

Linear growth and bone maturation are unaffected by 1 year of therapy with inhaled flunisolide hydrofluoroalkane in prepubescent children with mild persistent asthma: A randomized, double-blind, placebo-controlled trial

George W. Bensch, MD*; Leon S. Greos, MD†; Sandra Gawchik, DO‡; Euloge Kpamegan, PhD§; and Kenneth B. Newman, MD||

Background: Inhaled corticosteroids (ICS) are the preferred long-term therapy for subjects with persistent asthma. However, concerns remain about potential effects of long-term ICS use on growth in children.

Objective: To determine the effect of 1 year of inhalation therapy with flunisolide hydrofluoroalkane (HFA) on growth velocity and bone maturation in children with mild persistent asthma.

Methods: In this double-blind, placebo-controlled study, 218 prepubescent (Tanner Stage 1) children with mild persistent asthma ranging in age from 4 to 10 years were evaluated. After a 2-week run-in period, subjects were randomized (1:1) to 2 puffs flunisolide HFA twice daily (85 µg/puff) or placebo for 52 weeks. Height was assessed by stadiometry at each visit. Growth velocity (cm/52 weeks) was estimated by the slope of the linear regression of height over time. An independent assessor scored hand and wrist radiographs for bone development pretreatment and at week 52. Analysis of covariance was used for all efficacy endpoints.

Results: The 2 treatment groups were similar at baseline for sex, race, age, weight, and height. At the end of double-blind treatment, mean growth velocity was 6.01 ± 1.84 cm/52 weeks for flunisolide HFA ($n = 106$) and 6.19 ± 1.30 cm/52 weeks for placebo ($n = 112$) ($P = .425$). Mean advancement in bone age during the 1-year study was similar for the 2 groups: 0.93 ± 0.46 years for flunisolide HFA ($n = 70$) and 1.01 ± 0.41 years for placebo ($n = 75$) ($P = .128$).

Conclusions: In this study, flunisolide HFA did not suppress growth or bone maturation at the highest approved dose for children with persistent asthma.

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INTRODUCTION

Corticosteroids by oral inhalation are first-line therapy for persistent asthma in adults and children. The Expert Panel of the National Heart, Lung and Blood Institute, citing strong evidence from controlled clinical trials, concluded that inhaled corticosteroids (ICS) are the preferred long-term ther-

apy for subjects with persistent asthma.¹ However, although the therapeutic effect of ICS is widely accepted, some concern remains about the potential systemic effects of these agents with long-term use. Although the use of orally administered steroids suppresses growth, the effect of ICS on growth in children with asthma has been widely debated. Confounding this, poorly controlled asthma can also lead to poor growth, although no definitive consensus has been reached on the subject.²

Since 1999, the United States Food and Drug Administration has required all ICS product labels to disclose the potential for growth suppression in susceptible children. Controlled trials of ICS therapy for 1 year or longer in children with asthma have demonstrated growth suppression with beclomethasone,³ budesonide,^{4,5} fluticasone,⁶ triamcinolone,⁷ and mometasone.⁸ Although some maintain that final adult height is not significantly affected by the use of ICS,^{4,9} no adequate, prospective trials support this hypothesis.

Affiliations: * Allergy, Immunology, and Asthma Medical Group, Inc., Stockton, California; † Colorado Allergy and Asthma Centers, P.C., Centennial, Colorado; ‡ Asthma and Allergy Research Associates, Upland, Pennsylvania; § Novartis Pharmaceuticals, Florham Park, New Jersey; || Acton Pharmaceuticals, Marlborough, Massachusetts

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We report the first randomized, double-blind, placebo-controlled trial to measure the effect of flunisolide hydrofluoroalkane (HFA) on growth in prepubescent children with mild persistent asthma. This new formulation delivers flunisolide in solution from a metered-dose inhaler (MDI) pressurized by HFA incorporating a built-in spacer. High lung deposition achieved with flunisolide HFA provides efficacy at one-third the dose of flunisolide chlorofluorocarbon (CFC). The inhaled particles of flunisolide are smaller than those from the CFC propellant system, resulting in an improved deposition profile with an average of 68.3% of the administered dose reaching the lung¹⁰ and only 25.0% remaining in the oropharynx.¹¹

METHODS

Study Design

This was a randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study conducted at 45 centers in the United States in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. Patient assent and written informed consent from the subject's parent or legal guardian were obtained before performing any study procedures. The study was initiated in 2000 before the International Committee of Medical Journal Editors requirements for central registration of clinical trials data.

Study Population

The inclusion and exclusion criteria were designed to select prepubescent children with mild asthma who were not recently using steroids and were free of other significant illnesses. Subjects were included if they were between 4 and 9.5 years of age; had not used an ICS for 60 days, an oral steroid for 90 days, or a nasal steroid for 30 days before the 2-week run-in period; were in Tanner development stage ≤ 1 ; had screening height between the 5th and 95th percentile for age and sex; were able to use an MDI; and could perform spirometry and complete diary cards.

The spirometric requirements for study entry, which applied only to patients age 6 and older, were as follows: forced expiratory volume in 1 second (FEV_1) of at least 75% predicted after withholding short-acting β -agonists for 6 hours or more and before inhalation of 180 to 360 μ g of albuterol (2–4 puffs); at least 12% increase in FEV_1 after inhalation of albuterol; provocative dose causing a 20% decrease in FEV_1 to methacholine 8 mg/mL or less; or peak flow diurnal variability of at least 20% for 4 or more days in a week. Because children younger than 6 years of age have difficulty with spirometry, their enrollment was based on medical history rather than pulmonary function.

Subjects were excluded for any of the following: clinically significant pulmonary disease other than asthma; medical or psychiatric illness that could interfere with study assessments; hospitalization or emergency room or office visit for an exacerbation of asthma within 2 months before the start of the run-in; immunotherapy other than an established maintenance program; treatment with an investigational drug within

30 days of the run-in; hypersensitivity to albuterol, flunisolide, or HFA propellant; use of or intent to use any other steroid; and use of or intent to use any concomitant medication that could affect growth, such as methylphenidates.

Study Procedures

Qualified subjects entered a 2-week run-in period, during which albuterol was permitted by inhalation as needed for symptoms. Compliance with study procedures, baseline symptom scores, and demonstration of a need for ICS were obtained during the run-in. Historical height measurements from the period 6 to 18 months before study enrollment were collected. Eligible subjects were randomized 1:1 to 2 puffs flunisolide HFA twice daily (85 μ g/puff) or 2 puffs placebo twice daily. Double-blind treatment continued for 52 weeks, with subjects returning for study visits at weeks 4, 8, 12, 20, 28, 36, 44, and 52. A follow-up visit occurred 8 weeks after the end of double-blind treatment.

Long-acting β -agonists, cromolyn, and theophylline were allowed. Antihistamines and decongestants, but not steroids, could be used for symptoms of rhinitis. Oral steroids were permitted only for exacerbation of asthma, and leukotriene modifiers were not allowed.

Trained personnel measured the subject's height in triplicate with a stadiometer at each visit, recording the average of the 3 measurements. A radiograph of the left hand and wrist was taken at randomization and at week 52 for assessment of skeletal maturity.¹² The radiographs were sent to The Division of Human Biology at Wright State University in Dayton, Ohio, for scoring by trained personnel who were blinded to study medication assignment. Secondary sex characteristics were assessed using the Tanner staging criteria for pubertal development¹³ at screening and at week 52.

Safety monitoring included complete physical examination and hematology, clinical chemistry, and urinalysis before and after the treatment period. At each visit, blood pressure, pulse, and respiration were recorded; auscultation of the lungs was performed; and any potential adverse events were assessed.

Diary cards were provided to subjects to record daily asthma symptoms and the use of study medication and as-needed albuterol.

If an asthma exacerbation occurred (defined as symptoms requiring the use of systemic steroids or a decrease in FEV_1 greater than 40% from baseline), the subject could remain in the study unless the requirement for oral prednisone exceeded 10 days. A subject was removed from the study on a fourth asthma exacerbation.

Compliance with the study medication was monitored by self-recording of the number of puffs administered daily on the diary card, and by the weight of the drug canisters returned to the study site.

Statistical Analysis

A sample of 97 subjects per treatment group would provide 80% power to detect at least a 1.0 cm/52 weeks' difference in

growth velocity (estimated standard deviation [SD] 2.0 cm/52 weeks) with allowance for a 33% reduction in sample size by dropout or attainment of puberty.

The prospectively defined primary endpoint was growth velocity assessed by regression analysis estimated for each subject with at least 3 postrandomization measurements by the slope of the linear regression of height by stadiometry over time and expressed as cm/52 weeks. Analysis of covariance was used to compare the treatment effect between flunisolide HFA and placebo, adjusting for the baseline value, age at baseline, and sex. The secondary endpoint was change from baseline to week 52 in radiographic bone age based on bone maturation in the hand and wrist as assessed by radiographic appearance. In the analysis of radiographic bone age, the model also included treatment duration. The difference in least squares means between treatments, the 95% 2-sided confidence interval, and the *P*-value for the between-treatment comparison were calculated.

RESULTS

Subject Population

Two hundred forty-nine children with mild persistent asthma were randomized to flunisolide HFA (*n* = 122) or placebo (*n* = 127). Three subjects randomized to flunisolide HFA and 4 randomized to placebo did not receive study medication and were excluded from further consideration. Of the 242 subjects treated, 218 met the criteria for inclusion in efficacy analyses (at least 3 measurements of postbaseline height). One hundred sixty-three subjects (67.4%) completed 52 weeks of double-blind treatment, including 78 and 85 subjects in the flunisolide HFA and placebo groups, respectively. The number of subjects who did not complete 52 weeks of treatment was similar for the 2 study groups: 41 of 119 subjects (34.5%) in the flunisolide HFA group and 38 of 123 subjects (30.9%) in the placebo group. Among the 79 subjects who did not complete 52 weeks of treatment, 11 placebo and no flunisolide HFA subjects withdrew because of worsening asthma.

Compliance with study treatment based on weight of the study medication canisters was 86.1% and 87.7% in the flunisolide HFA and placebo groups, respectively, and was greater than 90% for both treatment groups based on review of diary cards.

Demographics

The 2 treatment groups were similar with respect to demographic and baseline characteristics (Table 1). Mean age at randomization across the 218 subjects was 6.4 years and ranged from 4 to 10 years; 45.4% of the subjects were younger than 6 years of age. More boys were enrolled than girls (59.2% and 40.8%, respectively). Approximately 19% and 6% of patients received long-acting β -agonists and cromolyn, respectively; 1 patient received theophylline.

Table 1. Baseline Characteristics

Characteristic	Flunisolide HFA (<i>N</i> = 106)	Placebo (<i>N</i> = 112)	<i>P</i>
Sex, <i>n</i> (%)			.547 ^a
Male	63 (59.4)	66 (58.9)	
Female	43 (40.6)	46 (41.1)	
Race, <i>n</i> (%)			.793 ^a
White	69 (65.1)	74 (66.1)	
Non-white	37 (34.9)	38 (33.9)	
Black	25 (23.6)	20 (17.9)	
Hispanic	10 (9.4)	15 (13.4)	
Asian	0	1 (0.9)	
Other	2 (1.9)	2 (1.8)	
Age (years), Mean $\pm$ SD	6.5 $\pm$ 1.57	6.4 $\pm$ 1.57	.619 ^b
Weight (kg), Mean $\pm$ SD	25.1 $\pm$ 7.76 ^c	24.9 $\pm$ 9.01	.974 ^b
Height (cm), Mean $\pm$ SD	119.2 $\pm$ 11.65	117.7 $\pm$ 10.92	.275 ^b
FEV ₁ (% predicted), Mean $\pm$ SD	96.4 $\pm$ 12.45	95.9 $\pm$ 13.34	.69 ^b
Baseline growth rate (cm/year)	6.47 $\pm$ 1.52	6.38 $\pm$ 1.48	.55

Abbreviations: HFA, hydrofluoroalkane; FEV₁, forced expiratory volume in 1 second; SD, standard deviation.

^a *P*-value from Cochran-Mantel-Haenszel test. The *P*-value for race is based on total white vs total nonwhite.

^b *P*-value from analysis of variance.

^c *n* = 105.

Sexual Development at the End of Double-blind Therapy

Thirty-six of the 218 subjects entered puberty during double-blind treatment. The proportions of subjects that were prepubescent at the end of therapy were similar for the flunisolide HFA (87/106, 82.1%) and placebo (95/112, 84.8%) groups.

Linear Growth

A summary of the results of growth velocity is provided in Table 2. Chronic treatment with flunisolide HFA did not affect growth velocity in children with mild persistent asthma in this study. Among the 218 subjects included in the primary analysis, mean growth velocity was 6.01 $\pm$ 1.84 cm/52 weeks for the 106 subjects in flunisolide HFA group and 6.19 $\pm$ 1.30 cm/52 weeks for the 112 subjects in the placebo group (*P* = .425).

Analysis of growth velocity including subjects who were prepubescent at the end of double-blind treatment (*n* = 182) yielded similar results for between treatment groups (*P* = .940). Among those subjects who had growth assessments at week 52 (completed cases, *n* = 163), mean growth velocity with flunisolide HFA also was similar to placebo (*P* = .289). Furthermore, little difference was seen between the 2 treatments when only prepubescent subjects who had growth assessments at week 52 (*n* = 157) were included in the analysis (*P* = .250).

At baseline, mean ($\pm$ SD) height was similar in the 2 treatment groups: 119.2 $\pm$ 11.7 and 117.7 $\pm$ 10.9 cm in the flunisolide HFA and placebo groups, respectively (*P* = .275).

Table 2. Primary and Secondary Analyses of Growth Velocity (cm/52weeks)

Analysis set ^a Population	Flunisolide HFA		Placebo		<i>P</i> ^b
	<i>N</i>	Mean $\pm$ SD	<i>n</i>	Mean $\pm$ SD	
Primary analysis:					
All patients	106	6.01 $\pm$ 1.84	112	6.19 $\pm$ 1.30	.425
Secondary analysis:					
Prepubescent patients	87	6.01 $\pm$ 1.87	95	6.08 $\pm$ 1.22	.940
All patients completing 52 weeks	78	5.87 $\pm$ 1.69	85	6.11 $\pm$ 1.15	.289
Prepubescent patients completing 52 weeks	74	5.85 $\pm$ 1.70	83	6.12 $\pm$ 1.15	.250

Abbreviations: HFA, hydrofluoroalkane; SD, standard deviation.

^a To be included in the analysis of growth velocity, patients were required to have at least 3 height assessments.

^b *P*-value from analysis of covariance.

(Table 1). As shown in Figure 1, mean change in height over time was similar for subjects receiving flunisolide HFA or placebo throughout the 52-week study, including the initial 3-month treatment period. The mean ($\pm$ SD) change in height over 52 weeks was 6.14 $\pm$ 2.12 cm (*n* = 76) for the flunisolide HFA group and 6.31 $\pm$ 1.26 cm (*n* = 85) for the placebo group (*P* = .343). Mean height increase over 52 weeks also was similar for prepubescent subjects who received flunisolide HFA or placebo (*P* = .333). The number of patients that dropped in the percentile of height for their age and sex also was examined. A total of 9 patients, 5 in the placebo group, and 4 in the flunisolide HFA group, had at least a 10% decrease in their height percentile. No patients had a 20% decrease. The lack of growth effects in this study was consistent across age groups. For patients ages 4 to 5, the growth velocity was 6.43 $\pm$ 1.77 cm/year and 6.75 $\pm$ 1.12

cm/year; for patients ages 6 to 9, it was 5.68 $\pm$ 1.84 cm/year and 5.70 $\pm$ 1.24 cm/year for flunisolide HFA and placebo groups, respectively. The 60-week assessment showed change from baseline height of 7.71 $\pm$ 1.44 cm and 7.89 $\pm$ 2.41 cm for patients ages 4 to 5, and 6.66 $\pm$ 1.32 cm and 6.50 $\pm$ 1.56 for those ages 6 to 9 for flunisolide HFA and placebo groups, respectively.

Bone Maturation

At baseline, mean radiographic bone age was similar in the 2 treatment groups: 6.70 $\pm$ 1.85 years (*n* = 94) for the flunisolide HFA group and 6.72 $\pm$ 1.99 years (*n* = 98) for the placebo group. Treatment with flunisolide HFA over 52 weeks did not affect bone maturation in children with mild asthma. The mean change in bone age at the end of the double-blind treatment period was similar for subjects who

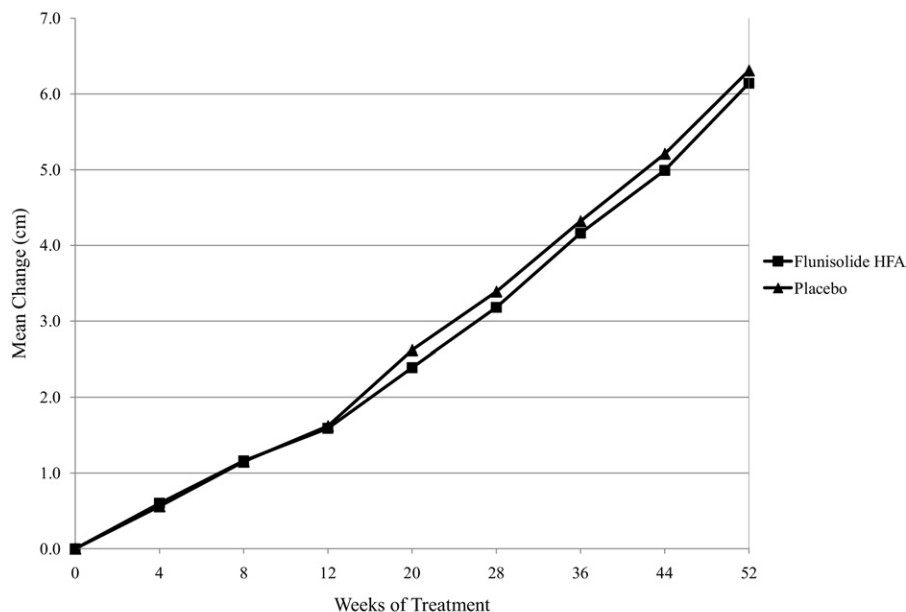


Figure 1. Mean change in height during double-blind treatment with flunisolide HFA or placebo.

received flunisolide HFA (0.93 ± 0.46 years; $n = 70$) and placebo (1.01 ± 0.41 years, $n = 75$) ($P = .128$).

Safety

Flunisolide HFA was well tolerated. The rate of oral candidiasis in subjects treated with flunisolide HFA was the same as with placebo (0.8% of subjects in both treatment groups). Dysphonia was reported in 4 subjects (3.4%) in the flunisolide HFA group and in no subjects in the placebo group. Asthma exacerbations were reported more frequently in subjects receiving placebo (28.7%) compared with those receiving flunisolide HFA (11.9%).

During the course of this 1-year study, discontinuations because of adverse events were uncommon, occurring in 4 subjects who received flunisolide HFA and 8 subjects who received placebo. The most common adverse event leading to discontinuation of treatment was asthma, reported for no subjects in the flunisolide HFA group and for 6 subjects in the placebo group.

DISCUSSION

The results of this randomized, double-blind, placebo-controlled study have shown that children with mild asthma treated with the highest approved dose of flunisolide HFA over a 1-year period grow at the same rate as children treated with placebo. This is consistent with an open-label safety study of children aged 4 to 12 that also demonstrated no effect on linear growth during 1 year of treatment with flunisolide HFA compared with cromolyn.¹⁴ The lack of growth suppression in a year-long trial with flunisolide HFA is in contrast to numerous well-controlled trials that have shown suppressed growth in children during treatment with other ICSs. A review was conducted of all published, prospective, randomized, double-blind, placebo (or nonsteroidal)-controlled studies of ICS in asthmatic children with a duration of treatment of at least 7 months. A summary of these trials is shown in Table 3. Review of these results shows significant reduction in growth with beclomethasone CFC,³ budesonide dry powder inhaler,^{4,5} and triamcinolone CFC⁷ relative to control. Beclomethasone CFC has been consistently demonstrated to have significant growth suppression in multiple studies.^{3,15} In a comparative study by Pederesen et al,¹⁶ beclomethasone HFA, at half the CFC dose, was shown to have greater growth suppression after 6 months of treatment, and similar effects after 12 months, as beclomethasone CFC. The statistical significance of the Flovent Rotadisk Diskhaler growth rate results has been debated, with the publication by Allen et al¹⁷ not showing statistical significance, but the analysis by Sharek and Bergman³ demonstrating a statically significant decrease in growth velocity compared with placebo. A study of fluticasone CFC in preschool patients demonstrated 1.1 cm of growth suppression over 2 years, the effect occurring predominantly during the first year of treatment.¹⁸ The effect of fluticasone on growth velocity may be different between formulations, because the MDI formulations have significantly higher lung deposition and

Table 3. Change in Height (cm/year) in Randomized, Controlled Trials of ICS of ≥ 7 Months Duration that Evaluated Growth

Steroid/form	Reference	No. evaluated	Age (years)	Duration of study	Dose	Change in height (cm/year)		P
						ICS	Control	
Beclomethasone/CFC MDI (meta-analysis)	[3]	450	6–16	7 mos–1 year	328–400 μ g/day	NR	NR (Placebo, salmeterol, or theophylline)	<.05
Budesonide/Inhalation Powder	[4]	1,041	5–12	4–6 years	200 μ g bid	22.7 ^a	23.8 (Placebo) ^a	.005
Budesonide/Inhalation Powder	[5]	7,241	5–15	1 year	200 μ g/day	NR	NR (placebo)	<.0001
Flunisolide/HFA	[13]	235	4–11	1 year	400 μ g/day	NR	NR (placebo)	<.0001
Fluticasone/Inhalation Powder	[6]	325	4–11	1 year	170 μ g bid	6.2	6.2 (Cromolyn sodium)	NS
Fluticasone/Inhalation Powder	[25]	60	4–10	1 year	50 μ g bid	6.07	6.32 (Placebo)	NR
Fluticasone/Inhalation Powder	[25]	60	4–10	1 year	100 μ g bid	5.66	6.32 (Placebo)	NR
Fluticasone/Inhalation Powder	[25]	60	4–10	1 year	50 μ g bid	6.0	6.5 (Sodium cromoglycate)	.08
Fluticasone/CFC MDI	[18]	285	2–3	2 years	88 μ g bid	12.6 ^b	13.7 ^b	<.001
Mometasone/Inhalation Powder	[8]	187	4–9	1 year	110 μ g bid	5.34	6.44 (Placebo)	NR
Mometasone/Inhalation Powder	[8]	187	4–9	1 year	220 μ g/day	5.93	6.44 (Placebo)	NR
Mometasone/Inhalation Powder	[8]	187	4–9	1 year	110 μ g/day	6.14	6.44 (Placebo)	NR
Triamcinolone/CFC MDI	[7]	NR	Pre-pubescent	1 year	Mean 600 μ g/day	5.3	6.1 (Nonsteroid)	<.001

Abbreviations: bid, twice daily; HFA, hydrofluoroalkane; NR, Not reported; NS, not significant; MDI, metered dose inhaler; mos, months.

^a Mean growth (cm) over 4 years of treatment.

^b Mean growth (cm) over 2 years of treatment.

subsequent systemic exposure than the Diskhaler.¹⁹ Growth rates were also lower for twice-daily dosing with mometasone compared with placebo, although results of statistical testing were not reported.⁸ A recent study with once-daily ciclesonide failed to demonstrate growth suppression; however, ciclesonide is not approved for use in children younger than 12 years of age.²⁰

As displayed in Figure 1, the growth curves for children treated with flunisolide HFA and placebo over the 52-week treatment period are overlapping, with no early change in growth noted with flunisolide HFA. The growth pattern during treatment with other steroids has shown greater growth suppression in the early treatment period, with a slowing of growth seen as early as 1 month after start of therapy. Pauwels et al⁵ found an average growth reduction of 1.34 cm during 3 years of treatment with budesonide. However, the average growth reduction was greater in the first year (0.58 cm) than in the second or third years (0.43 and 0.33 cm, respectively). Consistent with these findings, the Childhood Asthma Management Program study⁴ also showed a reduction in growth with budesonide throughout the 4-year treatment, with the difference from placebo being greater during the initial year. In this trial, although some children aged 4 to 5 may not use an MDI optimally, even with the attached spacer, there was consistency in growth effect across age groups. The 4- to 5-year-olds in this study were not required to have spirometry performed to help confirm the diagnosis of asthma.

Results of the current study indicate that 1 year of treatment with flunisolide HFA did not interfere with bone maturation in children. The progression of bone development was similar in the flunisolide HFA and placebo groups and represented an average 1-year advancement in bone age consistent with the duration of treatment. In general, bone maturation appears to be a less sensitive marker of steroid side effects than growth velocity. The Childhood Asthma Management Program investigators found that bone age was similar in budesonide- and placebo-treated subjects by the end of 4 years of treatment.⁴

Attempts have been made to determine whether children who experience slowing of growth during treatment with ICS achieve normal adult height. Agertoft and Pedersen⁹ concluded that "children with asthma who have received long-term treatment with budesonide attain normal height" based on 2 shorter retrospective trials^{21,22} and a prospective uncontrolled study.²³ The Childhood Asthma Management Program investigators suggested that budesonide-treated children would achieve adult height similar to that of controls, but this was based on projected height rather than actual observations.⁴ Although these projections are somewhat reassuring, no evidence from randomized controlled trials shows that height losses early in childhood are completely reversed before growth ends.

In conclusion, the results of this trial have clearly shown that linear growth and bone maturation are unaffected by 1 year of therapy with inhaled flunisolide HFA in prepubescent

children with mild persistent asthma. The previously described safety profile of flunisolide HFA was confirmed in this population.^{14,24} This lack of growth effect in this trial is in contrast to other approved ICSs that have shown suppressed growth in children during treatment, although the effect on adult height remains unclear.

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Requests for reprints should be sent to:
George W. Bensch, MD
Allergy, Immunology, and Asthma Medical Group, Inc.
4628 Georgetown Place
Stockton, CA 95207
E-mail: docbensch4@aol.com