Proventil HFA Provides Bronchodilation Comparable to Ventolin Over 12 Weeks of Regular Use in Asthmatics*  

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**Objective:** To compare the bronchodilator effectiveness of albuterol reformulated in the chlorofluorocarbon-free propellant hydrofluoroalkane (HFA)134a (Proventil HFA) to that of Ventolin and HFA placebo over 12 weeks of regular dosing.

**Design:** Randomized, double-blind, double-dummy, parallel group, placebo-controlled, multicenter trial of asthmatics requiring inhaled β-adrenergic bronchodilators for symptom control.

**Interventions:** Treatment qid with Proventil HFA, Ventolin, or HFA-134a placebo for 12 weeks.

**Measurements:** At weeks 0, 4, 8, and 12, spirometry was performed predose and serially over 6 h after dosing with study drug. Bronchodilator efficacy variables, based on FEV₁ response to study drug, were proportion of responders, time to onset of effect, peak percent change, time to peak effect, duration of effect, and area under the curve (AUC).

**Results:** Demographic and baseline characteristics were similar for patients randomized to Proventil HFA (193), Ventolin (186), and HFA-134a placebo (186). No significant differences were found between the Proventil HFA and Ventolin treatment groups for any FEV₁ efficacy variable, either predose or during 6 h of serial spirometry, at weeks 0, 4, 8, and 12. For all efficacy variables, except time to onset of effect, the Proventil HFA and Ventolin results were significantly greater than placebo. Time to onset of effect for the HFA-134a placebo group is misleading; only 13 patients (7%) were found to be responders in the intent-to-treat database. These efficacy results were found to be consistent across subgroup analyses of inhaled and nasal corticosteroid use, age (18 to 35 and 36 to 66 years), sex, race, weight (<60, 60 to 100, and >100 kg), and baseline FEV₁ (≤55% and >55% predicted). The peak FEV₁ effect, duration of FEV₁ effect, and AUC for FEV₁ were all significantly smaller at weeks 4, 8, and 12 than week 0 for both the Proventil HFA and Ventolin treatment groups.

**Conclusions:** Proventil HFA provided bronchodilation comparable to Ventolin and superior effects to HFA-134a placebo over 12 weeks of regular dosing. There was a diminution in bronchodilator response to both Proventil HFA and Ventolin after 4 weeks of use.

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**Key words:** albuterol; asthma; HFA-134a propellant

**Abbreviations:** ANOVA=analysis of variance; AUC=area under the curve; CFC=chlorofluorocarbon; HFA-134a=hydrofluoroalkane 134a; MDI=metered-dose inhaler

Albuterol, the most widely used β-adrenergic bronchodilator in the world, is usually administered by inhalation from a metered-dose inhaler (MDI). Albuterol-containing MDIs are convenient to use and carry, and provide rapid bronchodilation with a reassuringly high safety margin. International guidelines for the management of asthma incorporate the use of β adrenergic bronchodilators, taken by MDI, as an important component of symptom control in asthma care.\(^1\)\(^2\)

MDIs have historically used chlorofluorocarbons (CFCs) as propellants. Release of CFCs into the atmosphere has contributed to depletion of strato-
ospheric ozone.\textsuperscript{3,4} Loss of the stratospheric ozone layer would result in serious public health concerns. Consequently, \textgreater 100 nations have ratified the Montreal Protocol that mandates the cessation of production and use of CFCs by developed countries by January 1, 1996. Few exemptions have been granted to this agreement, the most significant in terms of total CFC use is as a propellant in MDIs.\textsuperscript{5} Because products like albuterol are so widely used and so critically important to asthma care, global regulatory authorities have required extensive safety testing of alternative MDI propellants before considering evaluation of albuterol products reformulated in CFC-free propellants.

The first CFC-free propellant shown to be as safe, or safer, than CFC propellants through a rigorous global safety testing program is hydrofluoroalkane 134a (HFA-134a). Albuterol reformulated in HFA-134a (Proventil HFA; Key Pharmaceuticals; Kenilworth, NJ) provided bronchodilation comparable to Ventolin (Glaxo Wellcome; Research Triangle Park, NC), a currently marketed albuterol MDI product formulated in CFCs, in short-term dosing studies.\textsuperscript{6,7} This study describes the results from a large group of asthmatics who regularly used Proventil HFA, Ventolin, or HFA-134a placebo for 12 weeks. Bronchodilator efficacy of Proventil HFA, assessed periodically throughout this long-term study, was found to be comparable to Ventolin and superior to placebo. In an accompanying article, the safety profiles from this 12-week study are shown to be similar for Proventil HFA and Ventolin.\textsuperscript{8}

\section*{MATERIALS AND METHODS}

\subsection*{Patient Population}

Patients 18 to 65 years of age with at least a 12-month history of asthma requiring inhaled \( \beta \)-adrenergic agonists for symptom control were eligible for enrollment. Asthma was stable over the month prior to study entry. (For the purposes of this study, stability was defined as no change in asthma therapy and no asthma-related hospital visits.) Patients were able to withhold treatment with inhaled bronchodilators for at least 8 hours and theophylline products for at least 24 hours prior to pulmonary function testing, had a baseline FEV\(_1\) of 40 to 80\% predicted, and had at least a 15\% increase in FEV\(_1\) within 30 min of inhaling 200 \( \mu \)g of Ventolin (administered as Ventolin Rotacaps with Rotahaler). Patients demonstrated satisfactory technique in the use of a placebo MDI. Women were nonpregnant, nonlactating, and using an acceptable method of contraception. Patients were not eligible for study entry if they had a history of significant concomitant disease, e.g., cardiac arrhythmias, congestive heart failure, hypertension, significant nonreversible pulmonary disease, a recent upper or lower respiratory tract infection, or reported recent (within 4 weeks) use of oral corticosteroids, oral \( \beta \)-adrenergic bronchodilators, monoamine oxidase inhibitors, tricyclic antidepressants, or \( \beta \)-blockers. A smoking history within 2 years of the screening visit was also an exclusion criterion. Prior to entry into the study, all patients provided written informed consent in accordance with participating institutional and US federal guidelines.

\subsection*{Study Design}

This was a randomized, double-blind, double-dummy parallel group, placebo-controlled, multicenter trial. Patients eligible for study entry after screening evaluation underwent a 7-day run-in period, during which they continued taking their usual asthma treatment regimens. At the end of this run-in period, patients were instructed to withhold treatment with theophylline products for 24 h and inhaled bronchodilators and caffeine-containing products for 8 h before reporting to the pulmonary function laboratory between 7 and 10 AM.

Pulmonary function testing was performed using spirometers meeting American Thoracic Society acceptability criteria and according to American Thoracic Society performance criteria.\textsuperscript{9} Predicted values for FEV\(_1\), FVC, and forced expiratory flow over 25 to 75\% of the vital capacity were determined by the method of Crapo et al.\textsuperscript{10} After baseline (pre-dose) spirometry, patients were randomized to one of the three different study drugs and self-administered their assigned study treatment. Serial spirometry was performed over 6 h postdose.

The three treatments were Proventil HFA, Ventolin, or HFA-134a placebo. Proventil HFA is a microcrystalline suspension of albuterol sulfate in ethanol and HFA-134a with oleic acid as a suspending agent. Each puff of Proventil HFA delivers 90 \( \mu \)g albuterol base equivalent from the actuator. Ventolin is a microcrystalline suspension of albuterol base in CFC-11/12 with oleic acid as a suspending agent. Each puff of Ventolin delivers 90 \( \mu \)g of albuterol base from the actuator. HFA-134a placebo consisted of propellant HFA-134a with oleic acid and ethanol. Randomization was stratified so that half of the patients assigned to each study treatment were taking inhaled corticosteroids.

A double-dummy technique was used to blind patients to the identity of their treatment (the MDIs for Proventil HFA and Ventolin were physically different in appearance) and to minimize the possible confounding effect of exposure to two different types of propellants. This was accomplished by preparing three separate placebos for this study. Propellant HFA-134a with ethanol and oleic acid was formulated in both a Proventil HFA MDI (white adapter, 25-\( \mu \)L valve) and a Ventolin MDI (blue adapter, 65-\( \mu \)L valve). Propellants CFC-11/12 with oleic acid were formulated in a Proventil HFA MDI (white adapter, 25-\( \mu \)L valve). Patients randomized to Proventil HFA treatment were given a blue MDI containing HFA-134a placebo and active drug in a white MDI. Patients in the Ventolin group had active drug in a blue MDI and CFC-11/12 placebo in a white MDI. The HFA-134a placebo group had both a blue and a white MDI containing propellant HFA-134a.

Patients were instructed to follow dosing instructions, two puffs from the blue MDI and two puffs from the white MDI qid, throughout the 12 weeks of the active treatment portion of the study. To prevent a possible confounding effect of exposure of the HFA groups to CFCs, Ventolin Rotacaps were used as rescue medication. Every 2 weeks throughout the study, the patients returned to the clinic to review compliance with study drug use and MDI technique. At weeks 4, 8, and 12, patients returned to the pulmonary function laboratory, after observing washout requirements, between 7 and 10 AM for spirometry before dosing with study drug and serially for 6 h postdose.

Safety assessments performed throughout the study are described in the accompanying article.\textsuperscript{9} Study MDIs were collected from patients and weighed. Number of puffs used from each MDI was calculated by dividing
change in MDI weight after patient use by individual puff weight. Patients were considered compliant if calculated number of puffs used was ±40% of predicted.

Data Analysis

The primary efficacy variables were based on actual and percent change in FEV₁ from baseline after dosing with study drug at weeks 0, 4, 8, and 12. A patient was considered a responder at a visit if the FEV₁ exceeded baseline by at least 15% within 30 min postdose at that visit. Time to onset of bronchodilator effect was determined by linear interpolation as that point at which FEV₁ first exceeded 15% over baseline. The peak bronchodilator response, expressed as percent change, was defined as the maximum FEV₁ within 2 h postdose. The time to peak FEV₁ effect was measured as the time point of peak response. Duration of effect was defined as the time of termination of effect minus time of onset, where time of termination equaled the point where FEV₁ fell to 15% above baseline (linear interpolation). The FEV₁ area under the curve (AUC) for bronchodilator effect was calculated using the trapezoidal rule from the time of onset of effect to termination of effect.

At weeks 0, 4, 8, and 12, and for the intent-to-treat database (last data point carried forward), the FEV₁ efficacy responses (except for time to onset of effect) were tested using analysis of variance (ANOVA) with pooled center, inhaled corticosteroid use (yes or no), treatment group, and interactions as factors in the model. Because of the small number of HFA-134a placebo responders, the interaction of treatment with pooled center could not be tested for time to onset of effect. Time to onset of effect was tested using an ANOVA model with pooled center, inhaled corticosteroid use, treatment group, and inhaled corticosteroid user by treatment interaction as factors in the model. Contrasts comparing each active treatment group with HFA-134a placebo and comparing the two active treatments were also done. To maintain an overall type I error rate of 0.05, these contrasts were considered significant for p<0.017 (0.05/3). The mean square error from the ANOVA was used to estimate the SE of the difference in the means of the two active treatments.

A sample size of 150 completing patients per treatment was calculated to provide at least 80% power, with an alpha of 0.05, to detect a 20% difference in FEV₁ response between active treatments. Subgroup analyses were performed on the effect of inhaled and nasal corticosteroid use, age (18 to 35 and 36 to 66 years), sex, race, weight (<60, 60 to 100, and >100 kg), theophylline use, and baseline FEV₁ (≤55% and >55% predicted).

Equivalence of bronchodilator effect for Proventil HFA and Ventolin was assessed by defining equivalence intervals in the protocol as ±20% of the Ventolin mean values for the FEV₁ efficacy variables. Estimates of the difference in the means between the two active treatment groups and the SEs of these mean differences were used to form 90% confidence intervals for the difference in the mean responses, and the two one-sided t test method was used to test the null hypothesis of inequivalence between Proventil HFA and Ventolin.

Post hoc analyses were performed to evaluate the influence of therapy duration on FEV₁ efficacy variables using an ANOVA with treatment, study week (0, 4, 8, and 12), and treatment-study week interactions as factors in the model.

Demographic and baseline characteristics of the separate treatment groups were compared using two approaches. For continuous variables, the null hypothesis that the prestudy treatment group means were equal was tested using an ANOVA with terms for center, treatment, inhaled corticosteroid use, and interactions as factors. For categorical variables with either nominal or dichotomous values, the null hypothesis of marginal homogeneity was tested using categorical linear model methods.

Summary statistics, ANOVA, and categorical linear models were performed using software (SAS version 6.08; Cary, NC). Except where noted, p values ≤0.05 were considered significant.

RESULTS

Patient Population

Five hundred sixty-five patients from 33 sites across the United States were randomized to receive Proventil HFA (193), Ventolin (186), or HFA-134a placebo (186) between June 1993 and April 1994. Demographic and baseline characteristics were similar for the three treatment groups (Table 1). Per the protocol, approximately half of each treatment group was receiving inhaled corticosteroids and all patients had documented reversibility to inhaled albuterol. At study entry, asthma severity varied from mild to severe; 91 (16%) had a baseline FEV₁ below 50% predicted, one indicator of severe asthma at study entry, and 273 (49%) had a baseline FEV₁ above 70%, suggesting mild disease.1,2 Calculated mean compliance with study drug use for each 2-week interval was similar for all three treatment groups and ranged from 87 to 102%. Concomitant asthma medication use in the three treatment groups is shown in Table 2.

Bronchodilator Efficacy

No significant differences were observed between the Proventil HFA and Ventolin treatment groups.

### Table 1—Demographics and Baseline Characteristics at Study Entry

<table>
<thead>
<tr>
<th>Variable</th>
<th>Proventil HFA (n=193)</th>
<th>Ventolin (n=186)</th>
<th>HFA Placebo (n=186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, ±SD</td>
<td>36±12</td>
<td>36±12</td>
<td>36±12</td>
</tr>
<tr>
<td>Sex, F/M†</td>
<td>118/75 (61/39)</td>
<td>113/73 (61/39)</td>
<td>105/81 (56/44)</td>
</tr>
<tr>
<td>Race, W/B/O*†</td>
<td>172/174/4 (89/9/2)</td>
<td>169/15/2 (91/8/1)</td>
<td>169/12/5 (91/6/3)</td>
</tr>
<tr>
<td>Inhaled steroid user, Y/N*†</td>
<td>95/98 (49/51)</td>
<td>96/90 (52/48)</td>
<td>91/95 (49/51)</td>
</tr>
<tr>
<td>Duration of asthma, yr (1-5 yr/≥5 yr)*</td>
<td>33/158 (18/82)</td>
<td>21/165 (11/89)</td>
<td>27/159 (15/85)</td>
</tr>
</tbody>
</table>

*Values are numbers (%).
†W=white; B=black; O=other.
‡Y=yes; N=no.
Table 2—Concomitant Asthma/Allergy Medications Reported by >10% of the Patients in Any Treatment Group*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Proventil HFA (n=193)</th>
<th>Ventolin Placebo (n=186)</th>
<th>HFA Placebo (n=186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled corticosteroids</td>
<td>95 (49.2)</td>
<td>96 (51.6)</td>
<td>91 (48.9)</td>
</tr>
<tr>
<td>Nasal corticosteroids</td>
<td>28 (14.5)</td>
<td>18 (9.7)</td>
<td>19 (10.2)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>53 (27.5)</td>
<td>51 (27.4)</td>
<td>43 (23.1)</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>21 (10.9)</td>
<td>27 (14.5)</td>
<td>13 (7.0)</td>
</tr>
</tbody>
</table>

*Values are numbers (%).

for any FEV₁ efficacy variable during 6-h serial spirometry at weeks 0, 4, 8, and 12. Predose FEV₁ was also similar for the two active treatment groups throughout the study. The comparability of efficacy results for the two active treatments are shown for the intent-to-treat database in Table 3. For all efficacy variables, except time to onset of effect, the Proventil HFA and Ventolin results were significantly greater than placebo. Time to onset of effect for the HFA-134a placebo group is misleading; only 13 patients (7%) were found to be responders in the intent-to-treat database (Table 3). Predose FEV₁ in the HFA placebo group increased over time and was significantly greater than the two active treatment groups at week 12. Significant differences between the bronchodilator efficacy of Proventil HFA and Ventolin were not found in subgroup analyses of inhaled and nasal corticosteroid use, age, sex, race, theophylline use, and baseline FEV₁. Similar results were found for the analyses of forced expiratory flow over 25 to 75% of the vital capacity and FVC (data not shown).

The 90% confidence intervals around the mean difference between the active treatments for all FEV₁ efficacy variables, except time to onset of effect, were contained within the protocol-defined equivalence intervals (p<0.01), implying equivalence of bronchodilator effect for Proventil HFA and Ventolin (Table 4). The 90% confidence intervals around the FEV₁ efficacy variables peak effect, duration of effect, and AUC for Proventil HFA fell within 80 to 120% of the mean CFC values in the intent-to-treat database (Fig 1).

The peak FEV₁ effect, duration of FEV₁ effect, and AUC for FEV₁ were all significantly smaller at weeks 4, 8, and 12 than week 0 for both the Proventil HFA and Ventolin treatment groups (Fig 2). This can be seen by comparing the curves for the change in FEV₁ from predose over the 6 h of serial spirometry at week 0 and week 12 for the two active treatments (Fig 3). Inhaled corticosteroid users had a similar fall in bronchodilator efficacy at weeks 4, 8, and 12 as nonusers.

**DISCUSSION**

Three important conclusions are clear from the results of this study. Bronchodilator efficacy of Proventil HFA is comparable to that of Ventolin. Both Proventil HFA and Ventolin provide superior bronchodilation to HFA-134a placebo. Bronchodilation following Proventil HFA and Ventolin decreased with regular dosing over time.

In developing the new propellant HFA-134a for use with albuterol in MDIs, an important issue is to determine whether the new formulation alters the bronchodilator effectiveness of albuterol. Proventil HFA was designed to have the same medication delivery and particle size distribution as Ventolin (data on file, 3M Pharmaceuticals). This suggests that lung deposition patterns and amounts should be the same for both products. Previous work has shown that acute bronchodilation with Proventil HFA is comparable with Ventolin.5,6 In this study, bron-

Table 3—FEV₁ Efficacy Variables in the Intent-to-Treat Population*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Proventil HFA (73)</th>
<th>Ventolin (74)</th>
<th>HFA Placebo (74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of responders</td>
<td>140/193 (73)</td>
<td>138/186 (74)</td>
<td>13/186 (7)</td>
</tr>
<tr>
<td>Time to onset of effect</td>
<td>6.4±4.8</td>
<td>5.9±4.7</td>
<td>7.8±3.9</td>
</tr>
<tr>
<td>Peak percent change</td>
<td>32.0±25.7</td>
<td>32.9±24.4</td>
<td>7.9±14.4</td>
</tr>
<tr>
<td>Time to peak effect, min</td>
<td>50.6±36.1</td>
<td>45.1±35.1</td>
<td>63.2±44.1</td>
</tr>
<tr>
<td>Duration of effect, h</td>
<td>2.6±2.4</td>
<td>2.7±2.4</td>
<td>0.2±0.9</td>
</tr>
<tr>
<td>AUC, %×h</td>
<td>92.7±121.2</td>
<td>90.9±104.5</td>
<td>5.9±38.4</td>
</tr>
<tr>
<td>Predose FEV₁, L</td>
<td>2.25±0.74</td>
<td>2.25±0.73</td>
<td>2.42±0.80</td>
</tr>
</tbody>
</table>

*Values are either means±SD or number (%).

Table 4—Protocol Defined Equivalence Intervals for FEV₁ Efficacy Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Protocol Defined Equivalence Interval</th>
<th>90% Confidence Interval for Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of responders</td>
<td>±0.14</td>
<td>−0.07 to 0.07*</td>
</tr>
<tr>
<td>Time to onset of effect,</td>
<td>±1.18</td>
<td>−0.42 to 1.41</td>
</tr>
<tr>
<td>Peak percent change</td>
<td>±6.57</td>
<td>−4.62 to 2.98*</td>
</tr>
<tr>
<td>Time to peak effect, min</td>
<td>±9.0</td>
<td>−0.98 to 11.90</td>
</tr>
<tr>
<td>Duration of effect, h</td>
<td>±0.53</td>
<td>−0.41 to 0.30*</td>
</tr>
<tr>
<td>AUC, %×h</td>
<td>±18.16</td>
<td>−14.61 to 18.08*</td>
</tr>
</tbody>
</table>

*Results fall within protocol-defined equivalence interval, p<0.01, implying equivalence of effect for the two active treatments.
The 90% confidence intervals around the FEV₁ efficacy variables, AUC, peak percent change, and duration of effect, for the Proventil HFA group are shown in relation to the mean results, and the 80 to 120% range around these results, for the Ventolin group. Data are from the intent-to-treat database. The 90% confidence intervals for the Proventil HFA results fit within the 80 to 120% range around the Ventolin results, implying equivalence of effects for the two treatments.

Statistical testing for equivalence of bronchodilator effects between inhaled products is not well standardized. The two one-sided t test method showed that for most of the FEV₁ variables, the 90% confidence intervals for the difference between treatment effects fit within protocol-defined equivalence intervals. Expressed in a slightly different way, the 90% confidence interval around mean values for peak FEV₁ change, duration of effect, and FEV₁ AUC for Proventil HFA were within 80 to 120% of the Ventolin mean results. This method could be criticized because the equivalence intervals were arbitrarily established at ±20% of the Ventolin mean values. However, the actual 90% confidence intervals around differences between efficacy results for Proventil HFA and Ventolin were small, indicating that equivalence is clinically reasonable.

An important aspect of this study was the large sample size. Adequate numbers of patients were included with mild, moderate, and severe airway obstruction, in various age groups and using a variety of concomitant medications for asthma control to assure the clinician that a wide spectrum of asthma was represented in this study. The large size of this study allowed subgroup analyses to confirm that the bronchodilator effect of Proventil HFA was similar to that of Ventolin in theophylline users, inhaled and nasal corticosteroid users, older patients, and patients with severe airway obstruction.
Both active treatments provided superior bronchodilation to HFA-134a placebo propellant. This was to be expected. Inclusion of the placebo group allowed an in-depth assessment of the safety of HFA-134a propellant with regular use over an extended period. Review of most safety aspects of this study is provided in the accompanying article. An interesting observation was that predose FEV₁ increased over time in the HFA-134a placebo group and at week 12 was significantly greater in this group than in the two active treatment groups. This may have been due to the larger number of study discontinuations in the HFA-134a placebo group (43) than in the other two groups (29 from each).

Guidelines for treatment of asthma¹,² suggest that inhaled β-adrenergic bronchodilators should be used as needed for symptom control. This study, which was intended to support regulatory approval of Proventil HFA, required asthmatics using inhaled β-adrenergic bronchodilators on an as-needed basis to change to regular use of these products. This design feature, required by the Food and Drug Administration to enable complete safety evaluations, allowed an assessment of the bronchodilator response to Proventil HFA and Ventolin over 12 weeks of regular use. Previous work suggested that regular use of albuterol may lead to a diminished acute bronchodilator response. More recent studies have not supported this observation. With qid dosing of albuterol for 12 weeks to 1 year, the acute bronchodilator response to albuterol remained unchanged, or even improved.¹⁶⁻¹⁸ In this study, serial spirometry over 6 h showed that two puffs of Proventil HFA and Ventolin caused less of a bronchodilator effect after 4 weeks of regular use. The large sample size and the frequency of spirometry testing after dosing distinguished this study from previous work with different findings.¹⁶⁻¹⁸ The reason for this reduced effect is unclear. Possible explanations are drug tachyphylaxis and a statistical regression to the mean based on study entry criteria. Patients were required to demonstrate a >15% improvement in FEV₁ after albuterol to enter this study, but could have undergone reversibility testing on more than one occasion to achieve this requirement.

The reduced bronchodilator response was manifested by both a decrease in peak FEV₁ change and a shorter duration of action. The absolute magnitude of the reduced bronchodilator effect was small. For example, at week 0, the peak absolute change from predose was 0.76 L and 0.74 L for Proventil HFA and Ventolin, respectively. At week 4, the peak absolute change for the two active treatments was 0.67 L and 0.68 L, respectively. Further diminution of effect did not occur over the remaining 8 weeks of the study. The safety assessments in this study suggest that a reduced bronchodilator effect over time did not result in either an increase in adverse events or worsening of asthma control.⁸

In conclusion, in this large study of asthmatics with mild, moderate, and severe disease, Proventil HFA provided bronchodilation comparable to Ventolin and superior effects to placebo over 12 weeks of regular dosing. There was a diminution in bronchodilator response to both Proventil HFA and Ventolin after 4 weeks of use. These data confirm that the reformulation of albuterol in HFA-134a propellant has not altered its bronchodilator effectiveness.

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