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Patient Characteristics Associated with Improved Outcomes with Use of an Inhaled Corticosteroid in Preschool Children at Risk for Asthma

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Abstract

Background—Maintenance inhaled corticosteroid (ICS) therapy in preschool children with recurrent wheezing at high-risk for development of asthma produces multiple clinical benefits. However, determination of baseline features associated with ICS responsiveness may identify children most likely to benefit from ICS treatment.

Objective—To determine if demographic and atopic features predict response to ICS in preschool children at high-risk for asthma.

Methods—Two years of treatment with an ICS, fluticasone propionate (88mcg twice daily), was compared to matching placebo in a double-masked, randomized, multi-center study of 285 two and three year olds at high-risk for asthma development. Baseline demographic and atopic features were related to clinical outcomes in a *post-hoc* subgroup analysis.

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^hSee Appendix (Online Repository)

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Results—Multivariate analysis demonstrated significantly greater improvement with fluticasone compared to placebo in terms of episode-free days among males, Caucasians, participants with an emergency department (ED) visit or hospitalization within the past year, and those who experienced more symptomatic days at baseline. Children with aeroallergen sensitization experienced greater benefits in terms of oral corticosteroid use, urgent care and ED visits, and use of supplemental controller medications.

Conclusions—More favorable responses to ICS compared to placebo in high-risk preschool children over a 2-year period were more likely in those with a ED visit or hospitalization for asthma within the past year, children with aeroallergen sensitization, males and Caucasians.

Capsule Summary—A favorable response to ICS compared to placebo in high-risk toddlers over a 2-year period was more likely in children with a prior ED visit or hospitalization for asthma, aeroallergen sensitization, males, and Caucasians.

Keywords

childhood asthma; inhaled corticosteroids; response

INTRODUCTION

In school-age children with persistent asthma, treatment with ICS is associated with significant improvements in lung function, bronchial hyper-responsiveness, and clinical and humanistic outcomes in established mild to moderate persistent asthma ¹. There is conflicting evidence on the effectiveness of ICS in reducing illness burden in preschool children ²⁻³. Potential reasons for the varying study findings may derive from the different phenotypes of participants studied and the frequency and duration of medication administration.

One study in preschool children with recurrent wheeze reported that age ≥ 2 years, greater baseline symptom frequency, and family history of asthma were associated with an improvement in symptom-free days during ICS therapy ⁴. This report highlights the concept that not all patients respond equally well to a given therapy, with certain patient characteristics influencing the degree of response.

The Prevention of Early Asthma in Kids (PEAK) trial was performed to determine if early intervention with ICS in preschool children with recurrent wheezing and positive asthma predictive index (API) would alter the development of asthma symptoms after ICS discontinuation ⁵. In the PEAK trial, ICS therapy for 2 years did not appear to modify the natural history of asthma during the year after ICS discontinuation ². However, group mean response measures during the 2-year treatment phase clearly demonstrated the efficacy of ICS in reducing illness symptom burden in this high-risk cohort. Furthermore, there may be patient characteristics other than the presence of a positive API, or components of the API itself, that were associated with the magnitude of response to ICS relative to placebo. We now examine multiple demographic and atopic characteristics of participants in the PEAK trial in an attempt to further identify participant factors associated with greater response to ICS therapy in order to facilitate selection of appropriate high-risk recurrent wheezing preschool children for maintenance ICS therapy.

METHODS

A detailed description of the recruitment, design, and statistical analysis for the PEAK trial has been reported in detail elsewhere ^{2, 5}.

Overview of the PEAK Trial

PEAK was a multi-center, double-blind, randomized, placebo-controlled, parallel-group comparison trial of ICS (fluticasone propionate (Flovent®), 44 µg/puff, 2 puffs twice daily, via metered dose inhaler, provided by GlaxoSmithKline, Research Triangle Park, NC) or matching placebo, involving 285 children 2 and 3 years of age at high-risk for the development of asthma. Both ICS and placebo were delivered using an AeroChamber® with mask (Monaghan Medical, Plattsburgh, NY). Assignments were made with permuted blocks randomization with stratification according to clinic and age groups. Two years of continuous treatment was followed by a 1-year observation year off study medication. For this *post hoc* analysis, the primary focus was on the 2-year treatment phase to examine the baseline demographic and atopic features associated with ICS responses.

Adherence was promoted by an educational program and measured using an electronic meter (Doser®). The average percentage of days in which a child took the prescribed dose of study medication was similar in the two study groups (74% in the fluticasone group and 69% in the placebo group, $P = 0.10$)². Rescue therapy in the form of 2 puffs of albuterol MDI (90 µg/puff) or albuterol nebulization (2.5 mg) (both provided by Schering-Plough Corporation, Kenilworth, NJ) was used per written action plan. Four-day courses of oral prednisolone (provided by Muro Pharmaceutical, Inc., Tewksbury, MA) were prescribed by protocol for exacerbations as detailed previously⁵. Specific algorithms were used to treat participants who developed persistent symptoms^{2, 5}. Additional details on the protocols for the addition and stopping of supplementary medications and the criteria for assignment of treatment failure status are detailed elsewhere⁵.

Inclusion criteria for PEAK included children 2-3 years of age with a positive, modified asthma predictive index consisting of frequent wheezing (at least 4 episodes in the prior year) and either one major risk factor (parental history of asthma, personal history of atopic dermatitis, or aeroallergen sensitization) or two of three minor risk factors (peripheral blood eosinophilia $\geq 4\%$, wheezing without colds, or allergic sensitization to food). Children were eligible if they were healthy with no clinically significant medical disorders apart from wheezing or allergy and were excluded if they had received more than 4 months of inhaled corticosteroid use before enrollment or if they required controller medication during the run-in month^{2, 5}.

Skin-prick testing, with a core battery of 10 allergens in all clinical centers was performed at enrollment along with total serum IgE levels and peripheral blood eosinophil percentage^{5, 6}.

Follow-up visits occurred every 4 months following randomization and data were collected on medical and environmental history, medication use, physical exam findings, and lung function testing. Telephone assessments were conducted every two months during the 24 month treatment phase. These assessments collected parent-reported data on asthma-like symptoms (cough and wheeze), asthma medication use, and healthcare utilization for respiratory symptoms during the two weeks prior to the call^{2, 5}.

PEAK was reviewed by the CARE Network Protocol Review Committee, approved by the National Heart, Lung, and Blood Institute (NHLBI), the CARE Network Steering Committee and the Institutional Review Boards at all participating centers, and monitored by the Care Network Data and Safety Monitoring Board. Parents provided written informed consent.

Outcome Measures

Several factors reflective of response to ICS compared to placebo during the 2-year double-blind treatment phase were analyzed, including episode-free days (EFD, primary study

outcome), the number of systemic corticosteroid courses, urgent care visits, and use of any supplementary controller medication. Episode-free days were defined as those days during which there were no asthma-like symptoms, no unscheduled medical visits for respiratory symptoms, and no use of any supplementary asthma medications including pre-exercise albuterol. Episode-free days were reported by the parents during interviews based on two-week recalls.

Statistical analyses

EFD, exacerbations, and use of supplementary asthma medication were determined from the self-reported data corrected by the coordinator record in cases where the family did not self-report previously prescribed supplementary controller medication that was recorded and dispensed by the coordinators. The proportion of EFD for each participant was calculated as the number of EFD divided by the number of days observed. Data from all participants were used in the analysis regardless of how many days were observed.

EFD was analyzed on the logit scale within the linear regression framework, whereas supplementary controller medication use (guided per protocol ⁵), prednisone use, and urgent care/emergency department visits were analyzed within the Poisson regression framework. The following general analysis approach was used for each of the outcome measures in this *post hoc* analysis. The predictive value of each sub-grouping factor under consideration was screened by examining the subgroup by treatment interaction term in a multivariable model which also included the following ten covariate factors: age at randomization (ages 2 versus 3 years), gender, race (Caucasians vs. all others), aeroallergen skin test reactivity (at least one positive skin test vs. zero positive tests), peripheral blood eosinophils ($\geq 4\%$ vs $< 4\%$ based upon the asthma predictive index ²), total serum IgE levels (below the median (45kU/L) vs $\geq 45\text{kU/L}$), eczema (presence vs absence), proportion of EFDs during the run-in phase ($\geq 80\%$ vs $< 80\%$), emergency department (ED) visit or hospitalization during the preceding twelve months (yes vs. no), duration of asthma-like symptoms prior to randomization (< 2 years vs ≥ 2 years), and parental history of asthma (positive vs. negative). Adherence to treatment, both ICS and placebo, was recorded during the study and was included as an additional covariate in these models. These analyses were done under the intent-to-treat principle, and so the inclusion of this covariate is intended to reflect participant behavior across both treatment groups as opposed to the absolute dose of fluticasone received ($\mu\text{g/Kg}$) in the ICS group which would be confounded by body weight in this age group.

Those covariates which demonstrated significant (at the 0.10 level) interaction with the treatment effect were then examined simultaneously in a multivariable model including all of those interaction terms and the covariates listed above. The treatment effect within each sub-group was assessed by examining linear contrasts from this model. All analyses were carried out using the SAS statistical software system version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Study population

The two study groups were similar with respect to all baseline characteristics except that the ICS group had a higher percentage of peripheral blood eosinophils (Table 1).

Factors associated with greater improvement in EFDs

Characteristics of participants with significantly higher percentage of EFDs with ICS therapy relative to those receiving placebo who were: male sex ($p < 0.001$), Caucasians ($p < 0.001$), history of an emergency department visit or hospitalization for asthma within the

year preceding the trial ($p<0.001$), sensitization to aeroallergen ($p<0.05$), and having fewer than 80% EFDs during the run-in period ($p=0.02$), and (Table 2). Response to ICS therapy in terms of EFDs varied by ethnicity, with most favorable responses noted amongst non-Hispanic white participants and less favorable responses amongst other ethnicities, predominantly non-Hispanic black participants (data not shown). Age, duration of asthma, eczema status, peripheral blood eosinophil and IgE levels, and parental asthma did not influence EFD response. We found no difference in the results between the first and second years of therapy (data not shown).

In the multivariable analysis (Table 2), comparisons for effects of treatment on EFD between the two components of each subgroup revealed significant interactions indicating significantly greater ICS therapy benefits for males relative to females ($p=0.04$), Caucasians relative to non-Caucasians ($p=0.003$), those with an ED visit or hospitalization for asthma within the year preceding the trial relative to those without such visits ($p=0.004$), and participants with $<80\%$ EFD during run-in relative to those with $\geq 80\%$ EFDs ($p=0.02$). These differences in EFDs were a result of differing percent of EFD over the 2-year treatment period within the placebo group across the two strata. For example, among placebo-treated participants, males experienced 86% EFDs, whereas females experienced 92% EFDs. In contrast, males and females receiving ICS experienced comparable percent of EFDs (93% and 92%, respectively) (Table 3).

Factors associated with secondary trial outcomes

Several secondary trial outcomes were examined and the factors identified which were associated with ICS response in terms of EFDs were consistent with those identified in the multivariable analyses for these additional outcomes: Caucasians and those with a prior ED visit or hospitalization also had significantly greater likelihood of demonstrating favorable responses with respect to oral corticosteroid use, emergency department and urgent care visits, and supplementary controller use (Tables 2, E1, E2, E3). Aeroallergen sensitization was associated with greater ICS response in terms of oral corticosteroid use, emergency department and urgent care visits, and supplementary controller use (Table 2), but not EFDs. In addition, male participants receiving ICS therapy were less likely to receive oral corticosteroids ($p=0.004$), and participants with $<80\%$ EFDs during run-in who received ICS were less likely to require ED or urgent care during the trial ($p=0.005$). Multiple subgroups experienced significantly greater ICS therapy benefit in multivariable analysis in terms of supplementary controller medication use, including males ($p<0.001$), 3 year olds ($p=0.04$), participants without eczema ($p<0.001$), and IgE ≥ 45 kU/L ($p=0.02$).

Treatment Response and Observation-Year Outcomes

As previously reported², children in the ICS group who experienced a response during the 2-year treatment period (proportion of EFD $>92\%$) had more asthma-like symptoms during the observation year than did those in the placebo group. Thus, we examined the outcome of EFDs during the observation period based upon the subgroups described above. Similar to the findings for the entire cohort, none of the subgroups experienced a significant disease-modifying (i.e. greater proportion of EFDs by treatment group) effect during the observation year. Furthermore, the subgroups that demonstrated significantly better response during the treatment period also demonstrated a significant decrease in the proportion of EFDs after ICS therapy was discontinued (males ($p<0.01$), Caucasians ($p<0.05$), positive aeroallergen skin test ($p<0.01$), prior ED visit or hospitalization ($p<0.05$)).

DISCUSSION

When evaluating the results of a clinical trial, emphasis has been traditionally placed upon a comparison of mean responses between the treatment groups. A treatment is considered effective if a statistically significant difference exists between the average responses among those receiving the treatment of interest relative to the comparator treatment(s). The present *post hoc* subgroup analysis of the PEAK trial examined patient characteristics associated with favorable responses to ICS therapy. We found several factors, including male gender, Caucasian race, baseline EFD frequency and ED visit or hospitalization for asthma within the preceding year, that were independently related to favorable responses with ICS in terms of EFDs, as well as several secondary outcome domains. Among these factors, an asthma-related emergency department visit or hospitalization in the preceding year was identified as a strong predictor of ICS response as reflected by the large R^2 values for all four outcome measures, as patients with such events experienced more than twice the relative rates of EFDs, as well as lower oral corticosteroid use, ED visits, and supplementary medication use during the trial than did participants without a pre-trial ED visit or hospitalization. This is consistent with findings that prior indicators of substantial asthma morbidity, including recent severe exacerbations^{7, 8} or hospitalization⁹, are significant predictors of subsequent morbidity. In this study, the response to ICS therapy varied by ethnicity, with most favorable responses noted amongst non-Hispanic white participants and less favorable responses amongst other ethnicities, predominantly non-Hispanic black participants.

The asthma predictive index was developed as a tool to identify children at increased risk for persistence of asthma symptoms following recurrent wheezing in early life¹⁰. The PEAK trial enrolled children identified by a positive API and demonstrated that, on average, children who received ICS for 2 years experienced more episode free days and lower rates of asthma exacerbations requiring oral corticosteroids and supplementary controller medication use than children who received placebo⁵. Based upon these findings, the most recent NAEPP Guidelines¹¹ recommend consideration of daily controller therapy in young children with positive APIs. However, despite the substantial symptomatic benefits noted during the treatment phase of PEAK, once ICS therapy was discontinued, participants who received ICS therapy for 2 years did not have an advantage in terms of asthma symptoms during the third year of the study, indicating an absence of a disease-modifying effect of ICS in this population. The *post hoc* analyses reported here was performed in an effort to determine if additional patient factors may help identify children who derive the greatest benefits from continuous ICS therapy. We have demonstrated that there is indeed significant heterogeneity and variability among API positive children in response to ICS, as well as having identified several factors beyond the API itself that are associated with favorable responses to ICS therapy. Factors associated with greater ICS responsiveness reflect greater disease severity, either in terms of morbidity (EFDs during run-in, prior ED visit/hospitalization) or atopy (IgE levels and aeroallergen sensitization). While global aeroallergen sensitivity was predictive of ICS benefit, we found no consistent patterns of specific sensitivity (pet vs. other aeroallergen) which differentially predicted ICS benefit (data not shown). Since not all children with positive APIs have or will go on to have asthma¹⁰, the presence of aeroallergen sensitization as a marker of atopic disposition appears to further identify a subgroup of API positive children who are most likely to have more favorable response to anti-inflammatory therapy with ICS as compared to placebo in terms of oral corticosteroid use, acute care visits, and need for supplementary controller medication use during the PEAK trial.

Participants with indicators of greater pre-trial disease severity experienced the greatest improvement in EFDs, as well as other secondary outcome measures, with ICS therapy relative to placebo. However, ICS treatment brought the outcomes in these subgroups of

children to the same level as the children in the less severe stratum who received either ICS or placebo, since children in the strata which did not experience a differential response in EFDs to ICS relative to placebo had very little room to improve with treatment, as evidenced by 90-93% EFDs during the trial in both treatment arms. In contrast, the children in the strata that experienced differential responses in EFDs had greater potential room to improve (84-87% EFDs during the trial in the placebo group, Table 3). These results thus suggest that the main effect of ICS in this population is to attenuate indicators of disease burden in children in whom the presence of certain risk factors is associated with increased severity of symptoms.

This subgroup analysis of the PEAK trial provides an extensive report of factors that are associated with ICS response among preschool children at high risk for asthma. Roorda and colleagues examined subgroups of preschool children (12-47 months) with symptoms of wheeze, cough, or shortness of breath or who needed albuterol on at least 7 of the last 14 days of a 4-week run-in period, from pooled data of two 12-week studies that compared maintenance ICS at varying doses to placebo⁴. They reported that only the subgroups with frequent symptoms during run-in (>3 days per week and >75% of days) and a family history of asthma (a component of the API) achieved the beneficial response to ICS compared to placebo⁴. Similar to our findings for the outcome of EFDs, a personal history of eczema did not influence ICS responsivity as measured by days or nights without asthma symptoms in the analyses by Roorda *et al*⁴. The present study extends considerably these types of analyses as it was based on multiple predictors, several different outcomes, longer-term therapy (two year treatment period), and examines the interrelationships of these findings using multivariate analysis methods.

Limitations to these findings are largely related to the *post hoc* nature of these subgroup analyses. Subgroup analyses may be limited by diminished power to detect differences between groups and/or by a potential loss of comparability of groups. Furthermore, multiple comparisons increase the likelihood of a false finding which achieves a pre-specified level of statistical significance (i.e. $p < 0.05$). However, given the large overall sample size of the cohort, the consistency of the findings, the high levels of statistical significance seen for most of our findings, and the adjustment for multiple baseline characteristics, it seems likely the findings are valid; still, we cannot totally dismiss inadequate power to determine some relationships.

These analyses present a clinical dilemma. It is clear that certain patient phenotypes achieve greater benefit from ICS therapy, and they should remain the prime targets for therapy. Our findings suggest that among preschool children with a positive asthma predictive index, the following characteristics may predict children most likely to respond to ICS therapy with reduced illness burden: 1) more severe disease as reflected by ED visits or hospitalization within the past year or higher frequency of asthma symptoms, and 2) allergy features such as aeroallergen sensitization and elevated IgE levels. These findings also reinforce the recommendation that ICS therapy in children with positive APIs should be targeted at symptom control and improvement in quality of life rather than disease modification. Unfortunately, it is not clear what approach is most appropriate for the subgroups that did not demonstrate as favorable, albeit not necessarily poor, responses to ICS therapy. It could be argued that the strata not showing good responses (e.g., females, non-Caucasians, not aeroallergen sensitive, $\geq 80\%$ EFDs during run-in, or absence of a prior ED visit or hospitalization) should not be treated with ICS. However, the fact that no differences were found between children treated with placebo and those treated with ICS within these strata does not infer that no child within these strata will respond to ICS. On the contrary, our results suggest that within females, for example, those with a history of ED visit in the previous year or who are atopic are more likely to respond to ICS therapy than those with no

such history. It is thus advisable that a trial of daily ICS be initiated in API positive children with sufficiently severe or frequent symptoms to justify such treatment; such therapy may be discontinued after a reasonable period of time and clinical reassessment about the need to continue it should be made, taking into account, among other factors, the presence or absence of some of the risk factors we have described in this study. Furthermore, given the *post hoc* nature of these analyses and the potential for insufficient statistical power resulting in a type II error, it is premature to recommend avoidance of ICS therapy among any of the sub-groups examined herein that did not demonstrate improvement with ICS unless confirmed in prospective comparative studies.

In summary, favorable responses to ICS compared to placebo in high-risk toddlers over a 2-year period were more likely in those with an ED visit or hospitalization within the past year, children with aeroallergen sensitization, males, and Caucasians. When contemplating prolonged treatment with ICS in high-risk preschool children, specific response profiles may be considered.

Clinical Implications

Preschool children at high-risk for asthma experience favorable responses to ICS therapy, particularly when indicators of greater disease severity and aeroallergen sensitization are present.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CARE	Childhood Asthma Research and Education Network
EFD	Episode-free days
ICS	inhaled corticosteroids
MDI	metered dose inhaler
NHLBI	National Heart, Lung and Blood Institute

REFERENCES

1. Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054–63. [PubMed: 11027739]
2. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szeffler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985–97. [PubMed: 16687711]
3. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354:1998–2005. [PubMed: 16687712]

4. Roorda RJ, Mezei G, Bisgaard H, Maden C. Response of preschool children with asthma symptoms to fluticasone propionate. *J Allergy Clin Immunol* 2001;108:540–6. [PubMed: 11590379]
5. Guilbert TW, Morgan WJ, Krawiec M, Lemanske RF Jr, Sorkness C, Szeffler SJ, et al. The Prevention of Early Asthma in Kids study: design, rationale and methods for the Childhood Asthma Research and Education network. *Control Clin Trials* 2004;25:286–310. [PubMed: 15157730]
6. Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol* 2004;114:1282–7. [PubMed: 15577824]
7. McCoy K, Shade DM, Irvin CG, Mastronarde JG, Hanania NA, Castro M, et al. Predicting episodes of poor asthma control in treated patients with asthma. *J Allergy Clin Immunol* 2006;118:1226–33. [PubMed: 17157651]
8. Miller MK, Lee JH, Miller DP, Wenzel SE. Recent asthma exacerbations: a key predictor of future exacerbations. *Respir Med* 2007;101:481–9. [PubMed: 16914299]
9. Bloomberg GR, Trinkaus KM, Fisher EB Jr, Musick JR, Strunk RC. Hospital readmissions for childhood asthma: a 10-year metropolitan study. *Am J Respir Crit Care Med* 2003;167:1068–76. [PubMed: 12684246]
10. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403–6. [PubMed: 11029352]
11. National Asthma Education and Prevention Program. Expert Panel Report III: Guidelines for the diagnosis and management of asthma. US Department of Health and Human Services; Bethesda, MD: 2007.

Table 1
Characteristics of the Participants at Baseline

Characteristic	Baseline	
	Fluticasone (n=143)	Placebo (n=142)
Age - yr	3 (0.6)	3 (0.6)
Race or ethnic group - no. (%) [†]		
Non-Hispanic white	76 (53.2)	76 (53.5)
Non-Hispanic black	17 (11.9)	21 (14.8)
Hispanic	29 (20.3)	26 (18.3)
Other	21 (14.7)	19 (13.4)
Sex- no. (%)		
Female	55 (38.5)	53 (37.3)
Male	88 (61.5)	89 (62.7)
Age of onset of asthma symptoms - yr	0.97 (0.7)	0.93 (0.6)
Age of first asthma diagnosis by a doctor - yr	1.46 (0.9)	1.28 (0.8)
Parental History of Asthma -no. (%)	94 (65.7)	90 (63.4)
Parental History of Atopy - no. (%)	86 (60.1)	78 (54.9)
Cigarette Exposure First 2 years of life - no. (%)	39 (27.3)	43 (30.3)
Children with pets in house - no. (%)	66 (46.2)	63 (44.4)
Symptoms during month prior to randomization:		
Symptom-free days-% [‡]	72.6(±24.2)	74.4 (±24.3)
Albuterol use - average days per week	1.0 (±1.1)	1.1 (±1.5)
Night awakenings due to asthma-like symptoms - average days per month	2.2 (±2.9)	2.2 (±3.8)
At least 1 emergency department visit for an asthma exacerbation in year before enrollment - no. (%)	67 (46.9)	66 (46.5)
At least 1 hospitalization for an asthma exacerbations in year before enrollment – no. (%)	10 (7.0)	10 (7.0)
Height - cm	94.9 (±6.1)	94.7 (±5.4)
Eczema - no. (%)	83 (58.0)	70 (49.3)
≥1 Positive aeroallergen skin test - no. (%)	88 (61.5)	81 (57.0)
IgE - IU/mL [§]	42.5 (5.4)	37.7 (5.1)
Peripheral Blood Eosinophil - % [‡]	4.5 (±3.3)	3.6 (±2.7)

* Plus-minus values are means ± SD. Not all percentages add to 100, due to rounding.

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

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

[§] Values are geometric means (geometric SD)

[‡] p-value at Baseline Visit =0.01

Table 2

Multivariate analyses for predictors of response to ICS

Stratifying variable	Percent Episode Free Days		Oral Corticosteroid Use		Emergency Department & Urgent Care Visits		Supplementary Controller Medication Use	
	Absolute Difference: ICS vs Placebo (95% CI)	P-value : Treatment by subgroup interaction (R ²)	Relative Rate: ICS vs Placebo (95% CI)	P-value : Treatment by subgroup interaction (R ²)	Relative Rate: ICS vs Placebo (95% CI)	P-value : Treatment by subgroup interaction (R ²)	Relative Rate: ICS vs Placebo (95% CI)	P-value : Treatment by subgroup interaction (R ²)
Male	7.3 (3.9, 11.1) ‡	0.04 (15%)	0.62 (0.47, 0.82) ‡	0.004 (16%)	No interaction **		0.27 (0.20, 0.38) ‡	<0.001 (8%)
Female	0.1 (−3.4, 3.5)		1.15 (0.82, 1.62)				0.61 (0.41, 0.92) *	
Caucasian	9.1 (4.8, 13.9) ‡	0.003 (31%)	0.60 (0.46, 0.80) ‡	0.002 (18%)	0.67 (0.51, 0.87) *	<0.001 (23%)	0.26 (0.19, 0.37) ‡	<0.001 (10%)
Non-Caucasian	−1.0 (−3.9, 1.7)		1.18 (0.84, 1.67)		1.44 (1.05, 1.98)		0.63 (0.43, 0.94) *	
2 years old	No interaction **							
3 years old								
ED/Hospitalization History	7.7 (3.9, 11.6) ‡	0.004 (29%)	0.54 (0.40, 0.73) ‡	<0.001 (36%)	0.57 (0.42, 0.78) ‡	<0.001 (44%)	0.20 (0.14, 0.29) ‡	<0.001 (23%)
No ED/Hospitalization History	−1.1 (−4.4, 2.1)		1.33 (0.97, 1.82)		1.69 (1.27, 2.24)		0.82 (0.56, 1.20)	
≥1 Positive Aeroallergen Skin Test	6.5 (3.2, 10.0) ‡	0.11 (9%)	0.61 (0.47, 0.80) ‡	0.004 (16%)	0.75 (0.58, 0.98) *	0.009 (11%)	0.26 (0.18, 0.36) ‡	<0.001 (12%)
Negative Aeroallergen Skin Tests	0.9 (−2.5, 4.4)		1.17 (0.82, 1.66)		1.28 (0.93, 1.76)		0.66 (0.45, 0.95) *	
IgE ≥ 45 kU/L	No interaction **		0.97 (0.70, 1.34)	0.25 (3%)	0.92 (0.67, 1.25)	0.52 (1%)	0.31 (0.21, 0.47) ‡	0.02 (3%)
IgE < 45 kU/L			0.74 (0.54, 1.02)		1.05 (0.80, 1.38)		0.54 (0.38, 0.76) ‡	
Eosinophils >= 4%	No interaction **		0.82 (0.58, 1.16)	0.76 (1%)	No interaction **		0.41 (0.28, 0.61) ‡	0.97 (1%)
Eosinophils <4%			0.88 (0.66, 1.16)				0.41 (0.29, 0.58) ‡	
Eczema	No interaction **							
No eczema								
Asthma Duration <2yrs	No interaction **		0.77 (0.56, 1.05)	0.34 (2%)	1.14 (0.88, 1.48)	0.14 (3%)	0.68 (0.52, 0.88) ‡	<0.01 (9%)
Asthma Duration >=2yrs			0.93 (0.70, 1.25)		0.85 (0.62, 1.16)		0.25 (0.15, 0.41) ‡	
					1.04 (0.77, 1.41)	0.55 (1%)	No interaction **	
					0.93 (0.71, 1.21)			

Stratifying variable	Percent Episode Free Days		Oral Corticosteroid Use		Emergency Department & Urgent Care Visits		Supplementary Controller Medication Use	
	Absolute Difference: ICS vs Placebo (95% CI)	P-value : Treatment by subgroup interaction (R ²)	Relative Rate: ICS vs Placebo (95% CI)	P-value : Treatment by subgroup interaction (R ²)	Relative Rate: ICS vs Placebo (95% CI)	P-value : Treatment by subgroup interaction (R ²)	Relative Rate: ICS vs Placebo (95% CI)	P-value : Treatment by subgroup interaction (R ²)
Run-in EFD <80%	8.6 (4.2, 13.2) [†]	0.02 (18%)	No interaction **	0.74 (0.57, 0.96) [*] 1.30 (0.95, 1.78)	0.005 (13%)	0.35 (0.24, 0.49) [‡] 0.48 (0.34, 0.70) [‡]	0.10 (2%)	
Run-in EFD ≥80%	0.0 (-2.5, 2.5)							

* p<0.05

[†] p<0.01

[‡] p<0.001

** Note: empty cells denote factors which were not included in the final multivariate model due to lack of a significant interaction with treatment effect (at the 0.10 level) in univariate analysis.

Table 3
Percent Episode Free Days

Stratifying Variable	ICS Mean (95% CI)	Placebo Mean (95% CI)	Difference (95% CI)	P-value (ICS vs Placebo)
Male	93 (92, 95)	86 (83, 89)	7.3 (3.9, 11.1)	0.0005
Female	92 (89, 94)	92 (89, 94)	0.1 (−3.4, 3.5)	0.9493
Caucasian	93 (91, 95)	84 (80, 88)	9.1 (4.8, 13.9)	0.0001
Non-Caucasian	92 (89, 94)	93 (91, 94)	−1.0 (−3.9, 1.7)	0.6028
Run-In EFD <80%	92 (90, 94)	84 (79, 87)	8.6 (4.2, 13.2)	0.0009
Run-In EFD ≥80%	93 (91, 95)	93 (91, 95)	0.0 (−2.5, 2.5)	0.9856
ED/Hospitalization History	95 (93, 96)	87 (83, 90)	7.7 (3.9, 11.6)	0.0004
No ED/Hospitalization History	90 (87, 92)	91 (89, 93)	−1.1 (−4.4, 2.1)	0.6218
≥1 Positive Aeroallergen Skin Test	93 (91, 94)	86 (83, 89)	6.5 (3.2, 10.0)	0.0027
Negative Aeroallergen Skin Test	93 (90, 95)	92 (89, 94)	0.9 (−2.5, 4.4)	0.6809