, this study was conducted primarily to assess safety and the sample size was not expected to provide enough statistical power to detect differences for any of the efficacy parameters, however, these analyses are presented here.

All efficacy analyses were conducted on the intent-to-treat (ITT) population, which comprised all patients who received at least one dose of study medication. Two-sided statistical tests with a 0.05 level of significance were used. Analyses of 24-hour asthma symptom scores, daytime asthma symptom scores, and FSII(R) total scores were performed using analysis of covariance, with baseline, age, gender, and region (by geographic location) as the covariates, in addition to treatment effect. Analyses of the percentage of symptom-free days and 24-hour rescue albuterol use were performed using the van Elteren modification of the Wilcoxon rank sum test. For the primary efficacy measure, subgroup analyses were performed by holding chamber and use of concurrent asthma medication. Subgroup analysis for the FSII(R) total scores was performed by using results from patients for whom the same parent/guardian completed the questionnaire at all visits. No statistical testing was conducted on safety measures, which were summarized using descriptive statistics. All statistical analyses were performed using SAS (SAS Institute, Cary, NC) software version 8.

## RESULTS

*Patient demographics and disposition*

Of the 97 patients screened for this study, 20 were not randomized primarily because of failure to meet study requirements for asthma symptoms and albuterol use prior to randomization. Demographic characteristics of the 77 patients randomized to the study were similar across treatment groups (Table 2). The mean age of onset of asthma symptoms was 10 months, with the most commonly identified risk factors for asthma being family history of asthma (92%), seasonal (55%) and year-round (35%) hay fever, and history of eczema (35%). Seven patients (3 in the placebo group and 2 each in the albuterol HFA treatment groups) withdrew from the study. Three patients withdrew because of protocol violations; 2 for lack of efficacy, and 1 each for being lost to follow-up or withdrawal of consent. Approximately two thirds of the patients in each treatment group used other concurrent asthma medications. Mean compliance was high in all treatment groups (87%–96%).

*Safety*

A total of 33 patients (43%) reported at least one AE during treatment, with 11 (42%) in the placebo group, 9 (35%) in the albuterol HFA 90  $\mu\text{g}$  group and 13 (52%) in the albuterol HFA 180  $\mu\text{g}$  group. The most frequently reported events included pyrexia (2 patients each in the placebo and albuterol HFA 90  $\mu\text{g}$  groups), vomiting (2 patients in the placebo group and 1 patient in the albuterol HFA 90  $\mu\text{g}$  group) and diarrhea (2 patients in the albuterol HFA 180  $\mu\text{g}$  group). QT prolongation occurred in 4 subjects, 3 subjects in the albuterol HFA 180  $\mu\text{g}$  and 1 subject in the albuterol HFA 90  $\mu\text{g}$  group. One patient in the albuterol HFA 90  $\mu\text{g}$  group experienced a serious adverse event (asthma exacerbation) that occurred 28 days after discontinuing study medication and was not considered by the investigator to be study-drug-related. No patients withdrew from the study due to adverse events.

Most subjects had normal ECGs at screening visit 1 (64%–92%); and week 4 (end of treatment) (87%–100%). One subject in the albuterol HFA 90  $\mu\text{g}$  group had an unfavorable change at the week 4 post-dose ECG (nonspecific T-wave abnormality and prolonged QT interval) compared to the visit 1 predose ECG. This subject did not have any other adverse events or serious adverse events (SAEs) and the condition resolved 1 week after treatment discontinuation and the subject had a normal ECG at this time. Two subjects in the albuterol HFA 180  $\mu\text{g}$  group also had one unfavorable change each at the week 4 postdose ECG compared with the week 4 predose ECG (prolonged QT interval and increased heart rate, respectively). There were no further AEs at follow-up for these subjects. ECG data, including heart rate, QT interval, QTc interval, PRS interval, and QRS duration are summarized in Table 3. At week 4, mean changes

TABLE 2. DEMOGRAPHICS AND DISPOSITION OF PATIENTS AT BASELINE

	Placebo (n = 26)	Albuterol HFA 90 $\mu\text{g}$ TID (n = 26)	Albuterol HFA 180 $\mu\text{g}$ TID (n = 25)
Gender			
Male, n (%)	16 (62)	21 (81)	13 (52)
Female, n (%)	10 (38)	5 (19)	12 (48)
Age, mean (range), months	35.7 (24–47)	36.4 (24–47)	35.8 (24–47)
Ethnic origin, n (%)			
White	16 (62)	16 (62)	10 (40)
American Hispanic	6 (23)	4 (15)	4 (16)
Black	3 (12)	6 (23)	9 (36)
Other	1 (4)	0	2 (8)
Holding chamber, n (%)			
Aerochamber Plus	14 (54)	14 (54)	10 (40)
Optichamber	12 (46)	12 (46)	15 (60)
Concurrent asthma medications, n (%)	18 (69)	16 (62)	18 (72)

HFA, hydrofluoroalkane; TID, three times daily; ICS, inhaled corticosteroids.

TABLE 3. SUMMARY OF ECG MEASURES, MEAN (CHANGE FROM BASELINE)

<i>ECG measure</i>	<i>Placebo</i> (n = 26)	<i>Albuterol HFA</i> 90 µg TID (n = 26)	<i>Albuterol HFA</i> 180 µg TID (n = 25)
Heart Rate (bpm)			
Baseline <sup>a</sup>	108.2	104.0	112.4
Week 4 predose	105.3 (-2.5)	100.0 (-4.1)	103.8 (-6.5)
Week 4 postdose	108.7 (0.5)	98.8 (-5.0)	111.0 (0.0)
QT interval (msec)			
Baseline <sup>a</sup>	312.3	315.8	307.2
Week 4 predose	314.4 (1.6)	324.7 (9.9)	318.4 (8.9)
Week 4 postdose	313.8 (0.9)	328.0 (13.0)	310.4 (1.4)
QTc interval <sup>b</sup> (msec)			
Baseline <sup>a</sup>	378.5	378.0	376.1
Week 4 predose	377.5 (-1.2)	383.0 (6.1)	380.7 (3.8)
Week 4 postdose	380.0 (1.0)	384.7 (7.9)	378.2 (1.5)
PR interval (msec)			
Baseline <sup>a</sup>	116.3	119.9	126.7
Week 4 predose	117.7	120.2	124.3
Week 4 postdose	117.6	119.1	123.9
QRS duration (msec)			
Baseline <sup>a</sup>	70.3	75.7	70.1
Week 4 predose	70.3	75.2	72.5
Week 4 postdose	70.5	74.6	72.9

<sup>a</sup>Baseline, value obtained at screening visit.

<sup>b</sup>Corrected for heart rate using Fridericia's formula.

HFA, hydrofluoroalkane; TID, three times daily.

from baseline in heart rate and QT interval were small. Mean PR intervals and QRS durations at week 4 were similar to baseline values.

There were four subjects who had an ECG with QT interval prolonged in the albuterol HFA treatment group but none of the same subjects had an ECG with prolonged QT interval when corrected for heart rate. One subject in the albuterol 90 µg group exhibited a prolonged QTc thought to be related to the study drug. There were no further AEs at follow-up for this subject. The maximal change from baseline (visit 1) in QT when corrected for heart rate ranged between 44–67 msec and the individual QT intervals were not greater than 396 msec. No patients had a QT or QTc interval greater than 460 msec.

Mean values for systolic and diastolic blood pressure at week 4 were comparable to those observed at baseline. Mean changes from baseline were very small, ranging from -0.1 to 1.2 mm Hg for systolic blood pressure and -1.1 to -1.6 mm Hg for diastolic blood pressure. Mean values for heart rate, body temperature, and respiratory rate at week 4 were also comparable to those observed at baseline and did not differ between treatment groups. No clinically significant differences were observed between treatment groups in laboratory evaluations, vital signs or physical examination. No cases of drug-related abnormalities in blood glucose or serum potassium levels were reported in the albuterol HFA groups. One patient in the albuterol HFA 90 µg group exhibited an increased blood alkaline phosphatase potentially related to study drug that resolved in 14 days.

Mild tremor (on a four-point scale of none to severe) was observed in 3 patients in the albuterol HFA 90 µg group, 2 patients in the albuterol HFA 180 µg group and 1 patient in the placebo group. No cases of drug-related tachycardia were reported in the albuterol HFA treatment groups. Another potentially drug-related adverse event occurred in one patient with psychomotor hyperactivity treated with albuterol HFA 180 µg that resolved in 1 day.

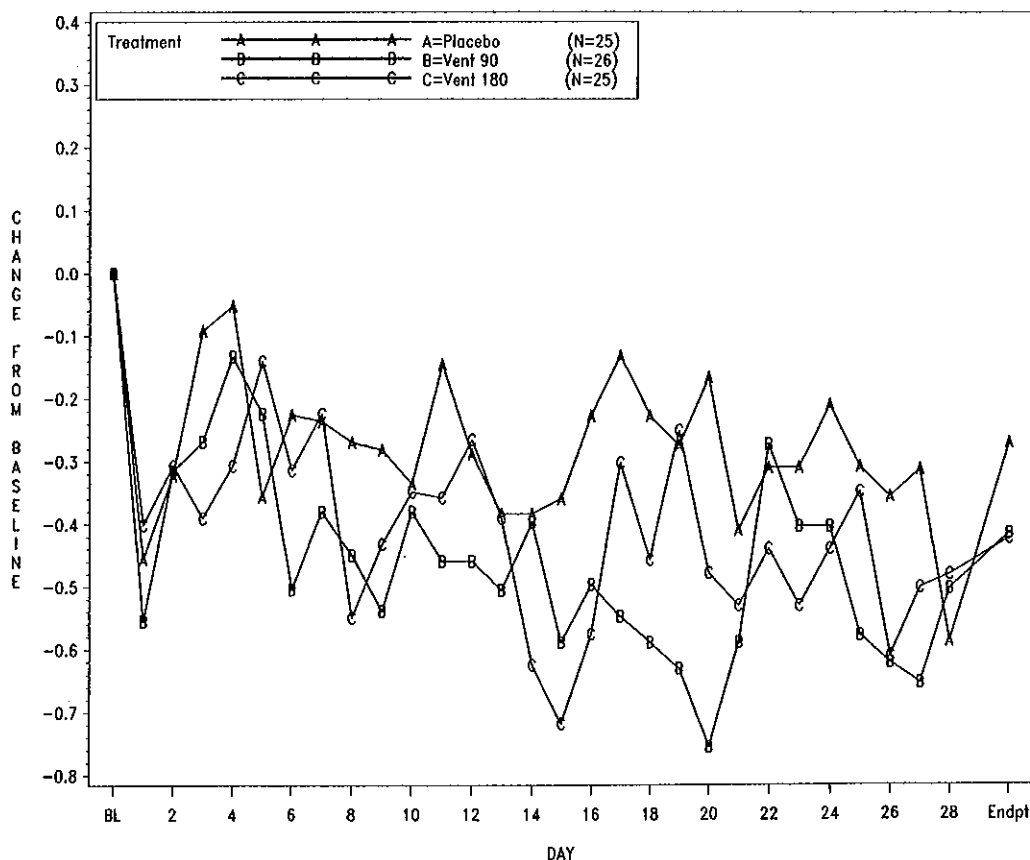
Summary scores of the 7 individual items selected from the FSII(R) questionnaire to evaluate potential signs and symptoms of adrenergic stimulation included sleep well, content/cheerful, act moody, unusually

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irritable, sleep through the night, unusually difficult, and react by crying. Mean scores were similar across treatment groups at baseline and end point. With the exception of the content/cheerful score, this remained high and unchanged in the placebo group, mean scores increased for all the selected items in all treatment groups. Based on these scores, there was no evidence of adrenergic stimulation. Similar results were seen with data obtained from the same parent completing the questionnaire at baseline and end point (data not shown).

### *Efficacy*

The primary efficacy parameter of mean change from baseline in 24-hour asthma symptom scores at end-point did not differ significantly between the albuterol HFA and placebo groups. At baseline, mean 24-hour asthma symptom scores were mild (noticeable symptoms, but no interference with daily activities or sleep) and similar across treatment groups. Asthma scores declined slightly in each group over 4 weeks of treatment (Fig. 1). Mean percent change from baseline to end point in daytime asthma symptom scores, percentage of symptom-free days and 24-hour albuterol use showed some improvements in both albuterol HFA groups compared to placebo, although these differences were not statistically significant. Compared to placebo, both albuterol HFA treated groups showed a trend of having a greater percentage of nights with no awakenings due to asthma. Mean change from baseline to endpoint in morning and evening peak expiratory flow (measured only in 11–13 patients in each treatment group who were capable of performing this maneuver) increased slightly in both albuterol HFA-treated groups but decreased in the placebo group.



**FIG. 1.** Change from baseline to end point in daily 24-hour asthma symptom score (3-point scale with 0 = no symptoms and 3 = severe symptoms). Baseline = average of 7 days prior to study drug administration; end point = average of 4-week treatment period.

Again because of the lack of power for these analyses the differences were not statistically significant. Results of subgroup analyses by type of holding chamber and in patients with and without concurrent asthma medication showed no differences between the subgroups.

## DISCUSSION

Albuterol sulfate (Ventolin™) reformulated in hydrofluoroalkane propellant and administered via a MDI is currently approved for administration to children over 4 years of age for relief of asthma symptoms. The HFA and CFC formulations of Ventolin™ HFA have been shown to have clinically comparable efficacy and safety in adults and children over 4 years of age.<sup>16,17</sup> However, because Ventolin™ HFA could potentially be used in younger children, this placebo-controlled study was conducted to evaluate the safety and efficacy of this formulation in children aged 2 to less than 4 years.

In this study, children were administered albuterol HFA via a MDI that was used in conjunction with the two most commonly used valved holding chambers and a face mask. National asthma guidelines state that MDIs with auxiliary devices and face masks can be used in children less than 4 years of age and recommend nebulizers for children under 2 years of age and children of all ages who cannot use MDIs with auxiliary devices.<sup>3,9</sup> Yet, because of the perception that nebulizers are more effective for the treatment of children, they are used more frequently, especially in the acute care setting.

The advantages of using a MDI over a nebulizer include lower costs, greater portability, no requirement for a power source, less time-consuming and lower chances of contamination and less systemic side effects.<sup>18-21</sup> Comparative trials in 1- to 5-year-old children with recurrent wheezing, and in children 2 years and older treated in an emergency department for acute asthma exacerbations, demonstrated that albuterol administered via a MDI with spacer was therapeutically equivalent to that delivered by a nebulizer.<sup>22,23</sup>

When  $\beta$ -agonists are absorbed into the systemic circulation, pharmacologically predictable adverse effects that are dose-related can occur as a result of the stimulation of extrapulmonary  $\beta$ -adrenergic receptors.<sup>24</sup> Stimulation of cardiac  $\beta$ -adrenergic receptors may cause increased blood pressure, tachycardia, arrhythmias, and palpitations,<sup>25-27</sup> while stimulation of skeletal muscle  $\beta$ -adrenergic receptors can induce tremor.<sup>26,28,33</sup> Adverse metabolic effects include hypokalemia resulting from an influx of potassium into cells and hyperglycemia caused by increased glycogenolysis.<sup>26-28</sup> Tolerance to systemic effects but not to airway response was shown after 14 days of treatment with a high dose (4000  $\mu$ g) of inhaled salbutamol in patients with asthma.<sup>29</sup>

Few studies have evaluated the safety of bronchodilators in children younger than 4 years of age. In a study that compared the effectiveness of albuterol administered to 1- to 4-year-old children via a nebulizer or a MDI with spacer in an emergency department, significantly greater increases in heart rate were observed in the nebulizer group. No differences were seen in rates of tremor or hyperactivity.<sup>12</sup> In another comparative study, children 2 years and older with asthma exacerbations treated with  $\beta$ -agonists via a MDI and spacer required shorter treatment times in the emergency department, had fewer episodes of vomiting and smaller increases in heart rate than the nebulizer group.<sup>23</sup>

Changes in ECG parameters have generally been reported with the use of  $\beta$ -agonists at high doses in adults but its clinical significance is debatable.<sup>30,31</sup> Conflicting results have also been reported with regard to the cardiotoxic effects of  $\beta$ -agonists in children with asthma. Treatment of 4- to 15-year-old children with moderate to severe asthma with nebulized albuterol was found to significantly increase corrected QT dispersion (QTcd) defined as the difference between the maximum and minimum QTc for a given heart rate.<sup>32</sup> No significant increases were seen in heart rate, blood pressure, and serum potassium or urea values.<sup>32</sup> On the other hand, no statistically or clinically significant changes were observed in heart rate, blood pressure or ECG intervals in 4- to 11-year-old children with asthma treated with either albuterol HFA or albuterol CFC at doses of 180  $\mu$ g 4 times daily for 2 weeks.<sup>17</sup>

In this study, a similar profile of adverse events, clinical laboratory, and ECG findings were observed across treatment groups. There was no evidence of adrenergic stimulation based on AE data and results of a health status questionnaire. Mild tremor was reported in less than 10% of patients. No tachycardia was observed. Treatment with albuterol HFA did not result in metabolic abnormalities such as hypokalemia and

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hyperglycemia. There were no clinically relevant differences in the mean change from baseline in the QT interval between treatment groups and overall results of ECGs at end of treatment compared to baseline. In addition there were no significant differences between ECGs conducted predose and postdose at visits 1 and 5. Treatment with albuterol HFA resulted in improving trends in most efficacy parameters, though none were significantly different from placebo. Similar improvements were seen regardless of the type of holding chamber used and whether or not patients received concomitant inhaled corticosteroid therapy.

In conclusion a safety profile comparable to placebo with no significant ECG, adrenergic or metabolic abnormalities was observed in children under 4 years of age treated with albuterol HFA via MDI in conjunction with a holding chamber and face mask.

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