

Growth, Systemic Safety, and Efficacy During 1 Year of Asthma Treatment With Different Beclomethasone Dipropionate Formulations: An Open-Label, Randomized Comparison of Extrafine and Conventional Aerosols in Children

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ABSTRACT. *Objective.* To assess the long-term safety of hydrofluoroalkane 134a (HFA)-beclomethasone dipropionate (BDP) extrafine aerosol administered by the Autohaler compared with chlorofluorocarbon (CFC)-BDP administered by a press-and-breathe metered-dose inhaler (pMDI) and spacer (+S) in the treatment of children with asthma.

Methods. This 12-month, open-label, randomized, multicenter study enrolled 300 children who were aged 5 to 11 years and had well-controlled asthma on inhaled CFC-BDP or budesonide; 256 patients were using doses within the recommended range (200–400 µg) and were analyzed separately. Patients were randomized in a 1:3 ratio to continue on CFC-BDP+S at approximately the same dose as they were using before study entry or switch to HFA-BDP at half the daily dose.

Results. Asthma control was well maintained in the HFA-BDP group as evidenced by lung function tests and asthma symptoms compared with CFC-BDP+S at approximately twice the dose. There were no significant differences between the HFA-BDP 100 to 200 µg and CFC-BDP+S 200 to 400 µg treatment groups in mean change from baseline in height (5.23 cm vs 5.66 cm at month 12, respectively) or mean growth velocity from day 1 to month 12 (5.27 cm/y vs 5.71 cm/y, respectively). There were no significant differences between groups in adrenal function tests or markers of bone metabolism.

Conclusions. In this long-term study in children with asthma, extrafine HFA-BDP provided long-term maintenance of asthma control at approximately half the dose compared with CFC-BDP+S. There were no clinically meaningful differences between HFA-BDP extrafine aerosol and conventional CFC-BDP+S with regard to growth or other systemic effects. *Pediatrics* 2002;109(6). URL: <http://www.pediatrics.org/cgi/content/full/109/6/e92>

e92; children, asthma, inhaled corticosteroid, CFC-free, hydrofluoroalkane-134a beclomethasone dipropionate, growth.

ABBREVIATIONS. BDP, beclomethasone dipropionate; CFC, chlorofluorocarbon; HFA, hydrofluoroalkane; pMDI, press-and-breathe metered-dose inhaler; +S, plus spacer; FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow; PICP, carboxy propeptide of procollagen type 1; 1-CTP, 1-collagen telopeptide; ACTH, adrenocorticotrophic hormone; UFC, urinary free cortisol; EPX, eosinophilic protein X; CI, confidence interval.

Inhaled corticosteroids, such as beclomethasone dipropionate (BDP), have been used effectively for many years for the treatment of asthma in both adults and children. However, high doses of inhaled corticosteroids in children may affect biochemical markers of bone formation and resorption and short-term lower leg growth.¹ Therefore, it is important to assess the long-term safety of inhaled corticosteroid preparations in children with asthma, while maintaining efficacy.

A new chlorofluorocarbon (CFC)-free formulation of BDP, hydrofluoroalkane-134a (HFA)-BDP extrafine aerosol, has been developed in a press-and-breathe metered-dose inhaler (pMDI) and in a breath-activated device (QVAR Autohaler; 3M Pharmaceuticals, St Paul, MN). Breath actuation may assist children who have difficulties in coordinating the actuation and inspiration required during the use of conventional pMDIs. These new BDP pressurized-solution inhalers produce an extrafine aerosol of medication that consists of much smaller particles than those produced from traditional CFC-BDP inhalers. Thus, the pattern of drug deposition with HFA-BDP is improved, with a greater proportion of drug deposited in the small airways (those <2 mm in diameter) and less deposited in the throat, compared with CFC-BDP.^{2,3} Improved delivery to the airways has resulted in the opportunity to maintain asthma control with a lower dose of corticosteroid. Topical delivery of inhaled medication to the inflammation present in the small airways is particularly important in children, because a greater proportion of the child's lungs comprises small airways compared with adult lungs.

Clinical studies in adult patients have shown a favorable safety profile of HFA-BDP at approxi-

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mately half the dose (with improvements in asthma control) compared with conventional CFC-BDP.⁴⁻⁷ However, the safety profile of HFA-BDP extrafine aerosol has yet to be fully determined in children.

The primary objective of this study was to assess the long-term safety profile of HFA-BDP administered by the breath-actuated Autohaler device compared with CFC-BDP administered by a pMDI and large volume spacer (+S; CFC-BDP+S) during 12 months of treatment of children with asthma. In addition, efficacy assessments were conducted to confirm the relative efficacies of these 2 formulations during long-term treatment.

METHODS

Patients

Girls who were between the ages of 5 and 10 years and boys who were between the ages of 5 and 11 years and had a clinical diagnosis of asthma⁸ extending back for ≥ 6 months from the prestudy visit were eligible for inclusion in the study. Patients were also required to have asthma symptoms that remained stable during the previous month on 200 to 800 $\mu\text{g}/\text{d}$ (ex-valve) BDP or budesonide from a pMDI (+ or -S) or a dry powder inhaler with inhaled short-acting β -agonist on an as-needed basis, and a prestudy forced expiratory volume in 1 second (FEV_1) of $\geq 60\%$ of predicted normal after withholding inhaled β -agonist for 4 hours. Eligible patients demonstrated the need for inhaled steroid treatment (before starting inhaled corticosteroid therapy) by 1 or more of the following criteria: need for β -agonist at least once daily; asthma symptoms not controlled on cromoglycate, nedocromil sodium, theophylline plus as-needed β -agonist; bronchial hyper-responsiveness; exercise-induced asthma not prevented by previous β -agonist use; nighttime symptoms other than cough; and diurnal peak expiratory flow (PEF) variation (morning [AM] to evening [PM]) $\geq 20\%$. Patients had to demonstrate satisfactory technique in the use of the Autohaler, a pMDI+S, and a pediatric Mini-Wright (Clement Clarke International Ltd, Essex, England) peak flow meter; provide reproducible pulmonary function test results; and be willing to withhold β -agonist for at least 4 hours before clinic visits. In addition, patients had to be prepubescent, ie, have a Tanner's stage⁹ no greater than 1 on study day 1.

Patients were excluded from the study when any of the following criteria applied: significant chronic disease other than asthma; acute upper or lower respiratory tract infection within 2 weeks before the prestudy visit; immobilized (eg, because leg was in a plaster cast); use of intra-articular, intramuscular, or injectable steroids within 8 weeks or oral corticosteroids within 4 weeks before the prestudy visit; current use of >200 $\mu\text{g}/\text{d}$ BDP or equivalent of nasal steroids; antibiotic treatment for respiratory disorders within the 2 weeks before prestudy visit or during run-in; visible oropharyngeal candidiasis at the 2-week run-in clinic visit and/or on study day 1; or obesity, defined as height and weight $>95\%$ percentile or a body mass index (weight [kg]/height squared [m^2]) >30 . Patients who missed >2 complete days of diary data or >10 diary card entries during the last 2 weeks of the run-in period were ineligible for randomization.

Ethical Considerations

Ethics committee approval was obtained at each site before study start, and the study was conducted in accordance with the Food and Drug Administration Code of Federal Regulations and the revised declaration of Helsinki (Hong Kong 1989; South Africa 1996).

After a full explanation of the study and before entry, patients gave their verbal assent and their parent or legal guardian gave written informed consent. Patients could withdraw from the study at any time.

Study Design

This was an open-label, randomized, parallel-group, multinational study conducted in 56 sites (United States, 26 sites; United Kingdom, 10 sites; Germany, 7 sites; Belgium and the Netherlands, 3 sites; Scandinavia, 3 sites; France, 4 sites; and Australia, 3

sites). Patients were enrolled for either 6 months of treatment (the results of which are reported by Szefer et al, manuscript submitted) or 12 months of treatment. Only patients from sites in the United States, the United Kingdom, Germany, Australia, and the Netherlands were enrolled for 12 months of treatment.

Patients who fulfilled the inclusion and exclusion criteria entered a 4-week run-in period during which they received, via a pMDI+S, CFC-BDP at approximately the same total daily dose of CFC-BDP or budesonide as they were taking before study entry. Each patient recorded daily on a diary card AM and PM PEF values, asthma symptom and sleep disturbance scores, and β -agonist use. After 2 weeks, patients returned to the clinic and were asked to withhold their morning dose of CFC-BDP. The following procedures were conducted: review of patients' pMDI and PEF techniques, adverse event assessment, examination for signs of oropharyngeal candidiasis, diary card review, and collection of blood and urine samples for safety assessments.

After the 4-week run-in period, eligible patients were randomized (in a 1:3 assignment ratio) to receive CFC-BDP pMDI (Beclome [Glaxo Wellcome, London, England] or Becotide [Glaxo Wellcome/Allen and Hanburys, London, England]) and spacer (Volumatic [Glaxo Wellcome]) at their current total daily dose or HFA-BDP via the Autohaler (QVAR Autohaler [3M Pharmaceuticals]) at half their current CFC-BDP dose for 12 months. Patients were randomized to treatment in blocks of 4, according to a computerized randomization schedule; within each block, 3 patients were allocated to receive HFA-BDP and 1 was allocated to receive CFC-BDP+S. Patients were instructed to take their study medication twice daily, once in the morning and once in the evening, at approximately the same time each day. The dose of study medication was to remain unchanged during the first 2 months after randomization. Use of short-acting inhaled β -agonist was permitted as needed throughout the study. Clinic visits for safety and efficacy assessments took place on study day 1 and at the end of months 1, 2, 4, 6, 9, and 12.

Treatment Compliance

For assessing compliance, study inhalers that were used from study day 1 to the end of month 2, during month 5 to the end of month 6, and month 10 to the end of month 12 were weighed. Patients were considered compliant during these periods when the total number of actuations fired from the inhalers was $\pm 40\%$ of the number of shots predicted, ie, within 60% to 140% of the predicted number.

Safety Evaluations

The patients' height (cm) was measured at the beginning and end of the run-in period and at all clinic visits using a stadiometer or wall-mounted height board. The same video was used for training at each site to ensure that height measurements were taken correctly and consistently. In addition, for avoiding potential sources of error, measurements at each site were taken by the same person, at approximately the same time of day, and using the same piece of equipment. Patients were queried about possible adverse events at each clinic visit, and details of any adverse signs, symptoms, or events were evaluated and recorded by the study investigator. The investigator also performed an oropharyngeal examination for visual signs of candidiasis infection at each clinic visit. Any incidents of asthma exacerbations were treated and recorded. Patients who experienced >2 exacerbations within the first 2-months after randomization or >4 during the whole study period were withdrawn.

In addition to clinical laboratory tests (routine hematology and serum chemistry) and urinalysis, the following tests were performed on samples taken at week 2 of the run-in period and at study months 6 and 12. Blood samples for AM plasma cortisol analysis were taken before 10:00 AM and within ± 30 minutes of the baseline measurement. Bone markers (serum osteocalcin, carboxy propeptide of procollagen type 1 [PICP], 1-collagen telopeptide [1-CTP], and urine deoxypyridinoline) were assessed at a subset of sites.

At study sites that agreed to take part, patients were invited to consent to a low-dose adrenocorticotropic hormone (ACTH) stimulation test. On the test day, patients withheld the morning dose of inhaled steroid and a preinjection blood sample was taken before 10:00 AM. A 1 $\mu\text{g}/1.73$ m^2 bolus dose of a 1.0 $\mu\text{g}/\text{mL}$ cosyntropin solution was then injected intravenously; blood sam-

ples were taken 15, 30, and 45 minutes postinjection; and plasma cortisol levels were analyzed. The criteria for a normal response was the attainment of 2 of the following: a prestimulation serum cortisol >138 nmol/L, an increase in serum cortisol of ≥ 200 nmol/L above the prestimulation level, and an increase in serum cortisol to a peak values of ≥ 500 nmol/L postcosyntropin. The low-dose ACTH stimulation test has been shown to be more sensitive than the standard ACTH test in detecting subtle insufficiency of the HPA axis in patients treated with inhaled steroids.^{10,11} Patients at selected sites collected 24-hour urine samples before clinic visits at week 2 of run-in and study months 6 and 12. These samples (excluding those that were <500 mL) were used to analyze urinary free cortisol (UFC). At sites with appropriate facilities, patients who agreed to the procedure had the bone mineral density of their lumbar spine measured by dual energy radiograph absorptiometry.

Efficacy Evaluations

Patients measured AM and PM PEF using a pediatric Mini-Wright peak flow meter daily and recorded the measurement on a diary card. FEV₁ was measured at clinic visits by spirometry. Patients were asked to withhold short-acting inhaled β -agonists for at least 4 hours before pulmonary function testing. Patients also recorded asthma symptoms, sleep disturbance, and β -agonist use on their diary cards during run-in, from study day 1 to month 2, during month 6, and during month 12. For a subset of patients, eosinophilic protein X (EPX) measurements were taken from early morning urine samples.

Statistical Methods

The International Conference on Harmonization suggested a study to assess safety in at least 100 patients receiving HFA-BDP for 12 months. It was estimated that for testing the null hypothesis, mean growth velocity was equal in the 2 treatment groups, a sample size of 100 patients treated with HFA-BDP and 33 patients treated with CFC-BDP+S would provide 80% power to detect a difference of 0.8 cm/y between the 2 groups.

Most analyses presented in this article were performed on the subset of patients who were randomized to receive 12 months of study medication at the recommended doses (100–200 μ g HFA-BDP or 200–400 μ g CFC-BDP+S). Growth analyses were also performed on all patients who were randomized to receive 12 months of study medication (ie, over the entire dosing range 100–400 μ g HFA-BDP or 200–800 μ g CFC-BDP+S) as well as on an evaluable population in whom patients and data points were excluded on the basis of defined criteria believed to influence growth or height measurements. An “evaluable” population was used for all adrenal suppression and bone marker parameters; data for these tests were excluded on the basis of the use of concomitant medication and/or the timing of the assessment. All analyses performed over time were conducted using the data available at that particular time point.

All statistical tests were 2 sided with treatment differences below the 0.05 level considered statistically significant. Height velocity was assessed by fitting a linear regression line to each patient’s height versus time data. For calculating height velocity for a specific time interval, patients were required to have a height assessment at both the beginning and end of the interval. All growth, adrenal suppression, bone marker, and efficacy parameters were analyzed using an analysis of variance model, with terms for treatment, country, and treatment by country interaction. Height centiles were calculated using the growth reference curves developed by the National Center for Health Statistics and Centers for Disease Control and Prevention using data from the Fels Research Institute and US Health Examination Surveys.¹² Adverse events were tabulated by treatment group and analyzed for treatment differences using the Mantel-Haenszel test adjusting for country.

RESULTS

Patients

A total of 300 patients were enrolled into this 12-month study (United States, 184 patients; Germany, 52 patients; United Kingdom, 49 patients; Australia, 10 patients; and the Netherlands, 5 pa-

tients). Of these, 221 patients were randomized to receive HFA-BDP and 79 were randomized to receive CFC-BDP+S. However, 44 of the originally enrolled patients were taking doses of BDP or budesonide that resulted in their being randomized to doses of BDP greater than that recommended for children. To reflect the clinical situation in which HFA-BDP is to be used, the results reported in this article, therefore, focus on the 256 patients who were using 200 to 400 μ g/d CFC-BDP or budesonide at enrollment. Of these patients, 189 were randomized to HFA-BDP (100–200 μ g/d) and 67 were randomized to continue on CFC-BDP+S (200–400 μ g/d).

Nineteen patients (10%) from the HFA-BDP 100 to 200 μ g/d group and 8 patients (12%) from the CFC-BDP+S 200 to 400 μ g/d group withdrew from the study. Reasons for withdrawal included lost to follow-up (3% and 3% in the 2 treatment groups, respectively), withdrawal of study site (3% and 4%, respectively), and withdrawn consent (2% and 3%, respectively). Subsequent analyses exclude patients from the withdrawn study site (6 patients randomized to HFA-BDP 100–200 μ g and 3 patients randomized to CFC-BDP+S 200–400 μ g). This site was withdrawn from the study as it lacked the training, experience, and time required to adhere to Good Clinical Practice guidelines. The 2 treatment groups were similar in terms of baseline characteristics, height, lung function, and daily β -agonist (Table 1).

During the first 2 months of the study, 64.5% of patients in the HFA-BDP 100 to 200 μ g group and 70.3% in the CFC-BDP+S 200 to 400 μ g group were deemed compliant. Compliance rates were similar throughout the study; 63.1% and 56.5% of patients in the 2 groups, respectively, were compliant during months 5 and 6, and 58.5% and 55.9%, respectively, were compliant during months 10 and 12.

In the HFA-BDP 100 to 200 μ g group, most patients (87%) remained on the same dose of study medication at month 12 as they initially received and just 13% had their dose increased. In the CFC-BDP+S 200 to 400 μ g group, 81% of patients remained on the same dose, 12% had their dose increased, and 7% had their dose decreased. At month 12, the mean (standard deviation) daily dose received by patients was 172.8 (95.89) μ g in the HFA-BDP 100 to 200 μ g group and 303.5 (125.31) μ g in the CFC-BDP+S 200 to 400 μ g group.

Safety Evaluations

Growth

There was no significant difference in mean change from baseline in height between treatments, except at month 6 (2.60 cm vs 3.04 cm in the HFA-BDP 100–200 μ g/d and CFC-BDP+S 200–400 μ g/d groups, respectively). The mean change from baseline in height at month 12 was 5.23 cm for HFA-BDP 100 to 200 μ g and 5.66 cm for CFC-BDP+S 200 to 400 μ g (95% confidence interval [CI] for difference between groups: -1.020 – 0.158 ; $P = .150$; Table 2, Fig 1).

Taking into account those patients who received higher-than-recommended doses, there seemed to be

TABLE 1. Patient Characteristics and Lung Function at Baseline

	Number of Patients	
	HFA-BDP 100-200 μg (<i>n</i> = 183)	CFC-BDP+S 200-400 μg (<i>n</i> = 64)
Male/female (%)	130/53 (71.0/29.0)	47/17 (73.4/26.6)
Age (y)*		
Mean (SD)	8.65 (1.766)	8.42 (1.550)
Range	5.3-12.1	5.3-12.0
Duration of asthma (%)		
<1 y	8 (4.4)	1 (1.6)
1-5 y	104 (56.8)	35 (54.7)
>5 y	70 (38.3)	27 (42.2)
Unknown	1 (0.5)	1 (1.6)
Height (cm)		
Mean (SD)	131.79 (11.204)	131.33 (11.128)
Range	109.0-157.5	108.3-157.9
AM PEF (L/min; mean [SD])	253.7 (62.47)	255.8 (62.84)
FEV ₁ (% predicted; mean [SD])	88.8 (13.69)	90.4 (12.87)
Days without symptoms (%; mean [SD])		
Wheeze	86.7 (29.62)	83.3 (29.74)
Cough	70.4 (36.80)	72.2 (36.51)
Shortness of breath	90.1 (25.01)	84.9 (26.68)
Chest tightness	91.3 (22.48)	83.4 (29.89)
Nights without sleep disturbance (%; mean [SD])	92.1 (20.07)	89.1 (24.26)
Daily β -agonist use (puffs; mean [SD])	1.2 (1.85)	1.1 (1.73)

SD indicates standard deviation.

* According to the study inclusion criteria, patients were aged 5 to 11 years, and this was confirmed at the screening visit. Baseline measures were assessed after a 4-week run-in phase; hence, some children had reached their 12th birthday by study baseline.

TABLE 2. Summary of Height and Growth Data (Mean [SE])

	HFA-BDP 100-200 μg	CFC-BDP+S 200-400 μg	<i>P</i> Value
Baseline height (cm)	131.79 (0.914) <i>n</i> = 183	131.33 (1.535) <i>n</i> = 64	.796
Change from baseline at month 12 (cm)	5.23 (0.146) <i>n</i> = 156	5.66 (0.260) <i>n</i> = 56	.150
Height velocity (cm/y)			
Day 1-month 12*	5.27 (0.141) <i>n</i> = 156	5.71 (0.251) <i>n</i> = 56	.129
Day 1-month 6†	5.21 (0.210) <i>n</i> = 147	6.16 (0.404) <i>n</i> = 52	.038
Month 6-month 12†	5.33(0.222) <i>n</i> = 147	5.09 (0.427) <i>n</i> = 52	.609

SE indicates standard error.

* Includes patients with height assessments at day 1 and month 12.

† Includes patients with height assessments at day 1, month 6, and month 12.

an inverse dose-response relationship, with smaller increases from baseline in height with higher doses of both HFA-BDP and CFC-BDP+S. At month 12 in the HFA-BDP group, mean change from baseline was 5.67 cm in patients who received 100 $\mu\text{g}/\text{d}$, 4.87 cm in those who received 200 $\mu\text{g}/\text{d}$, 4.79 cm with 300 $\mu\text{g}/\text{d}$, and 4.45 cm with 400 $\mu\text{g}/\text{d}$. In the CFC-BDP+S group, mean change at month 12 was 6.13 cm, 5.58 cm, 5.82 cm, and 5.05 cm in patients who received 200, 400, 600, and 800 $\mu\text{g}/\text{d}$, respectively. The small numbers of patients who received the higher doses, however, limit the conclusions that can be drawn from these data.

There was no significant difference between treatments for mean growth velocity from day 1 to month 12; mean values were 5.27 cm/y for the HFA-BDP 100 to 200 μg group and 5.71 cm/y for the CFC-BDP+S 200 to 400 μg group (95% CI for difference between groups: -1.006-0.129; *P* = .129).

When the analysis included those patients who received higher-than-recommended doses, the mean growth velocity decreased with increasing dose of study medication. In the HFA-BDP group, growth velocity from day 1 to month 12 was 5.67 cm/y for those who received 100 $\mu\text{g}/\text{d}$, 4.97 cm/y with 200 $\mu\text{g}/\text{d}$, 4.68 cm/y with 300 $\mu\text{g}/\text{d}$, and 4.27 cm/y with 400 $\mu\text{g}/\text{d}$. In the CFC-BDP+S group, growth velocity was 6.07 cm/y with 200 $\mu\text{g}/\text{d}$, 5.60 cm/y with 400 $\mu\text{g}/\text{d}$, 5.45 cm/y with 600 $\mu\text{g}/\text{d}$, and 5.15 cm/y with 800 $\mu\text{g}/\text{d}$. Again, these results should be interpreted with caution as few patients were treated with the higher doses.

Growth velocity from day 1 to month 12 was analyzed by gender, race, pooled country (US vs non-US), use of nasal steroids, and Tanner's stage. No significant treatment interactions were found for any of these factors.

When the analysis of mean growth velocity was

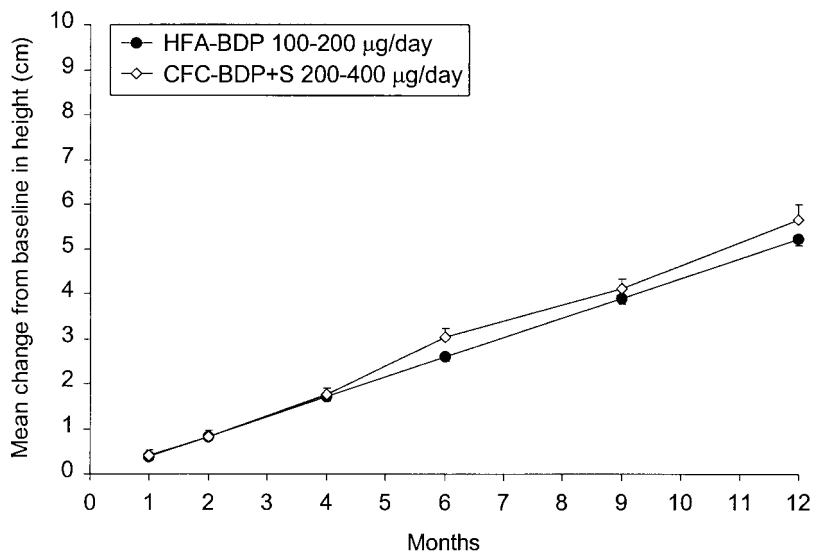


Fig 1. Mean (standard error) change from baseline in height by time over 12 months in patients who received HFA-BDP 100–200 µg/d or CFC-BDP+S 200–400 µg/d.

divided into the first and second 6 months of treatment, growth velocity from day 1 to month 6 was significantly greater in the CFC-BDP+S 200 to 400 µg group (6.16 cm/y) compared with the HFA-BDP 100 to 200 µg group (5.21 cm/y; 95% CI for difference: -1.848 to -0.051; $P = .038$), but there was no significant difference between groups for the period month 6 to month 12 (5.09 cm/y for CFC-BDP+S 200–400 µg/d and 5.33 cm/y for HFA-BDP 100–200 µg/d; 95% CI for difference: -0.703–1.197; $P = .609$).

Throughout, results of height assessments in the evaluable population were similar to those presented above. The height centile plots showed that children tended to stay within the same height centile at baseline and after 12 months of treatment with study medication (Fig 2).

Adverse Events and Asthma Exacerbations

There was no significant difference between treatments in the percentage of patients who reported at least 1 adverse event: 92%, HFA-BDP 100 to 200 µg/d; 91%, CFC-BDP+S 200 to 400 µg/d ($P = .856$; Table 3). Similarly, there was no significant difference between treatments (HFA-BDP and CFC-

BDP+S) in the percentage of patients who reported an adverse event associated with inhalation (3% and 2%, respectively) or a respiratory system adverse event (86% and 83%, respectively). Although a higher proportion of patients reported bronchitis in the HFA-BDP 100 to 200 µg/d group than in the CFC-BDP+S 200 to 400 µg/d group ($P = .009$), no incident of bronchitis was reported to be severe and no incidents were considered to be treatment related. There was no candidiasis in either treatment group.

The percentage of patients who did not experience an asthma exacerbation was 77% in the HFA-BDP 100 to 200 µg/d group and 75% in the CFC-BDP+S 200 to 400 µg/d group. Only a small proportion of patients experienced more than 1 exacerbation during the 12 months of treatment (8% and 9%, respectively). There were no deaths during the study.

Clinical and Other Laboratory Tests

There was no significant difference between treatments in mean percentage change from baseline in 24-hour UFC at month 12 for patients who participated in the assessment (Table 4). Results of the

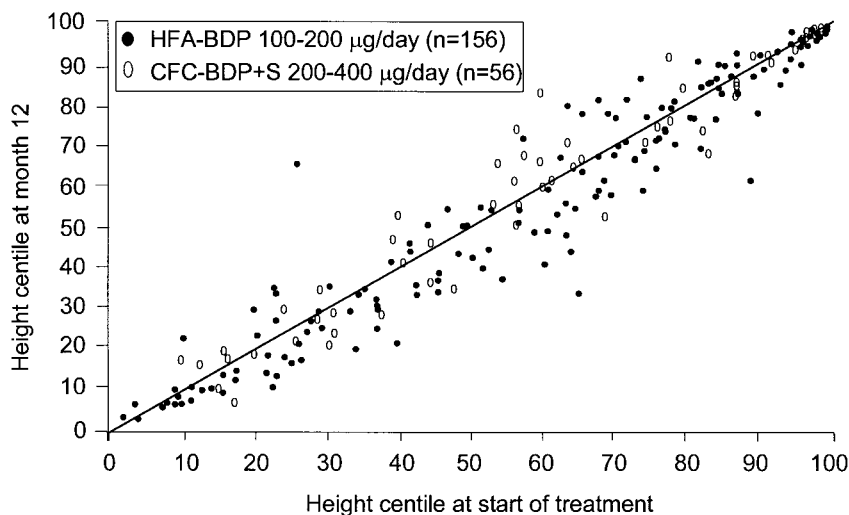


Fig 2. Scatter plot of individual height centiles at baseline and after 12 months of treatment with HFA-BDP 100–200 µg/d or CFC-BDP+S 200–400 µg/d. Line of identity is superimposed onto the plot for clarity.

TABLE 3. Percentage (Number) of Patients Reporting at Least 1 Adverse Event, an Inhalation Site Disorder, or a Respiratory System Disorder

	HFA-BDP 100-200 μg (<i>n</i> = 183)	CFC-BDP+S 200-400 μg (<i>n</i> = 64)	<i>P</i> Value
At least 1 adverse event	92 (169)	91 (58)	.856
Adverse event on inhalation	3 (6)	2 (1)	.480
Respiratory system disorder	86 (158)	83 (53)	.715
Acute asthma episode	8 (15)	11 (7)	.517
Bronchitis	10 (19)	0 (0)	.009
Coughing	26 (47)	25 (16)	.921
Increased asthma symptoms	43 (79)	41 (26)	.759
Pharyngitis	23 (42)	34 (22)	.092
Rhinitis	43 (79)	47 (30)	.659
Sinusitis	12 (22)	14 (9)	.676
Upper respiratory tract infection	45 (82)	53 (34)	.335

plasma cortisol assessments supported the 24-hour UFC results (Table 4). There was no significant difference between treatment groups with regard to transitions (from/to low, normal, or high, relative to the reference range) in plasma cortisol from baseline to month 12 ($P = .698$; Table 5).

In the HFA-BDP 100 to 200 $\mu\text{g}/\text{d}$ and CFC-BDP 200 to 400 $\mu\text{g}/\text{d}$ groups, similar proportions of patients had a normal response to the low-dose ACTH stimulation test at baseline and at month 12. There was no significant difference between treatments in mean percentage change from baseline for serum osteocalcin, PICP, 1-CTP, and urine deoxypyridinoline/creatinine at month 12, and change from baseline in bone mineral density was similar in the 2 treatment groups (Table 6). No clinically meaningful changes or trends were found in either treatment group with regard to blood chemistry, hematology tests, or urinalysis.

Efficacy Evaluations

There was no statistically significant difference between treatments in mean change from baseline in AM PEF at months 6 or 12 (Fig 3). At month 12, AM PEF had improved by 21.5 L/min in the HFA-BDP 100 to 200 $\mu\text{g}/\text{d}$ group and by 15.6 L/min in the CFC-BDP+S 200 to 400 $\mu\text{g}/\text{d}$ group (95% CI for difference between groups: -6.27 – 18.05 ; $P = .341$). At weeks 7 and 8; however, the difference between treatments was statistically significant in favor of HFA-BDP 100 to 200 $\mu\text{g}/\text{d}$ (5.9 vs -4.5 L/min; 95% CI for difference: 2.46 – 18.41 ; $P = .011$).

Similarly, there was no statistically significant dif-

ference between treatments in mean change from baseline in PM PEF at months 6 or 12. At month 12, PM PEF had improved by 20.4 L/min and 13.1 L/min, respectively (95% CI for difference: -3.64 – 18.22 ; $P = .190$). As with AM PEF, at weeks 7 and 8, the difference between treatments was statistically significant in favor of HFA-BDP: 5.4 L/min for HFA-BDP 100 to 200 $\mu\text{g}/\text{d}$ versus -8.5 L/min for CFC-BDP+S 200 to 400 $\mu\text{g}/\text{d}$ (95% CI for difference: 6.66 – 20.98 ; $P < .001$).

There were no statistically significant differences between treatments in mean change from baseline in FEV₁ percentage predicted at months 6 or 12, although there was a significant difference in favor of HFA-BDP 100 to 200 $\mu\text{g}/\text{d}$ over CFC-BDP+S 200 to 400 $\mu\text{g}/\text{d}$ at month 1 (1.6 vs -2.0% predicted; 95% CI for difference: 0.28 – 6.86 ; $P = .034$) and month 2 (0.5 vs -4.1% predicted; 95% CI for difference: 0.53 – 8.63 ; $P = .027$; Fig 4).

There were no significant differences between the 2 treatment groups in change from baseline in percentage of days/nights without asthma symptoms or sleep disturbance at months 6 and 12. At month 12, the percentage of days without wheeze was 89.4% and 86.0%, without cough was 78.1% and 77.3%, without chest tightness was 91.4% and 87.8%, without shortness of breath was 92.2% and 86.4%, and nights without sleep disturbance was 92.6% and 88.5% in the HFA-BDP 100 to 200 $\mu\text{g}/\text{d}$ and CFC-BDP+S 200 to 400 $\mu\text{g}/\text{d}$ groups, respectively. Similarly, no significant differences were seen between treatment groups in change from baseline in total daily β -agonist use at months 6 and 12, with patients using a mean of 1.0 and

TABLE 4. Mean (SE) Baseline and Percentage Change From Baseline at Month 12 in 24-Hour UFC and AM Plasma Cortisol (Patients Who Participated in the Assessment)

	HFA-BDP 100-200 μg	CFC-BDP+S 200-400 μg	<i>P</i> Value
24-h UFC			
Baseline ($\mu\text{g}/24$ h)	12.76 (0.789) <i>n</i> = 72	12.86 (1.630) <i>n</i> = 19	.955
% change at month 12	10.8 (10.81) <i>n</i> = 40	-1.5 (26.99) <i>n</i> = 10	.673
AM plasma cortisol			
Baseline (nmol/L)	294.02 (12.862) <i>n</i> = 173	299.02 (22.457) <i>n</i> = 59	.847
% change at month 12	3.4 (6.18) <i>n</i> = 89	14.7 (12.05) <i>n</i> = 29	.406

TABLE 5. Percentage of Patients at Baseline and Month 12 With a Normal Response to the Low-Dose ACTH Stimulation Test (Patients Who Participated in the Assessment)

	HFA-BDP 100-200 μg	CFC-BDP+S 200-400 μg
Baseline	<i>n</i> = 59	<i>n</i> = 19
Basal cortisol >138 nmol/L	85	95
Increment cortisol \geq 200 nmol/L	86	84
Peak cortisol \geq 500 nmol/L	83	89
Month 12	<i>n</i> = 24	<i>n</i> = 11
Basal cortisol >138 nmol/L	83	100
Increment cortisol \geq 200 nmol/L	83	100
Peak cortisol \geq 500 nmol/L	83	91

TABLE 6. Mean Baseline and Percentage Change From Baseline Values (SE) for Markers of Bone Metabolism and Bone Mineral Density (Patients Who Participated in the Assessment)

	HFA-BDP 100-200 μg	CFC-BDP+S 200-400 μg	<i>P</i> Value
Osteocalcin			
Baseline (ng/mL)	84.93 (2.129) <i>n</i> = 168	86.03 (3.611) <i>n</i> = 58	.794
% change at month 12	3.3 (3.31) <i>n</i> = 125	5.8 (5.99) <i>n</i> = 44	.711
1-CTP			
Baseline ($\mu\text{g/L}$)	10.20 (0.199) <i>n</i> = 160	10.77 (0.330) <i>n</i> = 57	.141
% change at month 12	15.8 (3.14) <i>n</i> = 122	25.7 (5.34) <i>n</i> = 45	.112
Urine deoxypyridinoline/ creatinine (nmol-d/nmol-c)			
Baseline	22.50 (1.172) <i>n</i> = 162	19.89 (2.056) <i>n</i> = 57	.270
% change at month 12	33.7 (8.36) <i>n</i> = 120	65.5 (14.09) <i>n</i> = 46	.054
PICP			
Baseline (ng/mL)	308.76 (14.877) <i>n</i> = 156	339.31 (25.560) <i>n</i> = 55	.303
% change at month 12	15.0 (4.26) <i>n</i> = 116	25.7 (7.49) <i>n</i> = 41	.218
Bone mineral density*			
Baseline (g/cm^3)	2.47 (0.104) <i>n</i> = 15	2.26 (0.201) <i>n</i> = 4	-
% change at month 12	7.1 (1.36) <i>n</i> = 14	11.0 (2.54) <i>n</i> = 4	-

* Between-group comparisons were not tested for bone mineral density.

1.1 puffs per day in the HFA-BDP and CFC-BDP+S groups, respectively, at month 12.

The EPX:creatinine ratio increased from baseline in both treatment groups: at month 12, the percentage increase from baseline was 78.8% in the HFA-BDP group and 29.7% in the CFC-BDP+S group. However, no statistically significant differences between treatment groups in mean percentage change from baseline in EPX:creatinine ratio were observed at months 2, 6, or 12.

DISCUSSION

The results of this randomized study indicate that the long-term (1 year) safety profile of extrafine HFA-BDP in children with asthma is similar to that of conventional CFC-BDP+S at approximately twice the daily dose. With the imminent phaseout of CFC-containing pMDIs, these results will be reassuring to physicians who are considering switching patients to the new HFA inhaler. Patients had previously been receiving CFC-BDP 200 to 800 $\mu\text{g/d}$ or equivalent and were randomized to 12 months of treatment of

the same dose of CFC-BDP+S or to half the dose of HFA-BDP. The current recommended dose of HFA-BDP for the treatment of pediatric patients with mild to moderate asthma is 100 $\mu\text{g/d}$, and the maximum recommended dose is 200 $\mu\text{g/d}$ (for severe asthma).

We chose to focus on the analysis of patients receiving doses within the recommended range to provide physicians with clinically relevant information. The inclusion criteria of this study did not set an upper limit for the dose of inhaled corticosteroids that patients could be using at enrollment. This resulted in a small number of children receiving doses higher than recommended after randomization. However, it is difficult to draw any conclusions on the comparative safety and efficacy of the higher doses of CFC- and HFA-BDP in this study as children were not randomized to dose level, dose titration was not encouraged, and sample sizes were very small for the high-dose groups. For example, in the assessment of change from baseline in height at month 12, only 8 patients were receiving HFA-BDP 300 $\mu\text{g/d}$, 16 patients were receiving 400 $\mu\text{g/d}$, and

Fig 3. Mean (standard error) change from baseline in AM PEF (L/min) at months 2, 6, and 12 in patients who received HFA-BDP 100–200 $\mu\text{g}/\text{d}$ or CFC-BDP+S 200–400 $\mu\text{g}/\text{d}$ (* $P = .011$ vs CFC-BDP+S).

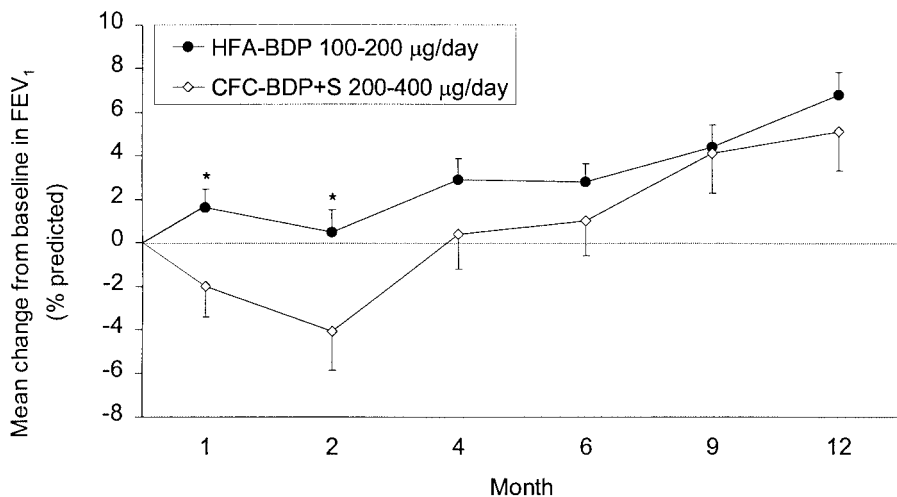
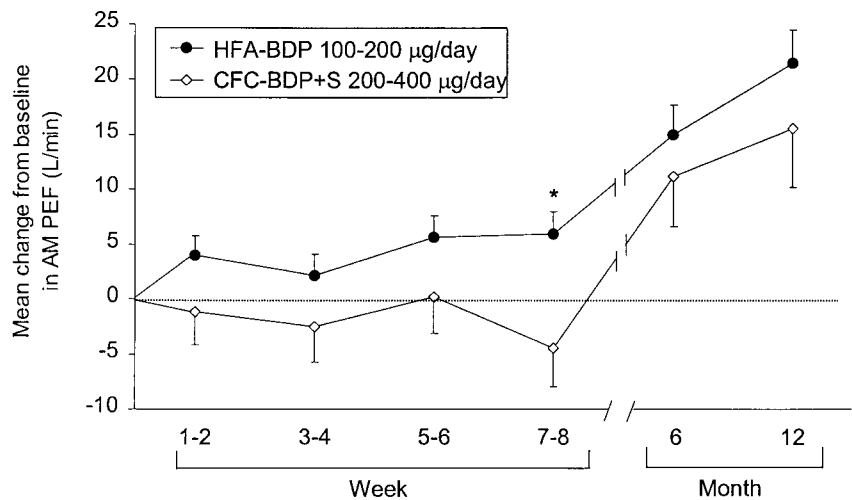


Fig 4. Mean (standard error) percentage change from baseline in FEV₁ over 12 months in patients who received HFA-BDP 100–200 $\mu\text{g}/\text{d}$ or CFC-BDP+S 200–400 $\mu\text{g}/\text{d}$ (* $P < .05$ vs CFC-BDP+S).

5 and 6 patients were receiving CFC-BDP 600 μg and 800 $\mu\text{g}/\text{d}$, respectively.

No dose adjustment is recommended with regard to maintaining asthma control with CFC-BDP administered via a pMDI+S in comparison with CFC-BDP from a pMDI alone. However, it is likely that the addition of a spacer reduces the total amount of corticosteroid delivered to the patient, as some of the medication is deposited on the walls of the spacer rather than being inhaled or swallowed. Consequently, the amount of systemic corticosteroid will be less. Therefore, by comparing HFA-BDP with CFC-BDP+S, this study took a conservative approach to assessing the comparative safety profiles of these 2 formulations. Because the devices in this study were of a different appearance (because of differences in technology) and the study duration was 1 year, blinding using a double-dummy technique was considered to be impractical. Thus, an open-label study design was believed to be the most suitable. To avoid potential bias in treatment assignment, investigators were unaware of treatment allocation until the patient's coded envelope was opened.

The incidence and type of adverse events reported

in the present study were similar in the 2 treatment groups. No serious adverse events were attributed to study medication. The results of the standard clinical laboratory tests and physical examinations were also similar.

The height and growth analyses in this study indicated no meaningful differences between treatments used at recommended doses. During the 12-month treatment period, mean height increased by a similar amount in both treatment groups (5.23 cm and 5.66 cm in the HFA-BDP 100–200 μg and CFC-BDP+S 200–400 μg groups, respectively), with no significant differences between groups at any time point ($P = .150$ at month 12). Likewise, there was no significant difference in growth velocity from day 1 to month 12 between the groups receiving HFA-BDP 100 to 200 μg (5.27 cm/y) and CFC-BDP+S 200 to 400 μg (5.71 cm/y; $P = .129$). These results were supported by those from the height centile plots, demonstrating that at recommended doses, the HFA-BDP Autohaler does not differ clinically in its effect on growth compared with CFC-BDP+S. There was some evidence of a dose-response effect on growth, with increasing doses of both treatments associated with decreasing change from baseline in height and

growth velocity. However, it is difficult to draw any conclusions from these data, as this study was not designed to examine dose-response relationships. The dose of study medication that patients received depended on the dose of BDP or budesonide they were using before entry into the study, and only small numbers of patients received the higher dose levels of study medication. From this study, there is no evidence to support the use of higher-than-recommended doses of HFA-BDP in children with asthma. Asthma control was maintained with doses within the recommended range (100–200 µg/d).

It is important to assess height over a long period of time (ie, for a minimum of 12 months) as the interpretation of height data from short-term studies is difficult and may not relate to long-term effects because growth is inherently an erratic process. This was illustrated in the present study. Growth velocity differed between the 2 treatment groups during the first 6 months of treatment, but there was no difference between groups during months 6 to 12, and the mean change in height at month 12 was not significantly different between the HFA-BDP 100 to 200 µg/d and CFC-BDP+S 200 to 400 µg/d groups.

The relationship between prepubertal height velocity and final adult height is poorly understood.¹³ Few studies have assessed the effect of inhaled CFC-BDP on final adult height. However, there is a growing belief that the effect of inhaled corticosteroids on growth velocity does not affect final height attainment.^{14,15} Although growth velocity may be reduced in the short term, in time, other, as yet poorly understood, mechanisms seem to come into play at long-term steady state, thus allowing the child to reach final “normal” height. Thus, final adult height is usually attained in association with the use of inhaled corticosteroids, as indicated by the results of 2 recently reported studies that investigated growth of children with asthma who were treated for many years with inhaled budesonide at doses of approximately 400 µg/d.^{16,17} In both studies, there was a reduction in growth velocity during the first year or so of budesonide treatment, followed by a recovery of growth velocity to a level similar to that in control groups. In the Agertoft and Pedersen¹⁶ study, which followed up children until they reached adult height, children who used inhaled budesonide were as likely to reach their target adult height as their healthy siblings or children who had asthma and had not used inhaled corticosteroids. The Childhood Asthma Management Research Group¹⁷ followed children for 4 to 6 years and found that at the end of the treatment period, children who were treated with budesonide had a similar projected final height to those in the placebo group. Children who entered the current study, however, were already receiving inhaled corticosteroid therapy. A possible implication of the observed transient reduction in growth velocity in the HFA-BDP group is that repeated changes to the inhaled corticosteroid regimen could have separate impacts on growth, although this hypothesis would require additional investigation in controlled clinical trials. Ultimately, asthma itself may hinder growth in children.^{18,19} For example, records from

18-year-old Swedish military conscripts from 1983 to 1996 showed that subjects with asthma were significantly shorter than healthy subjects and that asthma severity was correlated with growth suppression.²⁰ Thus, effective treatment may be of benefit to growth.¹⁴

Assessments of adrenal function (24-hour UFC, plasma cortisol, and ACTH response) and bone metabolism (serum osteocalcin, PICP, 1-CTP, and urine deoxypyridone) showed no differences between the 2 treatments. Bone turnover (formation and resorption) was consistent with the active growth expected for this study population. Adverse effects of inhaled BDP would be expected to increase markers of bone resorption and decrease markers of bone formation. However, it was not possible to quantify this in a non–placebo-controlled trial.

EPX may be used to evaluate the effect of medication on eosinophils, which are markers of airway inflammation. Consequently, EPX may be an indirect measure of the effect of anti-inflammatory treatment on lung function. In this study, the EPX:creatinine ratio increased from baseline in both treatment groups, which is indicative of increased eosinophil activation. This may be an age effect, as the ratio increased during the 1-year period irrespective of treatment. The lung function assessments demonstrated that asthma control was well maintained in children by both treatments during a period of 12 months. There was some evidence of superior efficacy with HFA-BDP compared with CFC-BDP+S during the first 2 months of the study.

CONCLUSION

In children with asthma, the use of the HFA-BDP Autohaler did not differ in its effect on growth compared with CFC-BDP+S. No clinically meaningful differences between treatments with regard to other systemic effects were found, and the profile and incidence of adverse events with HFA-BDP over the long-term were similar to that of CFC-BDP+S. Importantly, asthma control was maintained in the HFA-BDP group at half the daily dose compared with CFC-BDP+S during the 1-year study period.

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