

Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone

Theresa W. Guilbert, MD,^a David T. Mauger, PhD,^d David B. Allen, MD,^a Robert S. Zeiger, MD, PhD,^{e,f} Robert F. Lemanske, Jr, MD,^b Stanley J. Szeffler, MD, PhD,^g Robert C. Strunk, MD,^h Leonard B. Bacharier, MD,^h Ronina Covar, MD,^g Christine A. Sorkness, PharmD,^c Lynn M. Taussig, MD,^g and Fernando D. Martinez, MD,ⁱ on behalf of the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute *Madison, Wis, Hershey, Pa, San Diego, Calif, Denver, Colo, St Louis, Mo, and Tucson, Ariz*

Background: The effect on linear growth of daily long-term inhaled corticosteroid therapy in preschool-aged children with recurrent wheezing is controversial.

Objective: We sought to determine the effect of daily inhaled corticosteroid given for 2 years on linear growth in preschool children with recurrent wheezing.

Methods: Children aged 2 and 3 years with recurrent wheezing and positive modified Asthma Predictive Index scores were randomized to a 2-year treatment period of chlorofluorocarbon-delivered fluticasone propionate (176 µg/d) or masked placebo delivered through a valved chamber with a mask and then followed for 2 years off study medication. Height growth determined by means of stadiometry was compared between treatment groups.

Results: In the study cohort as a whole, the fluticasone group did not have significantly less linear growth than the placebo group (change in height from baseline difference, -0.2 cm; 95% CI, -1.1 to 0.6) 2 years after discontinuation of study treatment. In *post hoc* analyses children 2 years old who weighed less than 15 kg at enrollment and were treated with fluticasone had less

linear growth compared with those treated with placebo (change in height from baseline difference, -1.6 cm; 95% CI, -2.8 to -0.4 ; $P = .009$).

Conclusion: Linear growth was not significantly different in high-risk preschool-aged children with recurrent wheezing treated with 176 µg/d chlorofluorocarbon-delivered fluticasone compared with placebo 2 years after fluticasone is discontinued. However, *post hoc* subgroup analyses revealed that children who are younger in age and of lesser weight relative to the entire study cohort had significantly less linear growth, possibly because of a higher relative fluticasone exposure. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: Asthma Predictive Index, atopy, clinical trials, early childhood asthma, fluticasone, inhaled corticosteroids, intermittent wheezing, linear growth, research network

Interpretation of study results evaluating linear growth in childhood asthma is difficult because of competing effects on growth related to the uncontrolled disease itself versus those

From the Departments of ^aPediatrics and ^bMedicine and the ^cSchool of Pharmacy, University of Wisconsin–Madison; ^dthe Department of Public Health Services, Pennsylvania State University, Hershey; ^ethe Department of Allergy, University of California–San Diego; ^fKaiser Permanente San Diego; ^gthe Department of Pediatrics, National Jewish Health, Denver; ^hthe Department of Pediatrics, Washington University, St Louis; and ⁱthe Department of Pediatrics, Arizona Respiratory Center, University of Arizona, Tucson.

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Further details on the study group are provided in Appendix E1 in this article's Online Repository at www.jacionline.org.

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Reprint requests: Theresa W. Guilbert, MD, Department of Pediatrics, University of Wisconsin–Madison, 600 Highland Ave, K4/944, CSC-4108, Madison, WI 53716. E-mail: tguilbert@wisc.edu.

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Abbreviations used

CAMP: Childhood Asthma Management Program
 CARE: Childhood Asthma Research and Education
 Δ Ht: Change in height from baseline difference
 ICS: Inhaled corticosteroid
 PEAK: Prevention of Early Asthma in Kids

related to its treatment. Children with persistent asthma of at least moderate severity eventually attain adult height, usually in the predicted range.¹ However, these children might demonstrate a delay in linear growth² associated with inhaled corticosteroid (ICS) therapy. In the Prevention of Early Asthma in Kids (PEAK) study, we previously reported that toddler-aged children with recurrent wheeze at high risk for the development of asthma treated for 2 years with fluticasone (176 μ g/day) demonstrated a 1.1-cm reduction in height gained at the end of this treatment period caused by a delay in linear growth compared with those treated with placebo.³ However, after cessation of regularly scheduled fluticasone therapy in the next year, between-group differences were no longer significant because of an increase in linear growth in the ICS-treated group. On the basis of these findings, we hypothesized that the cohort of ICS-treated children overall would have linear growth similar to that of the placebo group 2 years after treatment discontinuation. However, we also evaluated whether particular subgroups of children could be at higher risk for growth-suppressing effects from ICS exposure.

METHODS

A detailed description of the screening, recruitment, design, algorithms for the addition and reduction/cessation of supplementary medications (eg, open-label ICS or montelukast), and criteria for assignment of treatment failure status and statistical analysis for the PEAK trial has been reported in detail elsewhere⁴ but will be described briefly here.

Study design and treatments

PEAK is a multicenter, double-blind, randomized, placebo-controlled, parallel-group comparison trial of inhaled fluticasone with placebo in children 24 to 35 months (2 years) and 36 to 47 months (3 years) of age at high risk for the development of asthma.⁴ These children were treated for 2 years by using an AeroChamber with a mask (donated by Monaghan Medical, Plattsburgh, NY) with fluticasone propionate or Flovent, 44 μ g/puff, 2 puffs twice daily, through a metered-dose inhaler or matching placebo (both donated by Glaxo-SmithKline, Research Triangle Park, NC), and then randomized treatment was stopped. Adherence was promoted by using a standardized educational approach and measured with an electronic meter (Doser), as detailed previously.⁴ The children were then followed for an additional year during which the primary outcome indicators were measured. Of the 285 children in the original study cohort, 204 were enrolled in a 12-month extension and completed the entire 4-year study. The primary safety analysis in the PEAK study was linear growth, and thus continued observation of this cohort was a high priority for the Childhood Asthma Research and Education (CARE) Network. The enrolled children had no clinically significant medical disorders apart from wheezing or allergy and were at high risk for asthma-like symptoms to continue during the school years based on a positive modified Asthma Predictive Index score.^{3,5}

Institutional review boards at all participating centers approved the protocol and consent forms; the trial was monitored by the CARE Network's Data and Safety Monitoring Board. The role of commercial sponsors was limited to donating drug and matched placebo, which they did after reviewing the drafted protocol. The text of the manuscript was made available to all the commercial sponsors 2 weeks before submission for finalization for comments.

Outcome measures

Height was measured every 4 months during the 36 months of the study and at the 48-month extension study visit with an upright stadiometer (Harpender, Holtain, United Kingdom) by using established CARE Network procedures.^{4,6} A medical history and symptom evaluation, family and environmental history, and eosinophil count were obtained during the enrollment visit. An exacerbation was defined as the need for a prednisolone course to control asthma-like symptoms as directed by protocol. Skin prick testing with a core battery of 10 allergens in all clinical centers was performed at enrollment.^{3,4,7}

Statistical analyses

The primary analysis focused on the difference in linear growth between the ICS-treated group and the placebo-treated group in the 204 children who completed the 4-year study including the extension. Growth was characterized as change from baseline with 2 different metrics: absolute height measured in centimeters and height *z* scores calculated with age- and sex-standardized growth charts (Centers for Disease Control and Prevention [CDC], 2000).⁸ Linear mixed-effects regression with absolute height (in centimeters) or height *z* score as the outcome was used to model the longitudinal effects of treatment at each study visit while adjusting for baseline covariates and for open-label ICS and oral corticosteroid use during both the treatment and follow-up periods. Linear contrasts were used to estimate the difference between treatment groups with respect to change from baseline at each study visit. We first examined models that incorporated age and weight as continuous variables. These analyses indicated a larger effect of ICSs among the younger children of lesser weight (results are fully reported below). Sensitivity analyses indicated that the results of the stratified analyses were very similar over a range of weight cut points between 15 and 17 kg and age cut points near 3 years. We further examined the effect of ICSs by incorporating an interaction between age dichotomized at 3 years and weight dichotomized at 15 kg. The selected cut points were chosen based on 2 considerations: first, that they were consistent with the effects seen in the continuous variable model, and second, that they were clinically useful. A complete description of the statistical methods is included in the *Methods* section in this article's Online Repository at www.jacionline.org.

Linear mixed-effects regression was performed with PROC MIXED in the SAS statistical software system, version 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS**Study population**

In the original cohort of 285 children, the 2 treatment groups were similar with respect to all baseline characteristics,³ except for a higher percentage of peripheral blood eosinophils in the ICS group. There were no significant differences in the number of completed clinic visits, dropouts, treatment failures, or serious adverse events between groups.³ Less than 12% were lost to follow-up (dropouts) in both groups 1 year after treatment discontinuation,³ with a total of 28% two years after treatment discontinuation, leaving 204 children for analysis (see Fig E1 in this article's Online Repository at www.jacionline.org).

The baseline characteristics of these 204 children who completed the extension study were similar to those of the original study cohort of 285 ($P > .5$ for all, see Table E1 in this article's Online Repository at www.jacionline.org). It should be noted that the results did not change when the analyses also included partial follow-up data from children who did not complete the study or if the models did not include baseline covariates.

Overall growth analysis of the 204 children who completed the 4-year study

Further data on the overall growth analysis of the 204 children who completed the 4-year study can be found in Fig E2 (available

TABLE I. Change in height (in centimeters) from baseline to 24 and 48 months*

Stratifying variable	Strata	No.	Change in height from baseline to 24 mo			Change in height from baseline to 48 mo		
			ICS mean (95% CI)	Placebo mean (95% CI)	ICS vs placebo (95% CI)	ICS mean (95% CI)	Placebo mean (95% CI)	ICS vs placebo (95% CI)
Overall cohort		204	12.6 (12.2 to 13.0)	13.5 (13.2 to 13.9)	−0.9 (−1.4 to −0.4)‡	25.7 (25.0 to 26.3)	25.9 (25.3 to 26.5)	−0.2 (−1.1 to 0.6)
Age	2 y	105	13.4 (12.8 to 13.9)	14.4 (13.9 to 15.0)	−1.1 (−1.8 to −0.3)‡	26.6 (25.8 to 27.4)	27.5 (26.7 to 28.3)	−0.8 (−1.9 to 0.3)
	3 y	99	11.9 (11.3 to 12.4)	12.7 (12.2 to 13.1)	−0.8 (−1.5 to −0.1)†	24.7 (23.8 to 25.7)	24.4 (23.5 to 25.2)	0.4 (−0.9 to 1.6)
Baseline weight	<15 kg	104	12.3 (11.8 to 12.8)	13.2 (12.7 to 13.7)	−1.0 (−1.7 to −0.3)‡	24.9 (24.2 to 25.7)	25.4 (24.6 to 26.3)	−0.5 (−1.6 to 0.6)
	≥15 kg	100	13.0 (12.3 to 13.6)	13.8 (13.4 to 14.3)	−0.9 (−1.6 to −0.1)†	26.4 (25.4 to 27.4)	26.4 (25.6 to 27.2)	0.0 (−1.1 to 1.2)
Sex	Female	124	12.7 (12.1 to 13.3)	13.6 (13.1 to 14.1)	−0.9 (−1.7 to −0.1)†	25.9 (24.9 to 27.0)	26.1 (25.1 to 27.0)	−0.1 (−1.5 to 1.2)
	Male	80	12.5 (12.0 to 13.0)	13.4 (13.0 to 13.9)	−0.9 (−1.6 to −0.2)‡	25.4 (24.7 to 26.1)	25.8 (25.1 to 26.4)	−0.3 (−1.3 to 0.6)
Race	White	118	12.3 (11.7 to 12.8)	13.3 (12.9 to 13.7)	−1.0 (−1.7 to −0.4)‡	25.7 (24.8 to 26.5)	26.0 (25.2 to 26.7)	−0.3 (−1.3 to 0.8)
	Nonwhite	86	13.0 (12.4 to 13.5)	13.7 (13.2 to 14.3)	−0.8 (−1.6 to 0.0)	25.7 (24.8 to 26.6)	25.9 (25.0 to 26.8)	−0.2 (−1.4 to 1.1)
Age 2 y: baseline weight	<15 kg	70	12.9 (12.4 to 13.5)	14.2 (13.6 to 14.8)	−1.3 (−2.1 to −0.5)‡	25.7 (25.0 to 26.5)	27.3 (26.4 to 28.3)	−1.6 (−2.8 to −0.4)‡
	≥15 kg	35	13.8 (12.8 to 14.8)	14.6 (13.8 to 15.4)	−0.8 (−2.1 to 0.4)	27.5 (26.2 to 28.9)	27.6 (26.4 to 28.8)	−0.1 (−1.9 to 1.7)
Age 3 y: baseline weight	<15 kg	34	11.6 (10.8 to 12.5)	12.3 (11.5 to 13.0)	−0.6 (−1.7 to 0.5)	24.1 (22.9 to 25.4)	23.5 (22.2 to 24.9)	0.6 (−1.3 to 2.4)
	≥15 kg	65	12.1 (11.3 to 12.9)	13.0 (12.6 to 13.5)	−0.9 (−1.8 to 0.0)†	25.3 (24.0 to 26.6)	25.2 (24.2 to 26.1)	0.1 (−1.4 to 1.7)

*The linear mixed-effects regression model was adjusted for baseline covariates, including clinical center, sex, race, history of eczema, percentage of blood eosinophils, aeroallergen skin test positivity, age, weight, and height.

†Difference between ICS and placebo is significant at a *P* value of less than .05.

‡Difference between ICS and placebo is significant at a *P* value of less than .01.

in this article's Online Repository at www.jacionline.org) and Tables I and II.

The height and weight at enrollment were not significantly different between treatment groups at enrollment in the 204 children who completed the 4-year study. Similar to a previous report, the fluticasone group that completed the study had a significantly lower increase in height adjusted for baseline covariates and for open-label ICS and oral corticosteroid use during both the treatment and follow-up periods than the placebo group (change in height from baseline difference [Δ Ht], 0.9 cm; *P* = .0007).³ Two years after study treatment discontinuation, the mean increase in height attained from baseline in the fluticasone group was not significantly different from that seen in the placebo group (Δ Ht, 0.2 cm; *P* = .6). The fluticasone group grew significantly faster than the placebo group after treatment discontinuation (6.5 vs 6.2 cm/y, *P* = .02). Weight gain was not significantly different between treatment groups during treatment or after treatment discontinuation.

Subgroup analyses

When examined in a *post hoc* analysis, patterns of linear height growth, but not weight, were different in certain subgroups of children (detailed below).

Subgroup analysis by weight at enrollment

Further data on subgroup analysis by weight at enrollment are shown in Fig 1, A and E.

By using a linear mixed-effects regression model with data from all study visits, children weighing less than 15 kg at enrollment demonstrated significantly less linear growth during fluticasone treatment compared with that during placebo treatment (Δ Ht, 1 cm; *P* = .007), but linear growth was not significantly different 2 years after treatment discontinuation (Δ Ht,

0.5 cm; *P* = .38). A similar pattern was seen in those who weighed at least 15 kg.

Subgroup analysis by age at enrollment

Further data on subgroup analysis by age at enrollment can be found in Fig 1, B and F, and Tables I and II.

By using a linear mixed-effects regression model with data from all study visits, children aged 2 years at enrollment demonstrated significantly less linear growth during fluticasone treatment compared with the placebo group (Δ Ht, 1.1 cm; *P* = .006), but linear growth was not significantly different 2 years after treatment discontinuation (Δ Ht, 0.8 cm; *P* = .13). A similar effect was seen in those who were 3 years of age.

Subgroup analyses by age and weight at enrollment

Children at particular risk for less linear growth during treatment were those who were 2 years of age and weighed less than 15 to 17 kg at enrollment (Fig 2, B).⁹ After the ICS treatment ended, these younger children of lesser weight (relative to the cohort) did not demonstrate the same catch up in linear growth demonstrated by the younger and heavier (relative to the cohort) children (Fig 2, E) or older children of any weight (Fig 2, F). Two years after treatment discontinuation ended, less linear growth was observed in only the younger children of lesser weight (Fig 2, H).

When weight was dichotomized at 15 kg, children who were 2 years of age and weighed less than 15 kg at enrollment demonstrated significantly less linear growth during fluticasone treatment compared with the placebo group (Δ Ht, 1.3 cm; *P* = .002; Fig 1, C and G, and Tables I and II). Two years after treatment discontinuation, these children still had significantly less linear growth from baseline (Δ Ht, 1.6 cm; *P* = .008; Fig 1, C

TABLE II. Change in height z score from baseline to 24 and 48 months

Stratifying variable	Strata	No.	Change in height z score from baseline to 24 mo			Change in height z score from baseline to 48 mo		
			ICS mean (95% CI)	Placebo mean (95% CI)	ICS vs placebo (95% CI)	ICS mean (95% CI)	Placebo mean (95% CI)	ICS vs placebo (95% CI)
Overall cohort		204	−0.10 (−0.19 to −0.01)	0.11 (0.03 to 0.18)	−0.20 (−0.31 to −0.09)‡	−0.08 (−0.20 to 0.03)	−0.04 (−0.15 to 0.06)	−0.04 (−0.18 to 0.10)
Age	2 y	105	−0.07 (−0.20 to 0.06)	0.19 (0.07 to 0.31)	−0.26 (−0.43 to −0.09)‡	−0.05 (−0.20 to 0.10)	0.09 (−0.06 to 0.24)	−0.14 (−0.34 to 0.05)
	3 y	99	−0.13 (−0.24 to −0.01)	0.02 (−0.06 to 0.11)	−0.15 (−0.28 to −0.01)†	−0.11 (−0.26 to 0.04)	−0.18 (−0.31 to −0.05)	0.07 (−0.12 to 0.26)
Baseline weight	<15 kg	104	−0.10 (−0.20 to 0.00)	0.11 (0.01 to 0.21)	−0.20 (−0.34 to −0.07)‡	−0.06 (−0.18 to 0.07)	0.03 (−0.10 to 0.15)	−0.08 (−0.26 to 0.09)
	≥15 kg	100	−0.10 (−0.24 to 0.04)	0.10 (0.00 to 0.21)	−0.20 (−0.37 to −0.03)†	−0.11 (−0.28 to 0.06)	−0.11 (−0.26 to 0.03)	0.01 (−0.20 to 0.21)
Sex	Female	124	−0.10 (−0.23 to 0.03)	0.11 (0.01 to 0.21)	−0.21 (−0.37 to −0.05)†	−0.13 (−0.30 to 0.05)	−0.13 (−0.27 to 0.02)	0.00 (−0.22 to 0.21)
	Male	80	−0.09 (−0.20 to 0.02)	0.10 (0.01 to 0.20)	−0.20 (−0.34 to −0.05)‡	−0.03 (−0.15 to 0.09)	0.04 (−0.08 to 0.16)	−0.07 (−0.23 to 0.09)
Race	White	118	−0.17 (−0.28 to −0.06)	0.04 (−0.05 to 0.13)	−0.21 (−0.34 to −0.07)‡	−0.08 (−0.22 to 0.06)	−0.07 (−0.19 to 0.05)	−0.01 (−0.17 to 0.15)
	Nonwhite	86	−0.03 (−0.16 to 0.10)	0.17 (0.06 to 0.28)	−0.20 (−0.37 to −0.03)†	−0.08 (−0.24 to 0.07)	−0.02 (−0.18 to 0.14)	−0.07 (−0.28 to 0.15)
Age 2 y: baseline weight	<15 kg	70	−0.13 (−0.25 to 0.00)	0.21 (0.07 to 0.34)	−0.33 (−0.51 to −0.16)‡	−0.08 (−0.23 to 0.06)	0.21 (0.05 to 0.37)	−0.30 (−0.50 to −0.09)‡
	≥15 kg	35	−0.01 (−0.24 to 0.21)	0.17 (−0.02 to 0.35)	−0.18 (−0.47 to 0.10)	−0.02 (−0.27 to 0.23)	−0.03 (−0.27 to 0.20)	0.01 (−0.31 to 0.34)
Age 3 y: baseline weight	<15 kg	34	−0.07 (−0.22 to 0.08)	0.01 (−0.14 to 0.15)	−0.07 (−0.28 to 0.13)	−0.03 (−0.22 to 0.17)	−0.16 (−0.35 to 0.04)	0.13 (−0.14 to 0.41)
	≥15 kg	65	−0.18 (−0.34 to −0.03)	0.04 (−0.06 to 0.13)	−0.22 (−0.40 to −0.04)†	−0.19 (−0.39 to 0.00)	−0.19 (−0.35 to −0.03)	0.00 (−0.24 to 0.24)

*The linear mixed-effects regression model was adjusted for baseline covariates, including clinical center, sex, race, history of eczema, percentage of blood eosinophils, aeroallergen skin test positivity, age, weight, and height.

†Difference between ICS and placebo is significant at a *P* value of less than .05.

‡Difference between ICS and placebo is significant at a *P* value of less than .01.

and *G*, and Tables I and II). In contrast, linear growth was not significantly different after treatment discontinuation in the younger children of greater weight (relative to the cohort; ΔHt, 0.1 cm; *P* = .94; Fig 1, *C* and *G*, and Tables I and II) or in the older children of any weight (<15 kg ΔHt, 0.6 cm [*P* = .53]; ≥15 kg ΔHt, 0.1 cm [*P* = .85]; Fig 1, *D* and *H*, and Tables I and II). In the younger children of lesser weight (relative to the cohort), 31% received ICSs, 51% received oral corticosteroids for respiratory symptoms, and 59% reported asthma symptoms or an asthma exacerbation in the past 12 months during the 2-year period after treatment discontinuation. These are similar to the younger children of greater weight and the older children of any weight (see Table E2 in this article's Online Repository at www.jacionline.org).

Subgroup analysis by other baseline characteristics

No significant differences in linear growth were seen during treatment or 2 years after treatment discontinuation for the following baseline characteristics: sex, race, exacerbations in the past year on ICS treatment, allergic sensitization, eczema, or eosinophilia (Tables I and II with some data not shown). No significant interactions on linear growth were seen during fluticasone treatment or 2 years after treatment discontinuation by age and the aforementioned baseline characteristics (data not shown).

DISCUSSION

The present growth analyses in the PEAK preschool-aged cohort with recurrent wheezing at high risk of asthma demonstrated that 2 years of treatment with fluticasone (176 μg/d) is associated with less linear growth that dissipates over time after treatment discontinuation when the cohort as a whole is evaluated. The ICS-treated group as a whole demonstrated catch-up linear growth during the 2 years after treatment discontinuation. However, *post hoc* analysis identified a subgroup of younger children of lesser weight (1 years of age and <17 kg at enrollment) who did not demonstrate catch-up linear growth. We confirm the findings of Murray et al,¹⁰ who showed that ICS compared with placebo had a greater effect on linear growth in younger (age 2 years) versus older (age 3 years) children. Similar to the PEAK study, school-aged children with persistent asthma treated with budesonide (400 μg/d) for an average of 4.3 years in the Childhood Asthma Management Program (CAMP) study had gained 1.1 cm less in height at the end of the study period compared with the placebo group.² The difference in mean height in the budesonide group relative to the placebo group at the end of the trial diminished but remained statistically significant (0.9 cm, *P* = .01) an additional 4.8 years¹¹ after the study medication was stopped. Participants in all CAMP treatment groups used ICSs during 30% of the posttrial period, which is similar to the 40% observed in the PEAK study. In this study the ICS-treated

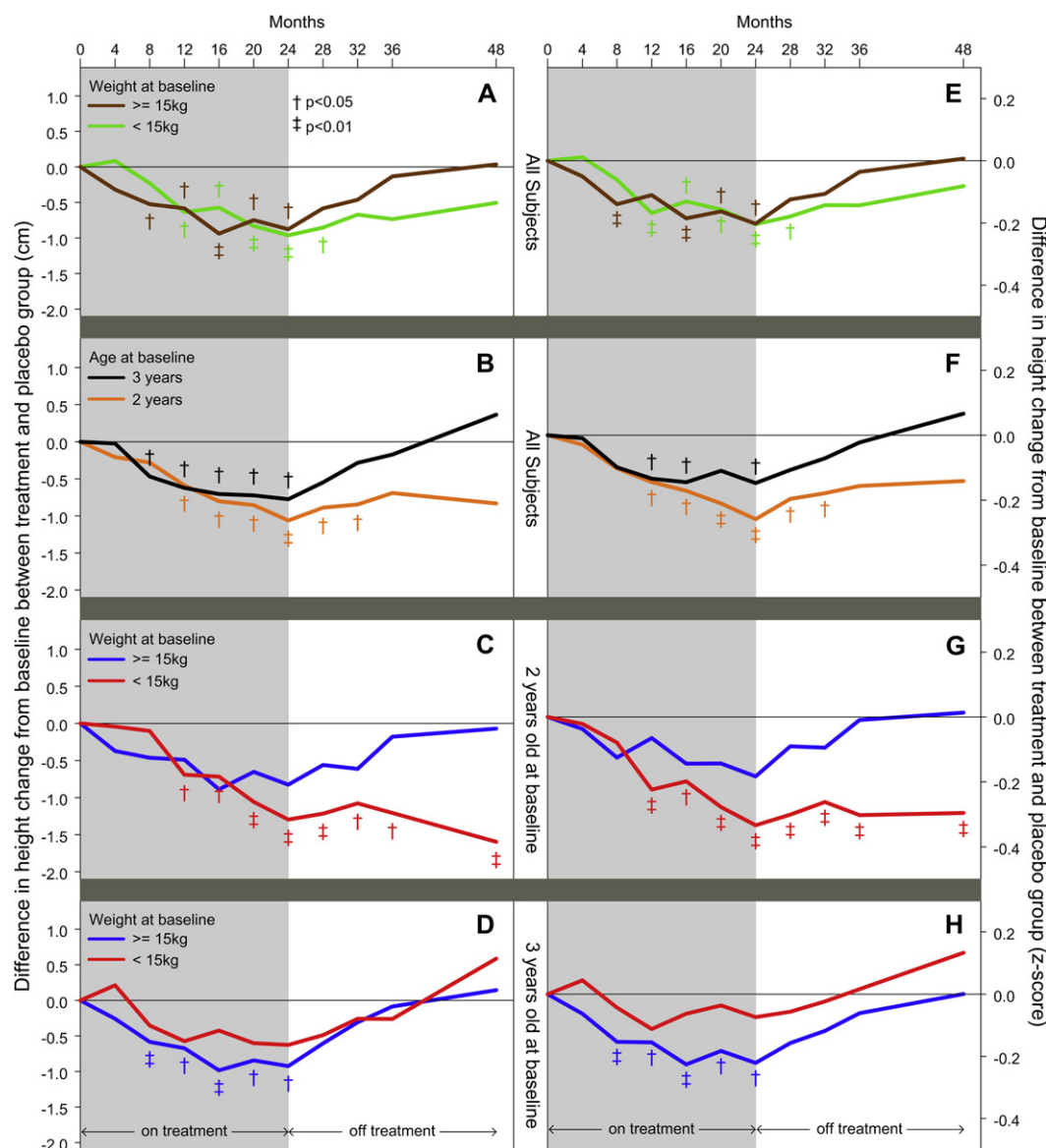


FIG 1. *Post hoc* subgroup analyses. Difference in height change (left panel, height change; right panel, zscore change) from baseline to 48 months for the fluticasone-treated group compared with the placebo-treated group. At the end of the 2-year observation period, linear growth was not reduced in the children who were lesser weight relative to the cohort versus those of greater weight (A and E) or children who were 2 years of age at enrollment versus those who were 3 years (B and F). Children at particular risk for less linear growth during treatment were those who were 2 years of age and weighed less than 15 kg at enrollment. At the end of the 2-year observation period, linear growth was only reduced in the children who were 2 years of age at enrollment and of lesser weight (relative to the cohort) versus the younger children with a greater weight (C and G) or the older children with any enrollment weight (D and H). Results were obtained by using linear mixed-effects regression, including data from all study visits, while adjusting for baseline covariates. Significant differences between treatment groups denoted as follows: † $P < .05$ and ‡ $P < .01$.

groups had less linear growth than the placebo-treated group; however, the effect diminished with time even while these children continued to receive ICS treatment and even more so once ICS treatment was discontinued. The PEAK study identified a group of younger children of lesser weight (relative to the cohort) for whom the growth-suppressive effects of ICSs were pronounced, and this effect did not diminish with time or after the ICS treatment was discontinued. This is in contrast to the effects observed in the younger children of greater weight (relative to the cohort) or the older children of any weight after adjusting for

open-label ICS and oral corticosteroid use during both the treatment and follow-up periods.

The effect of ICS exposure on linear growth might be more profound in younger children of lesser weight (2 years of age and <17 kg at enrollment) who might be predisposed to growth rates in the low to middle end of the normal range in early childhood.¹² In addition, the weight gain was not significantly different between treatment groups at baseline, during treatment, or after treatment was discontinued. Indeed, these children with an enrollment weight of less than 17 kg remained lighter relative

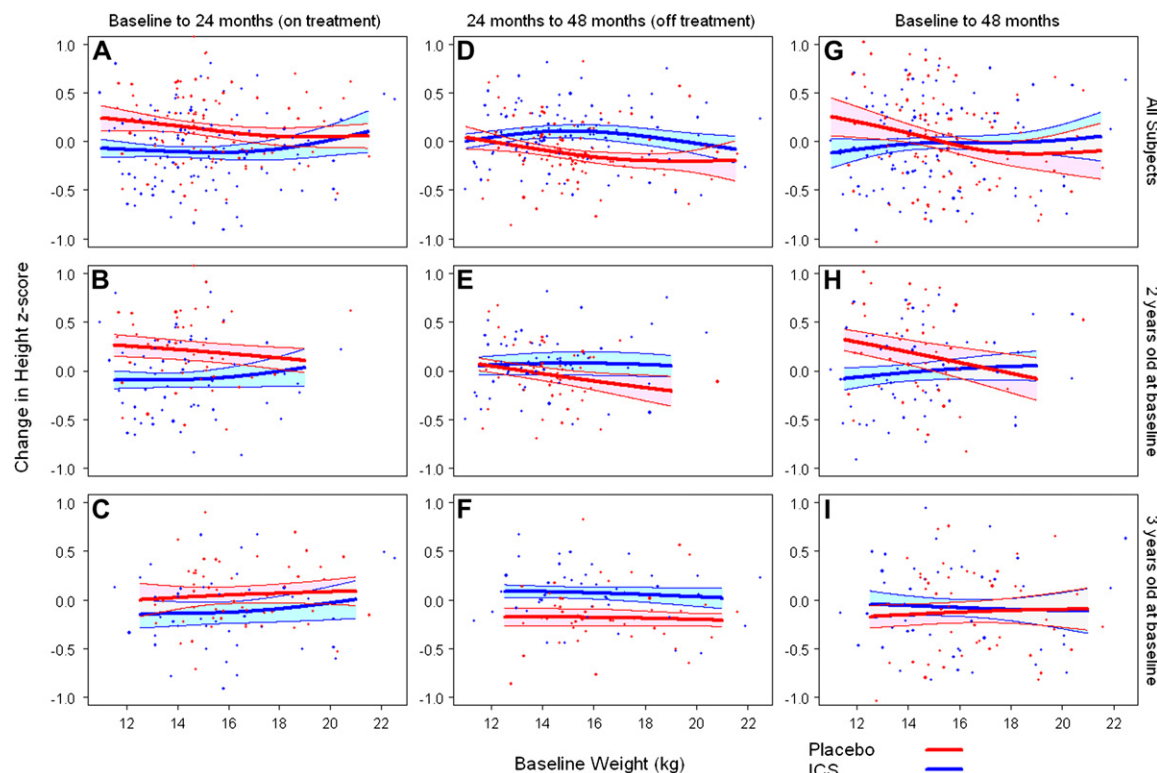


FIG 2. Scattergrams of growth from baseline (z score) during treatment versus enrollment weight by treatment group. *Top panels*, Overall cohort; *middle panels*, subjects 2 years old at enrollment; *bottom panels*, subjects 3 years old at enrollment. Children at particular risk for less linear growth during treatment were those with an enrollment weight of less than 17 kg versus those with lesser exposure compared with their respective placebo-treated counterparts (**A**). This was more pronounced in the children who were 2 years of age at enrollment (**B**) compared to those that were 3 years (**C**). After the ICS treatment ended, these younger children of lesser weight (relative to the cohort) did not demonstrate the same catch up in linear growth demonstrated by the overall cohort (**D**), younger children of greater weight (**E**) or older children of any weight (**F**). Two years after treatment discontinuation, less linear growth was observed in only the younger children of lesser weight (**H**) compared to the overall cohort (**G**) or older children of any weight (**I**). *Solid lines (blue, ICS; red, placebo)* represent fitted values from the nonparametric smoothing splines with 95% confidence bands.⁹ All data values were used for model fitting, but estimated regression lines are truncated to avoid extrapolation beyond the main part of the data.

to their peers at the end of the study. The younger children of lesser weight likely received a higher relative exposure (in micrograms per kilogram) of fluticasone than the older children. However, this does not appear to be solely a weight effect because the older children of lesser weight (3 years of age and <17 kg at enrollment) did not show the same growth effect and demonstrated significant catch-up growth once the ICS treatment was discontinued. Thus the ICS exposure might have occurred during a key period of rapid growth in these children who were 2 years of age and weighed less than 17 kg at enrollment, and they were unable to accelerate their growth rate to the degree needed to catch up to their peers. Furthermore, no consistent greater clinical benefit with respect to episode-free days or oral corticosteroid courses were seen in the younger children of lesser weight with a higher fluticasone exposure compared with those with a lower exposure (data not shown), and a previous analysis of this cohort demonstrated that 2-year-old children did not have more favorable responses to fluticasone than placebo compared with 3-year-old children.¹³ Thus a higher relative ICS exposure resulted in an increased risk of less linear growth in the younger children of lesser weight without a

correspondingly greater clinical benefit in symptom control or exacerbations.

In studies of this age group of children with recurrent wheezing^{10,14} and in other studies of older children with persistent wheezing,^{2,15} the inhibitory effect of ICSs on growth appears to be “front loaded” or occurs during the first year of ICS treatment, and the effect diminishes over time. However, in this study the younger children of lesser weight (relative to the cohort) had a different pattern in which they did not demonstrate catch-up growth over time. Unlike the CAMP study in older children with persistent asthma, we did not find that girls in the PEAK study were more likely to have less linear growth.¹¹ In addition, these observations differ from the normal growth velocities reported in a study of fluticasone treatment for 1 year¹⁶ in preschool children with recurrent wheezing. A larger-volume spacer,^{16,17} which might have led to a different ICS deposition pattern, less adherence, or the higher dropout rate seen in the study by Bisgaard et al,¹⁶ might explain these differences in findings.

On the basis of the observed effects of ICSs on growth in the younger children of lesser weight (relative to the cohort), an estimate for a cutoff for per kilogram of fluticasone dose that

would be expected to have the largest growth effect was determined. In this analysis we saw a growth effect in the children 2 years of age and weighing less than 17 kg at enrollment (Fig 2 and see Fig E3 in this article's Online Repository at www.jacionline.org) that persisted 2 years after treatment was discontinued. On the basis of the chlorofluorocarbon-delivered fluticasone dose of 176 $\mu\text{g}/\text{d}$ used in the PEAK study, we estimate that 10 $\mu\text{g}/\text{kg}/\text{d}$ is the upper limit of fluticasone dose to avoid the potential effects of long-term daily ICS use on growth in children 2 to 3 years of age. This dose range is speculative and would need to be studied prospectively.

Several limitations should be noted. The subgroup analyses described here are *post hoc* because the original study was not designed or powered to examine the linear growth effects of ICSs on smaller subgroups of children with particular baseline characteristics. The results presented herein can serve to generate hypotheses for future studies. The PEAK study was not initially designed to follow these children for an additional year of observation, and thus only 72% of the population had growth outcomes measured 2 years after the ICS treatment was stopped. However, these observations did not change when children who were lost to follow-up by the second observation period were added to the analysis. These results also did not change when the analyses were adjusted for parent-reported adherence. It should be noted that the sample size is smaller for the age-by-weight analyses. Height measurements in very young children can vary in their accuracy; however, we used a similar technique of repeated stadiometric measurements similar to that adopted in the CAMP trials and endocrinology literature.^{2,4,6} It is also possible that the height difference in the 2-year-olds in this group might resolve with time and be attributable to a younger cohort effect.

The PEAK study used a small-volume valved spacer (Aero-Chamber; Monaghan Medical Corp, Plattsburgh, NY) with a mask and a chlorofluorocarbon-based fluticasone inhaler, and we do not know how other types of spacer devices, other types of ICSs, or hydrofluoroalkane-based or dry-powder inhalers would alter these findings. Furthermore, *z* score analyses were used in a manner similar to other growth studies^{18,19} to standardize the study population to a larger reference population.⁸ The average height percentile range of the younger children of lesser weight at enrollment using this reference population was 43.2%. Our placebo population did not perfectly mirror the growth of this reference population, but children with recurrent wheezing might not demonstrate the same growth as a healthier population or have the same racial or ethnic composition, stressing the importance of a placebo group. An additional finding that might limit the generalizability of these results is that 33% of the 2- to 3-year-old children enrolled in the PEAK study cohort were greater than the 75th percentile for weight compared with a reference population (CDC), which might reflect recent observations of increased obesity rates in older children with asthma.²⁰⁻²⁴

ICSs continue to be recommended as the most effective therapy for children with persistent asthma⁹ based on studies clearly demonstrating significantly decreased disease impairment and risk.^{2,3,25} In preschool children at high risk for subsequent asthma, we have also demonstrated that ICS treatment significantly reduces disease burden.³ Previous studies have shown that, on average, the growth-suppressive effects of ICSs are small² and might improve with time,¹ but subgroups with variations in this response are potentially unrecognized when averaging the population. This study has identified a group of children in which ICS therapy was

associated with an increased risk of adverse growth effects without apparent increase in benefit. Therefore in this subgroup these effects need to be balanced with prospective regular assessments of asthma control and possible appropriate ICS dose reductions, discontinuation of medication, use of alternative controller medications, or formulation adjustment to maximize the benefit risk ratios of ICSs.

Clinical implications: The potential for reduced linear growth among children receiving ICSs who are 2 years of age and weigh less than 17 kg should be balanced with the level of asthma control to maximize the benefit/risk ratio of treatment.

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METHODS

Statistical analyses

Linear mixed-effects regression by using absolute height (in centimeters) or height z score as the outcome was used to model the longitudinal effects of treatment across all study visits while adjusting for baseline covariates, including clinical center, sex, race, history of eczema, percentage of blood eosinophils, aeroallergen skin test positivity, age, weight, and height. Growth measured at study visits until the end of the 2-year treatment period was also adjusted for open-label ICS and oral corticosteroid use during the treatment period. Growth measured at study visits during the 2-year follow-up period was adjusted for open-label ICS and oral corticosteroid use during both the treatment and follow-up periods. Linear contrasts were used to estimate the difference between treatment groups with respect to change from baseline at each study visit. Additive models based on smoothing splines^{E1} were used to characterize the effect of baseline weight and age at randomization in a continuous fashion in addition to the dichotomized analyses reported in the print text.

Initial analyses focused on growth based on height z scores at the end of the 2-year treatment period and again at the end of the 2-year follow-up period. Two hundred four of the 285 participants completed the 4 years of the extension study, and these analyses included only the 204 completers. Sensitivity analyses, including all available data at each study visit, yielded very similar results. Initial analyses also included stratified comparisons between the ICS- and placebo-treated groups. Stratification factors included sex, race (white vs nonwhite), baseline weight, and age at randomization. For the purposes of this

analysis, baseline weight and age at randomization were dichotomized at 15 kg and 3 years, respectively. The choices of 15 kg and 3 years were supported by the results of the spline models described above. Additional considerations for the choice of cut point included the desire to use a value that is clinically useful and the fact that the randomization scheme used in the PEAK study was stratified by age by using this cut point. Sensitivity analyses indicated that the results of the stratified analyses were very similar over a range of weight cut points between 15 to 17 kg and age cut points near 3 years. These analyses indicated a larger effect of ICS use among the children in the 2-year-old and less than 15-kg subgroup. Therefore we further investigated an interaction between age and weight by studying the change in height from baseline to the end of the 2-year treatment period and change from the end of the 2-year treatment period to the end of the 2-year follow-up period and from baseline to the end of the 2-year follow-up. Linear mixed-effects regression was performed with PROC MIXED in the SAS statistical software system, version 9.1 (SAS Institute, Inc). Additive models were fitted by using the S+ statistical software system version 8.1 (TIBCO Software, Inc, Palo Alto, Calif).

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APPENDIX E1

Collaborators: G. Larsen, A. Liu, J. Spahn, M. H. Moss, M. E. Krawiec, G. Heldt, M. H. Mellon, M. Schatz, N. J. Friedman, S. C. Christiansen, A. A. Jalowayski, G. R. Bloomberg, J. M. Corry, J. D. Mark, M. A. Brown, V. M. Chinchilli, and I. Paul.

The members of the CARE Network as of December 2005**Clinical centers**

National Jewish Health, Denver, Colo: Stanley J. Szefer, MD (Principal Investigator); Gary Larsen, MD (Co-Investigator); Joseph Spahn, MD (Co-Investigator); Ronina Covar, MD (Co-Investigator); Andrew Liu, MD (Co-Investigator); D. Sundstrom (Coordinator); Amy Grumann, RN (Coordinator); Melanie Phillips (Coordinator); Michael White (Research Assistant); Jay Markson (Referring Pediatrician); Jeffrey Barter (Referring Pediatrician); and Keith Breese (Research Assistant). We also thank the pediatric allergy and immunology fellows for their participation: Kirstin Carel, MD; Neal Jain, MD; Harvey Leo, MD; Beth Macomber, MD; Chris Mjaanes, MD; Ben Song, MD; and Lora Stewart, MD.

University of Wisconsin, Clinical Science Center, Madison, Wis: Robert F. Lemanske, Jr, MD (Principal Investigator); Christine A. Sorkness, PharmD (Co-Investigator); Mark H. Moss, MD (Co-Investigator); Marzena E. Krawiec, MD (Co-Investigator); David B. Allen, MD (Consultant); James Gern, MD; Kristen Blotz, RN (Coordinator); Sarah Garibay, RN (Coordinator); Kelly Miller (Coordinator); Holly Eversoll, RN (Coordinator); Alana Clark (Coordinator); Rick Kelley (Pulmonary Function Manager); Luke Weasler (Pulmonary Function Technician); and Ryan Burton (Pulmonary Function Technician).

University of California San Diego Medical Center and Kaiser Permanente Allergy Center, San Diego, Calif: Robert S. Zeiger, MD, PhD (Principal Investigator); Gregory Heldt, MD (Co-Investigator); Michael H. Mellon, MD (Co-Investigator); Noah J. Friedman, MD (Co-Investigator); Alfredo A. Jalowayski, PhD (Co-Investigator); Michael Schatz, MD, MS (Co-Investigator); Sandra C. Christiansen, MD (Co-Investigator); Kathleen Harden, RN (Coordinator); Catherine Nelle, RN; Eva Rodriguez, RRT; Linda Galbreath; and Elaine Jensen.

Washington University School of Medicine, St Louis, Mo: Robert C. Strunk, MD (Principal Investigator); Leonard B. Bacharier, MD (Co-Investigator); Gordon R. Bloomberg, MD (Co-Investigator); James M. Corry, MD (Co-Investigator); Tina Oliver-Welker, CRTT, CAE (Coordinator); Valerie Morgan, RRT (Coordinator); Kevin Hodgdon, RRT, CPFT (Coordinator); Wanda Caldwell, RRT, MBA (Coordinator); and Cindy Moseid (Secretary).

Arizona Respiratory Center, University of Arizona, College of Medicine, Tucson, Ariz: Fernando D. Martinez, MD (Co-Investigator); Wayne Morgan, MD (Co-Investigator); Theresa W. Guilbert, MD (Co-Investigator); John D. Mark, MD (Co-Investigator); Mark Brown, MD (Co-Investigator); James Goodwin (Coordinator); Melisa Celaya (Coordinator); Anna Valencia (Coordinator); Janet Lawless, RN; Rosemary Weese, RN; Shelley Radford, RT; and William Hall, RT.

Resource centers

Chair's Office, National Jewish Medical and Research Center, Denver, Colo: Lynn M. Taussig, MD (Study Chair).

Project Office, National Heart, Lung and Blood Institute, Bethesda, Md: James Kiley, PhD, (Director of the NHLBI

Division of Lung Diseases); Virginia Taggart, MPH (NHLBI Project Scientist); Gail Weinmann MD; and Gang Zheng, PhD.

Data Coordinating Center, Penn State University College of Medicine, Hershey, Pa: Vernon M. Chinchilli, PhD (Principal Investigator); David Mauger, PhD (Co-Investigator); Ian Paul, MD (Co-Investigator); Susan Boehmer, (Scientific Coordinator); Loretta Doty (Project Coordinator); Jill Kuennen; Jill Hofsass; Sherrie Whisler; Linda Ferrari; Pamela Arminavage; Liza Brandt; Cathy Goeckel; Jim Schmidt; Brenda Beers; Linda Miller; Judy Potteiger; Lori Schell; Venus Mintz-Grella; Liza Say (June 2000-April 2001); Margaret Sheely (June 2000-January 2001); Trina Armstrong; Holly Hess; Victor Sanchez; and Vanessa Simmons.

Committees

Data and Safety Monitoring Board: Thomas F. Boat, MD (Chair), Children's Hospital Medical Center, Cincinnati, Ohio; William C. Bailey, MD, University of Alabama at Birmingham, Birmingham, Ala; Mary Kay Garcia, PhD, RN, CPNP; Carolyn M. Kercsmar, MD, Case Western Reserve University, Cleveland, Ohio; H. William Kelly, PharmD, University of New Mexico Health Sciences Center, Albuquerque, NM; Lester Lyndon Key, Jr, MD, Medical University of South Carolina, Charleston, SC; James Tonascia, PhD, Johns Hopkins University, Baltimore, Md; and Benjamin Wilfond, MD, National Human Genome Research Institute, Bethesda, Md.

Protocol Review Committee: Philip Ballard, MD, PhD (Chair), Children's Hospital of Philadelphia, Philadelphia, Pa; Clarence E. Davis, PhD, University of North Carolina, Chapel Hill, NC; Diane E. McLean, MD, PhD, MPH, New York State Psychiatric Institute, New York, NY; Gail Shapiro, MD, ASTHMA, Inc, Seattle, Wash; Paul O'Byrne, MD, St Joseph's Hospital, Hamilton, Ontario, Canada; and Mark Liu, MD, Johns Hopkins Asthma and Allergy Center, Baltimore, Md.

Executive Committee: Lynn M. Taussig, MD; Virginia S. Taggart, MPH; Stanley J. Szefer, MD; Robert F. Lemanske, Jr, MD; Robert S. Zeiger, MD, PhD; Robert C. Strunk, MD; Fernando D. Martinez, MD; and Vernon M. Chinchilli, PhD.

Publication and Presentation Committee: Robert F. Lemanske, Jr, MD (Chair); Stanley J. Szefer, MD; and Fernando D. Martinez, MD.

Quality Control Committee: Robert S. Zeiger, MD, PhD, (Chair); Vernon M. Chinchilli, PhD; Robert C. Strunk, MD; Theresa W. Guilbert, MD; Dave T. Mauger, PhD; Timothy J. Craig, DO; Susan Boehmer, MA; Jill T. Kuennen, MA; James Goodwin; and James R. Schmidt, BS.

Equipment Committee: Wayne Morgan, MD (Chair); Gregory Heldt, MD; Gary Larsen, MD; Christine A. Sorkness, PharmD; Joseph D. Spahn, MD; Kevin Hodgdon; Rick Kelley; Shelley Radford; Eva Rodriguez; Melanie Phillips; Brenda Phillips; Loretta Doty; Richard Evans; Jason Lennon; Lori Sanders; and Jeff Davis.

Genetics Committee: Fernando D. Martinez, MD (Chair); Stanley J. Szefer, MD; Robert F. Lemanske, Jr, MD; Vernon M. Chinchilli, PhD; David T. Mauger, PhD; and Brenda Phillips, MS.

Pharmaceutical suppliers

GlaxoSmithKline, Inc, Research Triangle Park, NC; Muro Pharmaceutical, Inc, Tewksbury, Mass; Merck & Co, Inc, West Point, Pa; and Schering-Plough Corp, Kenilworth, NJ.

Equipment support

Lincoln Diagnostics (Multi-Test II kits), Decatur, Ill, and Monaghan Medical (Aerochamber and masks), Plattsburgh, NY.

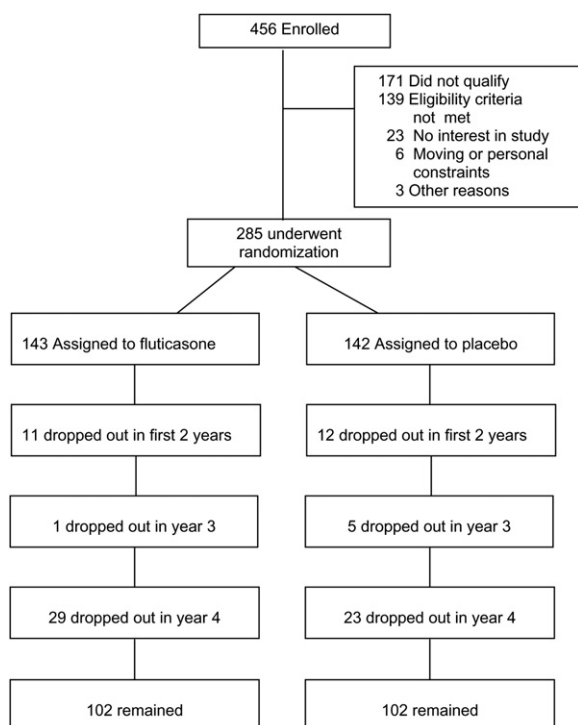


FIG E1. Presentation of enrollment and treatment assignments. Overall, less than 12% were lost to follow-up by the end of the observation year and 28% by the end of the second observation year (modified with permission from a previously published figure).^{E2}

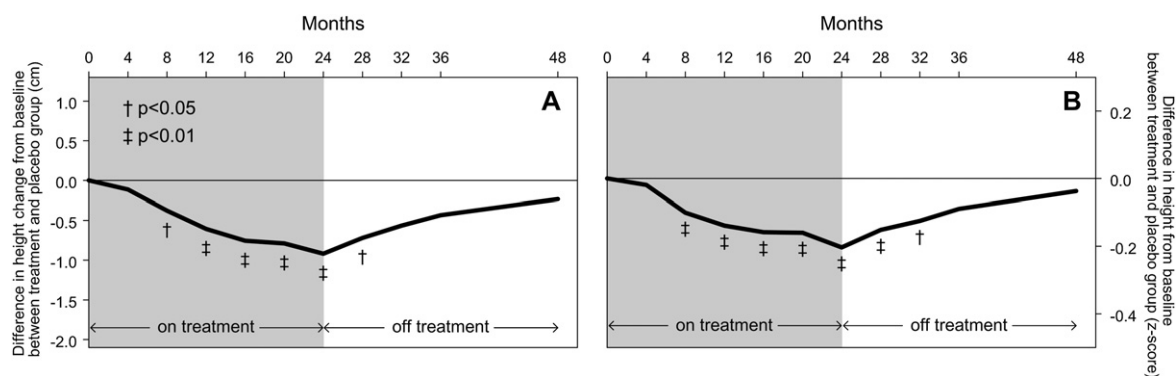


FIG E2. Overall cohort analyses. Difference in height change from baseline to 48 months (**A**, height change; **B**, z score change) for the fluticasone-treated group compared with the placebo-treated group in the overall cohort is shown. After 24 months of treatment, the ICS group grew, on average, 0.9 cm less and 0.2 z score less than the placebo group. At 48 months, 2 years after study treatment was discontinued, height and z scores were similar between treatment groups. Significant differences between treatment groups are denoted as follows: † $P < .05$ and ‡ $P < .01$.

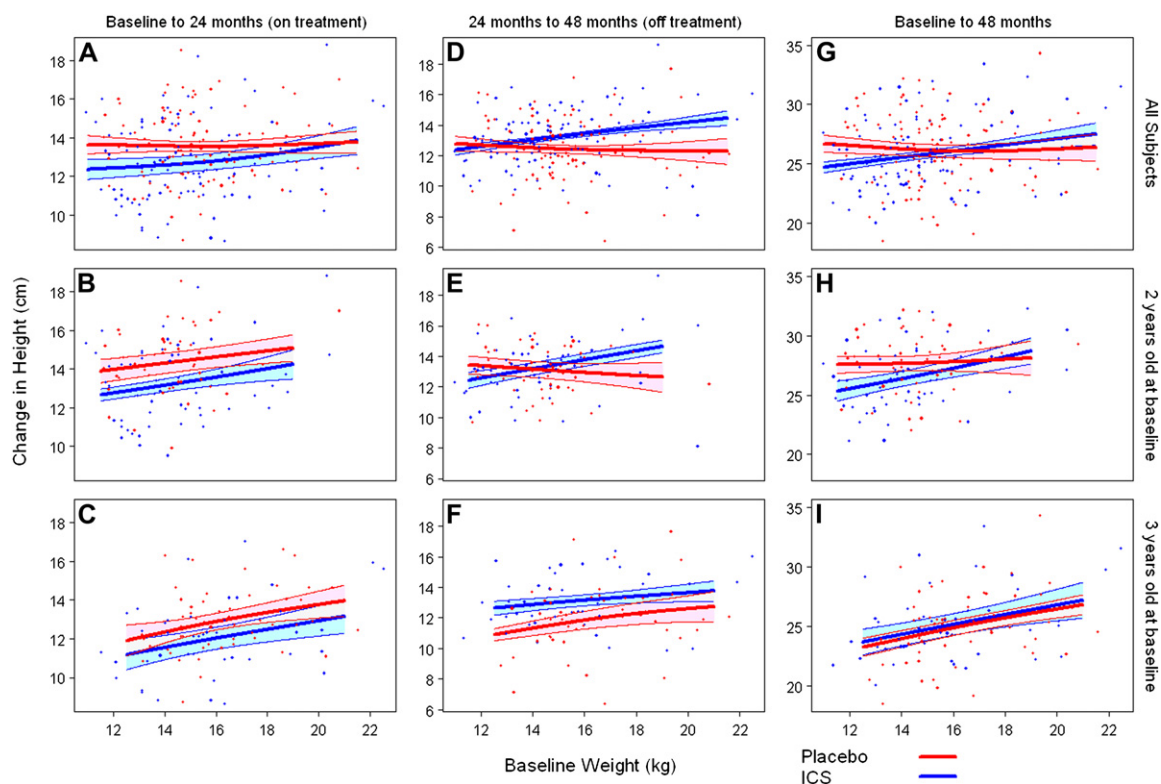


FIG E3. Scattergrams from baseline (height change) during treatment versus enrollment weight by treatment group. *Top panels*, Overall cohort; *middle panels*, subjects 2 years old at baseline; *bottom panels*, subjects 3 years old at baseline. Children at particular risk for less linear growth during treatment were those with a baseline weight of 12 to 17 kg versus those with a lesser exposure compared with their respective placebo-treated counterparts (**A**). This was more pronounced in the children who were 2 years of age at enrollment (**B**) compared to those who were 3 years old (**C**). After the ICS treatment ended, these younger children of lesser weight (relative to the cohort) did not demonstrate the same catch up in linear growth demonstrated by the overall cohort (**D**), younger children of greater weight (**E**) or older children of any weight (**F**). Two years after treatment discontinuation, less linear growth was observed in only the younger children of lesser weight (**H**) compared to the overall cohort (**G**) or older children of any weight (**I**). *Solid lines* (blue, ICS; red, placebo) represent fitted values from nonparametric smoothing splines with 95% confidence bands.^{E1} All data values were used for model fitting, but estimated regression lines are truncated to avoid extrapolation beyond the main part of the data.

TABLE E1. Demographic characteristics of the original cohort of 285 versus those children who completed all 4 years of the study

Characteristic	Baseline	
	All subjects (n = 285)	Completers (n = 204)
Race or ethnic group, no. (%) [†]		
Non-Hispanic white	152 (53.3)	118 (57.9)
Non-Hispanic black	38 (13.3)	24 (11.8)
Hispanic	55 (19.3)	32 (15.7)
Other	40 (14.0)	30 (14.7)
Sex, no. (%)		
Female	108 (37.9)	80 (39.2)
Male	177 (62.1)	124 (60.8)
Age at randomization (y)	3.00 ± 0.58	3.00 ± 0.58
Age of onset of asthma symptoms (y)	0.95 ± 0.67	1.02 ± 0.66
Age of first asthma diagnosis by a doctor (y)	1.37 ± 0.86	1.46 ± 0.87
Height (cm)	94.8 ± 5.8	94.9 ± 5.9
Weight (kg)	15.2 ± 2.4	15.2 ± 2.5
Parental history of asthma, no. (%)	184 (64.6)	127 (62.3)
Parental history of atopy, no. (%)	164 (57.5)	124 (60.8)
Cigarette exposure in first 2 y of life, no. (%)	44 (15.4)	22 (10.8)
Pets in house, no. (%)	129 (45.3)	88 (43.1)
Recordings during enrollment month		
Symptom-free days (%) [‡]	72.5 ± 24.4	74.9 ± 23.1
Albuterol use (average d/wk)	1.0 ± 1.3	1.1 ± 1.4
Nighttime awakenings because of asthma-like symptoms (average d/mo)	2.2 ± 3.4	2.0 ± 3.2
At least 1 emergency department visit for an asthma exacerbation in year before enrollment, no. (%)	133 (46.7)	84 (41.2)
At least 1 hospitalization for an asthma exacerbation in year before enrollment, no. (%)	20 (7.0)	15 (7.4)
Positive aeroallergen skin test result, no. (%)	186 (65.3)	139 (68.1)
Eczema, no. (%)	148 (51.9)	112 (54.9)
IgE (IU) [§]	39.3 ± 5.3	42.9 ± 5.2
Eosinophil (%)	4.1 ± 3.1	4.1 ± 3.1

*Values are presented as means ± SDs, where shown. Not all percentages add to 100 because of rounding.

[†]Race was determined by family self-report on questionnaire.

[‡]A symptom-free day was defined based on the diary card during the run-in period as a day with no nocturnal awakenings, no use of albuterol for symptoms, or other asthma medications, no need for unscheduled physician's office visits, no cold or cold symptoms, or any asthma symptoms.

[§]Values are geometric means (geometric SDs).

TABLE E2. Medication use and asthma symptoms reported by participants during the 2-year follow-up period after treatment discontinuation

Group	ICS	Oral corticosteroids	Reported symptoms or exacerbations in past 12 mo
Age 2 y	33%	53%	63%
Age 3 y	30%	60%	70%
Weight <15 kg	29%	52%	59%
Weight ≥15 kg	34%	61%	74%
Age 2 y and weight <15 kg	31%	51%	59%
Age 2 y and weight ≥15 kg	37%	57%	71%
Age 3 y and weight <15 kg	24%	53%	59%
Age 3 y and weight ≥15 kg	32%	63%	75%