Efficacy and Safety of Beclomethasone Dipropionate Extrafine Aerosol in Childhood Asthma*

A 12-Week, Randomized, Double-Blind, Placebo-Controlled Study

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Background: Beclomethasone dipropionate (BDP) has been formulated as an extrafine aerosol (hydrofluoroalkane-134a [HFA]-BDP) [QVAR; 3M Pharmaceuticals; St Paul, MN], which gives improved lung deposition compared with chlorofluorocarbon (CFC)-BDP. The clinical efficacy of HFA-BDP has been established in adult asthma at a required dose below that of CFC-BDP, but has not been evaluated in children.

Objective: To examine the efficacy and safety of HFA-BDP in childhood asthma.

Design: A 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study involving 353 children aged 5 to 12 years with moderate, symptomatic asthma. After a 2-week run-in period, patients were randomized to HFA-BDP, 80 µg/d (n = 115); HFA-BDP, 160 µg/d (n = 117); or HFA-placebo (n = 116) administered twice daily.

Setting: Hospital outpatient.

Results: HFA-BDP, 80 µg/d and 160 µg/d, produced a significant, dose-related increase from baseline in FEV₁ percent predicted compared with placebo. At week 12, mean changes from baseline in FEV₁ percent predicted were 9.2% (p < 0.01 vs placebo), 10% (p < 0.01 vs placebo), and 3.9% for the HFA-BDP 80 µg/d, HFA-BDP 160 µg/d, and placebo groups, respectively. There was also a significant decrease in daily β-agonist use, improvement in peak expiratory flow, and reduction in the percentage of days free from asthma symptoms (p < 0.05 for HFA-BDP, 160 µg/d, vs placebo at weeks 11 to 12). HFA-BDP was well tolerated, with no significant differences in the incidence or nature of adverse events between HFA-BDP and placebo groups. Neither were there significant differences between groups in mean percentage change from baseline in the morning plasma cortisol level at week 12 or in the percentage of patients with morning plasma cortisol levels below the reference range at baseline and week 12. In a subgroup tested, the percentage of patients with an abnormal response to low-dose adrenocorticotropic hormone stimulation at week 12 was low and similar among all groups.

Conclusions: HFA-BDP, 80 to 160 µg/d, is effective and safe in childhood asthma.

Key words: asthma; children; extrafine aerosol; hydrofluoroalkane-beclomethasone dipropionate

Abbreviations: ACTH = adrenocorticotropic hormone; BDP = beclomethasone dipropionate; CFC = chlorofluorocarbon; HFA = hydrofluoroalkane-134a; PEF = peak expiratory flow; pMDI = pressurized metered-dose inhaler

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much smaller particles than CFC-BDP (median particle size, 1.1 μm vs 3.5 μm, respectively).1

With its smaller median particle size, HFA-BDP has been shown to improve drug delivery compared with CFC-BDP in both adults and children, with a greater proportion of the drug deposited in the small airways and less deposited in the throat.3–7 Indeed, a recent deposition study in children with asthma has shown that three times as much BDP is delivered to the intrapulmonary airways with HFA-BDP compared with CFC-BDP.8 Enhanced delivery of inhaled corticosteroids is an important consideration in children with asthma, who have smaller caliber airways than adults. Moreover, improved lung deposition with HFA-BDP compared with CFC-BDP provides an opportunity to maintain asthma control adequately using a lower dose of BDP.

Inhaled corticosteroids can cause systemic adverse effects, such as adrenal suppression, short-term growth retardation, and a decrease in bone mineral density/bone loss, particularly when used in high doses.9,10 These systemic adverse effects generally occur when an inhaled corticosteroid is absorbed through the upper airway mucous membranes or when it is not rapidly metabolized (eg, when it is absorbed via the gut). Studies in adults have shown that, despite its improved lung deposition leading to a higher lung dose, HFA-BDP has a favorable safety profile (systemic and overall) compared with other inhaled corticosteroids.11–17

This 12-week study was designed to assess whether HFA-BDP is effective and safe in childhood asthma. The primary objective of the study was to determine whether HFA-BDP at lower doses than are normally used with CFC-BDP (80 μg/d and 160 μg/d) has superior efficacy over HFA-placebo in improving asthma control in children with symptomatic asthma of moderate severity.

**Materials and Methods**

**Patients**

Patients eligible to enter this hospital outpatient study were children aged 5 to 12 years with stable, moderate, symptomatic asthma of at least 6 months in duration, and receiving short-acting inhaled β-agonist therapy on an as-needed basis. Other inclusion criteria included the following: FEV₁ between 50% and 80% of predicted after withholding short-acting, inhaled β-agonist therapy for 4 h; demonstration of an increase in FEV₁ of ≥ 12% following inhalation of 400 μg (two puffs) of pirbuterol; and use of inhaled β-agonist therapy (pirbuterol) at least once a day on at least 50% of the days in the 2-week run-in period. Patients had two opportunities to meet the first two criteria, separated by at least 24 h.

Exclusion criteria included the following: any significant, non-reversible pulmonary disease other than asthma; evidence of any clinically significant immunologic, neoplastic, endocrine, hematoologic, cardiac, hepatic, renal, GI, neurologic or psychiatric abnormalities or illness; an upper or lower respiratory tract infection within 2 weeks or 4 weeks, respectively, prior to screening or during the run-in period; known hypersensitivity to BDP; and use of injectable, oral, or inhaled corticosteroids within 6 months, 8 weeks, and 6 weeks, respectively, of the start of the study. Use of other asthma maintenance therapies (eg, long-acting β-agonists and leukotriene receptor antagonists) was not permitted.

The study was conducted in accordance with the Code of Federal Regulations of the US Food and Drug Administration and the Declaration of Helsinki (Republic of South Africa, 1996). After a full explanation of the study, patients gave their verbal assent and their parents or legal guardians gave written consent prior to study entry. Patients could withdraw or be withdrawn from the study at any time. If the patient discontinued study treatment due to an asthma exacerbation, other adverse event, or laboratory finding, the event leading to discontinuation was treated or followed up to a satisfactory resolution as determined by the investigator.

**Study Design**

This was a 12-week, randomized, double-blind, placebo-controlled, parallel-group study involving 50 centers across the United States. At the end of a 2-week, placebo run-in period (study day 1), eligible patients were assigned a unique study number and randomized using a computer-produced randomization schedule to one of the following treatments: HFA-BDP, 80 μg (one puff bid from the 40-μg, ex-actuator-strength inhaler [50 μg ex-valve]); HFA-BDP, 160 μg (one puff bid from the 80-μg, ex-actuator-strength inhaler [100 μg ex-valve]); or HFA-placebo (one puff bid). All treatments were delivered using the Autohaler breath-actuated device (3M Pharmaceuticals). This device was used to maximize compliance with study medication by eliminating difficulties in coordinating actuation and inspiration, a problem that children may have when using conventional pMDIs. A study in adults has shown that the Autohaler is bioequivalent to the pMDI used with excellent technique.18

Clinic visits took place every 2 weeks during the 12-week treatment phase for lung function testing (spirometry), assessment of adverse events, and review of diary cards. Patients were provided with a short acting β-agonist (pirbuterol) for use as required. Patients were instructed to withhold their inhaled β-agonist for at least 4 h before lung function testing.

**Efficacy Assessments**

The primary efficacy measure was mean change from baseline in FEV₁ percent predicted at the end of the study. FEV₁ was assessed at each clinic visit by spirometry, which was performed according to the American Thoracic Society Standardization of Spirometry guidelines (1995).19 The value recorded for FEV₁ was the highest of three American Thoracic Society-acceptable curves from three separate tests. The predicted value for FEV₁ was determined using the prediction equation of Polgar and Promadhat.20 No correction was made for race, as the study population was primarily white in origin.

Secondary efficacy measures included morning and evening peak expiratory flow (PEF), daily asthma symptom scores, and total daily β-agonist use. Morning and evening PEF values were measured daily by patients or guardians at their homes using a MiniWright peak flowmeter (Clement Clarke; Columbus, OH). Patients or guardians recorded the highest of three PEF measurements in the morning and three in the evening on their diary cards before using their study medication. Each evening, patients
or guardians also recorded asthma symptoms that occurred during the day on their diary cards. Wheezing, shortness of breath, chest tightness, and cough were each scored on a 4-point scale (0 = none, 1 = mild symptoms not affecting normal daily activities, 2 = moderate symptoms affecting some of normal daily activities, 3 = severe symptoms, unable to carry out normal daily activities). For daily β-agonist use, patients or guardians recorded the total number of puffs used during the day and night, relying on their child’s reporting and on their own personal observations.

Safety Assessments

Details of all reported adverse events were recorded at each clinic visit, including the severity, duration, apparent relationship to study treatment, precipitating factors, action taken, and outcome. A serious adverse event was defined as one that resulted in death, a life-threatening experience, inpatient hospitalization or prolongation of an existing hospitalization, or a persistent or significant disability/incapacity.

Pulse rate and BP were recorded at the screening visit and at week 12. Standard hematology, serum chemistry, and special laboratory tests, including measurement of morning plasma cortisol and low-dose adrenocorticotropic hormone (ACTH 1–24) [Cortrosyn; Organon; West Orange, NJ] stimulation testing, were performed on blood samples collected from patients in a resting state at the screening visit and at week 12. All blood samples for plasma cortisol measurements were drawn prior to 9 AM following a 10-min rest, and prior to, or at least 30 min after, lung function testing. The plasma cortisol sample obtained at week 12 was required to be drawn within 15 min of the time at which the sample was drawn at the screening visit.

ACTH stimulation testing, which provides a sensitive, indirect measure of adrenal function in patients with asthma receiving inhaled corticosteroids, was only performed in a subset of patients from 13 centers on the basis of their willingness to undergo the test. For low-dose ACTH stimulation testing, blood samples were collected in the morning via an IV catheter before injection of ACTH and at 15 min, 30 min, and 45 min after injection for the determination of plasma cortisol levels. Doses of ACTH were calculated according to body surface area (1 µg/1.73 m²).

Statistical Analysis

All statistical analyses were performed on the intent-to-treat population, which included all patients who received at least one dose of study medication. Prestudy estimates for the mean change from baseline in FEV₁ percent predicted at the end of the study were 0% for placebo-treated patients and +7.5% for patients treated with HFA-BDP. The SD of the change from baseline in FEV₁ percent predicted was assumed to be approximately 12%. Given these estimates, it was presumed that a sample size of 65 patients for each treatment group would provide at least 90% power for testing the null hypothesis for each active treatment group at the α = 0.025 level. The sample size was increased to 126 per group to account for a possible 20% withdrawal rate and a 35% noncompliance rate.

For the primary efficacy measure (mean change from baseline in FEV₁ percent predicted at the end of study), the null hypothesis for each active treatment group was tested using an analysis of variance model, with terms for treatment group and center included in the model. If the overall F test was significant at the α = 0.05 level, comparisons of each active treatment with placebo were performed using the Dunnett multiple comparison test. A trend test (Jonckheere test, with treatment and center terms included) was employed to assess the increasing effect on change from baseline to end of study in FEV₁ percent predicted as the dose of BDP increased (from placebo to HFA-BDP 80 µg to HFA-BDP 160 µg).

Secondary efficacy measures (morning and evening PEF, daily asthma symptom scores, and total daily β-agonist use) were analyzed using the same methods. These measures were averaged over each 2-week period, with baseline values taken as the average of values recorded in the last 7 days of the run-in period. For asthma symptom scores, the percentage of days on which the patients did not have the symptom (ie, a reported score of 0) was determined for each patient for each biweekly interval.

Survival curves of time to onset of first asthma exacerbation or increased asthma symptoms were compared using a Wilcoxon test. Estimates of time without an exacerbation or increased symptoms were based on Kaplan-Meier estimates.

With regard to safety, the percentage of patients reporting adverse events in each treatment group was compared using a two-sided Fisher exact test. The secondary safety variable (percentage change from baseline in morning plasma cortisol at week 12) was analyzed using the same methods as those employed for the primary efficacy measure.

The results of the low-dose ACTH stimulation tests were analyzed by determining the increment value (the largest increase in plasma cortisol concentration at 15 min, 30 min, or 45 min after ACTH injection) and peak value (the maximum plasma cortisol concentration at 15 min, 30 min, or 45 min after ACTH injection). Each patient’s ability to obtain a normal response to the ACTH stimulation test was then evaluated. A patient was considered to show a normal response if they achieved two of the three following criteria: prestimulation cortisol level > 138 nmol/L, increment of at least 200 nmol/L above baseline, and increase in cortisol to a peak value of at least 500 nmol/L. The distribution of patients was compared between treatment groups using the Cochran-Mantel-Haenszel test, stratified by study center.

Treatment Compliance

All study inhaler canisters were weighed before dispatch to the study sites and after being returned by the patient. Predicted and actual inhaler canister weights were converted to number of doses administered using mean actuation weights. A patient was considered compliant if the calculated overall total number of actuations fired from the inhaler used during the study was 60 to 140% of that predicted for ideal compliance.

Results

Patients

A total of 684 children were screened for entry into the study. Of those, 353 children were found to be eligible and were randomized to receive either HFA-BDP, 80 µg/d (n = 120); HFA-BDP, 160 µg/d (n = 117); or HFA-placebo (n = 116). These patients constituted the intent-to-treat population.

Baseline characteristics and lung function were similar across the three treatment groups (Table 1). Approximately 85% of patients had an FEV₁ percent predicted between 60% and 80% at baseline; approximately 12% had an FEV₁ < 60% predicted. In terms of drug therapy history, 99.7% of patients were...
receiving short-acting β-agonist therapy prior to the study and 32.6% were receiving antihistamines. Only 0.8% of patients were receiving long-acting β-agonist therapy. The most common comorbid medical conditions were allergic rhinitis (reported by 75.1% of patients), symptoms involving the head and neck (24.9%), contact dermatitis (13.9%), and otitis media (13.3%). During the study, three patients (2.5%) in the HFA-BDP 80 µg/d group and one patient (0.9%) in the HFA-BDP 160 µg/d group received concomitant oral steroids. These patients were excluded from evaluable for safety and efficacy analyses from the time they received oral steroids.

Of the 353 randomized patients, 15 patients (4.2%) in the HFA-BDP 80 µg/d group, 9 patients (2.5%) in the HFA-BDP 160 µg/d group, and 19 patients (5.4%) in the placebo group withdrew prematurely. The most common reason for withdrawal was asthma exacerbations (5.7% of patients). More patients in the placebo group (9.5%) withdrew for this reason than in the HFA-BDP treatment groups (5.8% and 1.7% in the HFA-BDP 80 µg/d and HFA-BDP 160 µg/d groups, respectively). Only one patient (in the HFA-BDP 80 µg/d group) was withdrawn due to noncompliance with study medication.

**Efficacy**

**FEV₁:** Treatment with HFA-BDP resulted in a significant improvement in lung function (Fig 1). The mean change from baseline at week 12 in FEV₁ percent predicted (primary efficacy measure) was significantly greater than placebo for both HFA-BDP treatment groups (p ≤ 0.01). At week 12, the mean changes from baseline in FEV₁ percent predicted were 9.2%, 10.0%, and 3.9% for the 80 µg/d, 160 µg/d, and placebo groups, respectively. Furthermore, the mean change from baseline in FEV₁ percent predicted in the HFA-BDP 160 µg/d group was significantly different from placebo at all time points (p ≤ 0.05; Fig 1). In the HFA-BDP 80 µg/d group, the mean change from baseline in FEV₁ percent predicted was significantly different from placebo at all treatment weeks (p ≤ 0.05) except week 10 (p ≤ 0.1). These results were homogeneous between study centers. The Jonckheere trend test for the mean change from baseline in FEV₁ percent predicted at week 12 demonstrated a statistically significant trend toward greater improvement with increasing doses of HFA-BDP (p = 0.001).

The mean percentage change from baseline in absolute FEV₁ showed a similar trend. At week 12, the mean percentage change from baseline in absolute FEV₁ was 13.3% and 14.5% for the HFA-BDP 80 µg/d and 160 µg/d groups, respectively, compared with 5.7% for the placebo group (p ≤ 0.01, HFA-BDP 80 µg/d or 160 µg/d vs placebo). The percentages of patients who demonstrated an increase in FEV₁ of ≥ 12% (indicating a clinically relevant improvement in lung function) were 45.3% (p = 0.03 vs placebo), 57.8% (p = 0.001 vs placebo), and 34.2% in the 80 µg/d, 160 µg/d, and placebo treatment groups, respectively. The high proportion of patients reporting an increase in FEV₁ of ≥ 12% in the placebo group was unexpected, and no apparent explanation could be found for this.

**Secondary Efficacy Variables:** As with FEV₁, treatment with HFA-BDP also significantly improved PEF. In the 160 µg/d group, the mean change from baseline in morning PEF was significantly greater than placebo at all treatment weeks (p ≤ 0.01). At weeks 11 to 12, the mean change from baseline in morning PEF in the 160 µg/d group was 30.8 L/min compared with 9.2 L/min in the placebo group (p ≤ 0.01). In the 80 µg/d group, the mean

### Table 1—Baseline Characteristics and Lung Function

<table>
<thead>
<tr>
<th>Variables</th>
<th>HFA-BDP, 80 µg/d (n = 120)</th>
<th>HFA-BDP, 160 µg/d (n = 117)</th>
<th>HFA-Placebo (n = 116)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, No. (%)</td>
<td>80 (66.7)</td>
<td>67 (57.3)</td>
<td>77 (66.4)</td>
<td>0.31</td>
</tr>
<tr>
<td>Mean age (SD), yr</td>
<td>9.4 (2.0)</td>
<td>8.9 (1.9)</td>
<td>9.3 (2.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>White race, No. (%)</td>
<td>94 (78.3)</td>
<td>86 (73.5)</td>
<td>94 (81.0)</td>
<td>0.71</td>
</tr>
<tr>
<td>Asthma duration, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 yr</td>
<td>1 (0.8)</td>
<td>1 (0.9)</td>
<td>2 (1.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>1–5 yr</td>
<td>43 (35.8)</td>
<td>46 (39.3)</td>
<td>53 (45.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>&gt; 5 yr</td>
<td>76 (63.3)</td>
<td>70 (59.8)</td>
<td>61 (52.6)</td>
<td>0.42</td>
</tr>
<tr>
<td>Mean FEV₁ (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual value, L</td>
<td>1.6 (0.4)</td>
<td>1.5 (0.4)</td>
<td>1.6 (0.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>% predicted</td>
<td>71.8 (7.3)</td>
<td>72.3 (7.7)</td>
<td>71.0 (7.8)</td>
<td>0.42</td>
</tr>
<tr>
<td>Mean morning PEF (SD), L/min</td>
<td>232.5 (62.9)</td>
<td>217.0 (65.4)</td>
<td>235.4 (70.0)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*p Value for overall treatment comparison based on an analysis of variance or categorical linear model with treatment and pooled center terms included.
change from baseline in morning PEF was greater than placebo at all treatment weeks; however, a statistically significant difference was evident only at weeks 1 to 2 (p ≤ 0.05). Results for evening PEF were comparable to those seen for morning PEF.

HFA-BDP also significantly increased the percentage of days free from any asthma symptoms compared with placebo (Table 2). For HFA-BDP 160 µg/d, a significant improvement over placebo in the mean change from baseline in the percentage of days free from any asthma symptoms was observed from weeks 7 to 8 onwards (p ≤ 0.05). A significant improvement over placebo was also seen with HFA-BDP 80 µg/d at weeks 7 to 8 and weeks 9 to 10 (p ≤ 0.05).

In addition, treatment with HFA-BDP resulted in a significant reduction in daily β-agonist use (Fig 2). For HFA-BDP 160 µg/d, the mean change from baseline in daily β-agonist use was significantly different from placebo at all time points (p ≤ 0.05). Although this was a statistical difference, the clinical significance of decreasing daily β-agonist use by one puff or less is unclear. Although β-agonist use was reduced from baseline with HFA-BDP 80 µg/d, this was not significantly different from placebo.

Kaplan-Meier analysis revealed a trend toward a later onset of time to first asthma exacerbation or increased symptoms with increasing doses of HFA-BDP (Fig 3). However, an overall between-treatment comparison showed no statistically significant differences between the three treatment groups (p = 0.18).

Safety

Of the 353 randomized patients, 249 patients (70.5%) reported at least one adverse event, with

<table>
<thead>
<tr>
<th>Table 2—Percentage of Days Free From Any Asthma Symptoms*</th>
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</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Absolute change from baseline</td>
</tr>
<tr>
<td>Weeks 1–2</td>
</tr>
<tr>
<td>Weeks 3–4</td>
</tr>
<tr>
<td>Weeks 5–6</td>
</tr>
<tr>
<td>Weeks 7–8</td>
</tr>
<tr>
<td>Weeks 9–10</td>
</tr>
<tr>
<td>Weeks 11–12</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SE).
†p ≤ 0.05 vs placebo (Dunnett test).
‡p ≤ 0.01 vs placebo.

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similar proportions of patients reporting at least one adverse event in each treatment group (Table 3). The most frequently reported adverse events were respiratory system disorders.

Fourteen patients (3.9%) reported adverse events that the investigators considered to be probably or possibly related to study treatments. These adverse events included only one respiratory system disorder.
(increased asthma symptoms in the HFA-BDP 160 µg/d group). Most adverse events in each treatment group were categorized as mild or moderate in severity. Seven patients (5.8%) in the HFA-BDP 80 µg/d group, three patients (2.6%) in the 160 µg/d group, and nine patients (7.8%) in the placebo group reported a severe adverse event. In the placebo group, most of the severe adverse events were respiratory system disorders (seven patients), with four of the seven patients reporting at least one adverse event of increased asthma symptoms.

Two patients withdrew from the study due to adverse events. One patient in the HFA-BDP 80 µg/d group withdrew due an upper respiratory tract infection, and one patient in the 160 µg/d group withdrew due to insomnia and nervousness. Only one patient (HFA-BDP 160 µg/d group) reported a serious adverse event (asthma exacerbation and respiratory infection, resulting in one hospitalization).

Mean morning plasma cortisol levels increased from baseline to week 12 in all three treatment groups, with no statistically significant differences among the groups. The mean percentage changes from baseline in morning plasma cortisol at week 12 were +41.4%, +41.0%, and +35.4% for the 80 µg/d, 160 µg/d, and placebo groups, respectively. The percentage of patients with morning plasma cortisol below the reference range (166 to 828 nmol/L) at week 12 was reduced from baseline in both HFA-BDP treatment groups, but remained the same in the placebo group (Table 4); there were, however, no significant differences among the treatment groups.

For those patients who had morning plasma cortisol levels measured at baseline and week 12, baseline values were distributed at the low end of the normal range. Box and whisker plots demonstrated that median morning plasma cortisol levels in all three treatment groups moved toward the middle of the normal range at week 12, indicating that adrenal suppression was not induced by study treatment (Fig 4). In a subgroup of patients tested (n = 61), very few showed an abnormal response to low-dose ACTH stimulation at baseline or week 12, with no statistically significant differences between treatment groups at either time point (Table 5).

No clinically meaningful changes in serum chemistry or hematology were noted during the study in any treatment group. Similarly, there were no clinically meaningful or statistically significant changes in pulse rate, BP, or physical examination findings at any time point across the three treatment groups.

**DISCUSSION**

HFA-BDP has been shown to improve drug delivery to the lungs in children compared with conventional CFC-BDP. Improved drug delivery presents an opportunity to achieve and maintain clinical efficacy using a lower dose of BDP. The 80 µg/d dose of HFA-BDP was chosen for this study in an attempt to demonstrate efficacy at a dose below that recommended for CFC-BDP in children. The higher dose of 160 µg/d was chosen to assess whether there is a dose-response relationship between placebo and increasing doses of HFA-BDP.

**Table 3—Frequency of Overall and Respiratory System Adverse Events Reported by ≥ 3% of Patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>HFA-BDP, 80 µg/d (n = 120)</th>
<th>HFA-BDP, 160 µg/d (n = 117)</th>
<th>HFA-Placebo (n = 116)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one adverse event</td>
<td>84 (70)</td>
<td>83 (71)</td>
<td>82 (71)</td>
<td>0.99</td>
</tr>
<tr>
<td>Acute asthma episode</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>6 (5)</td>
<td>0.27</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (6)</td>
<td>9 (8)</td>
<td>9 (8)</td>
<td>0.84</td>
</tr>
<tr>
<td>Increased asthma symptoms</td>
<td>14 (12)</td>
<td>12 (10)</td>
<td>22 (19)</td>
<td>0.12</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>13 (11)</td>
<td>9 (8)</td>
<td>13 (11)</td>
<td>0.61</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>21 (18)</td>
<td>23 (20)</td>
<td>22 (19)</td>
<td>0.93</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>34 (28)</td>
<td>24 (21)</td>
<td>26 (22)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%).
†p Value for overall treatment comparison based on two-sided Fisher exact test.

**Table 4—Patients With Morning Plasma Cortisol Levels Below the Reference Range**

<table>
<thead>
<tr>
<th>Variables</th>
<th>HFA-BDP, 80 µg/d (n = 111)</th>
<th>HFA-BDP, 160 µg/d (n = 110)</th>
<th>HFA-Placebo (n = 104)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24 (21.6)</td>
<td>17 (15.5)</td>
<td>16 (15.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Week 12</td>
<td>12 (10.8)</td>
<td>8 (7.3)</td>
<td>16 (15.4)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%).
†p Value for overall treatment comparison based on two-sided Fisher exact test. Patients had to have data from both study time points to be included in the analysis.
Children selected for the study were those who would be expected to benefit from treatment with inhaled corticosteroids, according to National Heart, Lung, and Blood Institute guidelines, based on their asthma symptoms, β-agonist use, and decreased lung function.23

Studies in adults have shown that HFA-BDP is effective in improving asthma control in patients with symptomatic asthma.2,12,15,24–29 The results from this pediatric study demonstrate that HFA-BDP (80 to 160 μg/d) is also effective in improving asthma control in children with moderate, symptomatic asthma. The mean change from baseline in FEV1 percent predicted at the end of the study (the primary efficacy measure) was significantly superior to placebo for both doses of HFA-BDP, with a general dose-response trend seen among the treatment groups. In addition, a significantly higher proportion of HFA-BDP–treated patients showed a clinically relevant improvement in lung function (as determined by a ≥12% increase in FEV1 from baseline at end of study) than placebo-treated patients.23 Analysis of secondary efficacy measures (morning and evening PEF, daily asthma symptom scores, and daily β-agonist use) further supported the beneficial effect of HFA-BDP.

The magnitude of improvement in lung function observed in this study is similar to that reported in pediatric studies evaluating the efficacy of comparable doses (100 to 200 μg/d) of inhaled fluticasone propionate dry powder,30,31 and is slightly higher than that reported in studies investigating the efficacy of equivalent doses (200 to 400 μg/d) of inhaled budesonide dry powder.32,33 In these 12-week, randomized, double-blind, placebo-controlled studies in children with mild-to-moderate asthma, mean change from baseline in FEV1 percent predicted ranged from 6.5 to 12.7% in children who received fluticasone propionate, 200 μg/d, and from 3.3 to 7.3% in children who received budesonide, 400 μg/d. This compares with a change from baseline in FEV1 of 10% predicted with 160 μg/d of HFA-BDP in this study. It should be noted that, unlike in this study, most patients who received fluticasone or budesonide had been treated previously with inhaled corticosteroids. In an 8-week, randomized, double-blind, placebo-controlled trial of the leukotriene receptor antagonist, montelukast (5 mg/d), in children with mild-to-moderate asthma (as monotherapy or as add-on therapy to inhaled corticosteroids), there was an increase in FEV1 of 8.2% from baseline at the end of the study, which is slightly lower than that reported for HFA-BDP (80 to 160 μg/d) in this study.34

A gradual improvement in efficacy measures was also observed in placebo-treated patients, which is not uncommon in this type of study.35 This may have
been due to the fact that all patients and their parents/guardians received education about their asthma, which could have heightened awareness of how to identify and reduce exposure to allergens and environmental triggers of asthma, resulting in a change in their behavior and subsequent improvement in their asthma (sometimes referred to as the "Hawthorne effect").

There were no differences in the tolerability profiles of HFA-BDP and placebo, with a similar percentage of patients reporting at least one adverse event in each treatment group. Although the overall incidence of adverse events in all three groups was quite high, most were mild in severity, and very few were considered to be related to study treatment. The nature of adverse events reported with HFA-BDP was consistent with that seen in adult studies2,17 and, as in the adult studies, most adverse events were related to respiratory system disorders.

Pediatric deposition studies have shown that HFA-BDP has a similar lung deposition in children as it does in adults and that this is higher than that reported for other inhaled corticosteroids.6,7 Improved lung deposition of HFA-BDP allows the use of lower doses compared with CFC-BDP while maintaining equivalent efficacy. This has the potential to decrease the risk of systemic side effects. The results of this study demonstrate that the systemic effects of HFA-BDP, as measured by change from baseline in morning plasma cortisol levels, are no different from placebo. Responses to low-dose ACTH stimulation in HFA-BDP-treated patients were also no different from placebo. However, these ACTH-stimulation response data should be interpreted cautiously, due to the small number of patients tested.

Some patients in this study had morning plasma cortisol levels below the chosen reference range at baseline, but no apparent explanation could be found for this. In all three treatment groups, the percentage of patients with morning plasma cortisol levels below the reference range either decreased from baseline to week 12 (both HFA-BDP treatment groups) or remained the same (placebo group), again indicating that HFA-BDP causes no decline in adrenal function. The magnitude of increase from baseline to week 12 in morning plasma cortisol levels in the HFA-BDP treatment groups was also unexpected, and may suggest that some patients had been exposed to a drug or event prior to study entry that resulted in suppression of adrenal function.

A recently reported, 1-year, open-label, pediatric safety study also demonstrated that HFA-BDP at 80 to 160 μg/d has no adverse effect on adrenal function.36 In this long-term study, 24-h urinary-free cortisol levels increased in the HFA-BDP group, as observed with morning plasma cortisol levels in this study, confirming that HFA-BDP does not suppress adrenal cortisol secretion. The results of both of these pediatric studies of HFA-BDP are consistent with those reported for low doses of other inhaled corticosteroids, such as fluticasone propionate and budesonide. Several studies have demonstrated that there is no clinically significant effect on adrenal function when low doses of inhaled fluticasone (up to 200 μg/d) or budesonide (up to 400 μg/d) are administered to children with asthma.30–32,37

**Conclusion**

In conclusion, the results of this study indicate that HFA-BDP extrafine aerosol at doses of 80 and 160 μg/d is an effective and safe treatment option in childhood asthma.

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