

Characterization of within-subject responses to fluticasone and montelukast in childhood asthma

Stanley J. Szeffler, MD,^c Brenda R. Phillips, MS,^g Fernando D. Martinez, MD,^a Vernon M. Chinchilli, PhD,^g Robert F. Lemanske, Jr, MD,^b Robert C. Strunk, MD,^f Robert S. Zeiger, MD, PhD,^{d,e} Gary Larsen, MD,^c Joseph D. Spahn, MD,^c Leonard B. Bacharier, MD,^f Gordon R. Bloomberg, MD,^f Theresa W. Guilbert, MD,^a Gregory Heldt, MD,^d Wayne J. Morgan, MD,^a Mark H. Moss, MD,^b Christine A. Sorkness, PharmD,^b and Lynn M. Taussig, MD,^c for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute* *Tucson, Ariz, Madison, Wis, Denver, Colo, San Diego, Calif, St Louis, Mo, and Hershey, Pa*

Background: Responses to inhaled corticosteroids (ICSs) and leukotriene receptor antagonists (LTRAs) vary among asthmatic patients.

Objective: We sought to determine whether responses to ICSs and LTRAs are concordant for individuals or whether asthmatic patients who do not respond to one medication respond to the other.

Methods: Children 6 to 17 years of age with mild-to-moderate persistent asthma were randomized to one of 2 crossover sequences, including 8 weeks of an ICS, fluticasone propionate

(100 µg twice daily), and 8 weeks of an LTRA, montelukast (5-10 mg nightly depending on age), in a multicenter, double-masked, 18-week trial. Response was assessed on the basis of improvement in FEV₁ and assessed for relationships to baseline asthma phenotype-associated biomarkers.

Results: Defining response as improvement in FEV₁ of 7.5% or greater, 17% of 126 participants responded to both medications, 23% responded to fluticasone alone, 5% responded to montelukast alone, and 55% responded to neither medication. Compared with those who responded to neither

From ^aArizona Respiratory Center, University of Arizona, Tucson; ^bthe Clinical Science Center, University of Wisconsin, Madison; ^cthe Department of Pediatrics, National Jewish Medical and Research Center and University of Colorado Health Sciences Center, Denver; ^dthe Department of Pediatrics, University of California–San Diego; ^ethe Department of Allergy, Kaiser Permanente, San Diego; ^fthe Department of Pediatrics, Washington University, St Louis; and ^gthe Department of Health Evaluation Sciences, Pennsylvania State University, Hershey.

*See the Appendix.

Writing Committee: S. Szeffler (Chair), B. Phillips, F. Martinez, V. Chinchilli, R. Lemanske, R. Strunk, R. Zeiger, G. Larsen, and J. Spahn.

Supported by grants 5U10HL064287, 5U10HL064288, 5U10HL064295, 5U10HL064307, 5U10HL064305, and 5U10HL064313 from the National Heart, Lung, and Blood Institute. This study was carried out in part in the General Clinical Research Centers at Washington University School of Medicine (M01 RR00036) and National Jewish Medical and Research Center (M01 RR00051).

Potential conflicts of interest: Stanley J. Szeffler has consultant arrangements with AstraZeneca, GlaxoSmithKline, Aventis, and Merck, and has received grants/research support from National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) Childhood Asthma Management Program, NIH/NHLBI Inflammation, Airway Reactivity and Asthma, NIH/National Institute of Child Health and Development (NICHD) Pediatric Pharmacology Research Unit Network, NHLBI Childhood Asthma Research and Education Network, NIH/NHLBI Asthma Clinical Research Network, NIH/National Institute of Allergy and Infectious Diseases (NIAID) Inner City Asthma Consortium, Ross Pharmaceuticals, and AstraZeneca; Fernando D. Martinez serves on the Merck Advisory Board and has received lecture fees from GlaxoSmithKline and Merck; Vernon M. Chinchilli has consultant arrangements with Wyeth Pharmaceutical, Bristol-Myers Squibb Pharmaceutical, and Procter & Gamble Pharmaceutical, has a provisional patent application for “Genetic predictor

of efficacy of anti-asthmatic agent for improving pulmonary function,” and is the principal investigator for a Childhood Asthma Research and Education Network Data Coordinating Center, funded by the NHLBI; Robert Lemanske, Jr, has consultant arrangements with Aventis and AstraZeneca, has a patent pending on β receptor haplotypes and their relationship to responses to asthma medications, and is on the Speakers’ Bureau of Aventis, AstraZeneca, Merck, GlaxoSmithKline, Schering, and Novartis; Robert S. Zeiger has consultant arrangements with GlaxoSmithKline, Merck, Astra, and Novartis/Genentech; Gary L. Larsen is an Advair Pediatric Specialist for GlaxoSmithKline and has received grants/research support from NIH; Joseph D. Spahn has consultant arrangements with, has received grants/research support from, and is on the Speakers’ Bureau of GlaxoSmithKline and AstraZeneca, as well as receiving grants/research support from Merck; Leonard B. Bacharier has received grants/research support from NIH/NHLBI and is on the Speakers’ Bureau of GlaxoSmithKline, Merck, and Genentech/Novartis; Theresa Guilbert has consultant arrangements with, has received grants/research support from, and is on the Speakers’ Bureau of GlaxoSmithKline and is also on the Speakers’ Bureau of AstraZeneca; Wayne J. Morgan has consultant arrangements with Genentech; Christine A. Sorkness has consultant arrangements with and has received grants/research support from GlaxoSmithKline, as well as being on the Speakers’ Bureau for GlaxoSmithKline, AstraZeneca, and Genentech/Novartis; and Lynn M. Taussig has consultant arrangements with Glaxo.

Received for publication November 2, 2004; revised November 2, 2004; accepted for publication November 4, 2004.

Reprint requests: Stanley J. Szeffler, MD, National Jewish Medical and Research Center, Department of Pediatrics, Room J313, 1400 Jackson St, Denver, CO 80206. E-mail: szefflers@njc.org.

0091-6749/\$30.00

© 2005 American Academy of Allergy, Asthma and Immunology
doi:10.1016/j.jaci.2004.11.014

medication, favorable response to fluticasone alone was associated with higher levels of exhaled nitric oxide, total eosinophil counts, levels of serum IgE, and levels of serum eosinophil cationic protein and lower levels of methacholine PC₂₀ and pulmonary function; favorable response to montelukast alone was associated with younger age and shorter disease duration. Greater differential response to fluticasone over montelukast was associated with higher bronchodilator use, bronchodilator response, exhaled nitric oxide levels, and eosinophil cationic protein levels and lower methacholine PC₂₀ and pulmonary function values.

Conclusions: Response to fluticasone and montelukast vary considerably. Children with low pulmonary function or high levels of markers associated with allergic inflammation should receive ICS therapy. Other children could receive either ICSs or LTRAs. (J Allergy Clin Immunol 2005;115:233-42.)

Key words: Asthma, biomarkers, exhaled nitric oxide, fluticasone propionate, inhaled corticosteroids, montelukast, pulmonary response

Chronic airway inflammation characterizes persistent asthma. Currently, inhaled corticosteroids (ICSs) are recognized as the preferred long-term control therapy in patients with persistent asthma, including children of all ages, with nonsteroid long-term control medications positioned as alternative choices.¹ The preference for ICSs is based primarily on evidence from trials comparing mean responses between a treatment group and a control group; however, there is increased appreciation of the considerable interindividual variability in response to ICSs and leukotriene receptor antagonists (LTRAs).¹⁻¹³ Thus it is important to provide information that guides the clinician in selecting the medication most likely to achieve a favorable response for particular patients.

Few studies have addressed the factors that determine the marked variability in response to asthma control therapy. It is unknown, for example, whether patients who do not respond well to one medication might respond to the other medication. One recent study showed that pulmonary responses to an ICS in adults with mild-to-moderate persistent asthma are associated with specific patient characteristics and markers of airway inflammation.⁸

The National Heart, Lung, and Blood Institute Childhood Asthma Research and Education Network therefore examined the variability of response to ICSs and LTRAs in children with asthma to identify patient features that would serve as indicators for selection of the medication most likely to achieve a favorable response in individual patients.

METHODS

Details of study design and analyses have been reported.¹⁴ Children (n = 144) 6 to 17 years of age with mild-to-moderate asthma were enrolled. They had asthma symptoms or rescue bronchodilator use on average of 3 or more days per week during the previous 4 weeks and improvement in FEV₁ of 12% or greater after maximal bronchodilation or methacholine PC₂₀ of 12.5 mg/mL or less. They had no corticosteroid treatment within 4 weeks, no leukotriene-modifying agents within 2 weeks, and no history of

Abbreviations used

ECP: Eosinophil cationic protein
eDEM: Electronic Drug Exposure Monitor
eNO: Exhaled nitric oxide
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
LTRA: Leukotriene receptor antagonist
TEC: Total eosinophil count
uLTE₄: Urinary leukotriene E₄

respiratory tract infection within 4 weeks of enrollment. Children were excluded for severe asthma or FEV₁ of less than 70% of predicted value.¹⁴ The study was approved by each center's institutional review board. A parent/guardian gave informed consent, with verbal assent given by children less than 7 years of age, and written assent given by older children.

Study design

After a 5- to 10-day characterization period, participants were randomized to one of 2 crossover treatment sequences with 8-week periods of either an active ICS, fluticasone propionate (Flovent Diskus, GlaxoSmithKline, Research Triangle Park, NC; 100 µg per inhalation administered as one inhalation twice daily), or an active LTRA, montelukast (Singulair, Merck, West Point, Pa; 1 tablet at night, 5-mg chewable tablet for those 6 to 14 years of age and 10-mg tablet for those 15 to 18 years of age).¹⁴ During the active treatment period for one drug, the participant received a placebo for the alternative drug. The first 4 weeks of the second treatment period were considered a sufficient period for washout of study medication used in the first period of each treatment sequence.^{6,15-18} The 2 crossover sequences were stratified according to clinical center, age category, and FEV₁ percent predicted category by using the minimization method of randomization.¹⁹ Outcome parameters were determined every 4 weeks during the 16-week treatment phase.

Electronic peak flow measurements (AM1, Jaeger-Toennies GmbH, Hoechberg, Germany) and asthma symptom scores were recorded daily. An asthma-free day was defined as a day without the following: daytime or nighttime symptoms, use of rescue albuterol for asthma symptoms or low peak flow, asthma health care use, or missed school or work for asthma symptoms. Adherence to inhaled medication was measured from the Diskus dose indicator, and tablet medication was assessed on the basis of tablet count and an Electronic Drug Exposure Monitor (eDEM; AARDEX Ltd, Zug, Switzerland).

Procedures

Before randomization, asthma history, allergen skin tests, blood total eosinophil counts (TECs), serum eosinophil cationic protein (ECP) levels, serum total IgE levels, urinary leukotriene E₄ (uLTE₄) levels, methacholine PC₂₀ values, and exhaled nitric oxide (eNO) levels were obtained.¹⁴

Spirometry was performed¹⁴ at least 4 hours after the last use of a short-acting bronchodilator.²⁰ Maximal postbronchodilator spirometry was performed 15 minutes after a total of 6 to 8 puffs of inhaled albuterol administered through a metered-dose inhaler plus an Aerochamber (Monaghan Medical, Plattsburgh, NY).¹⁴ Airway responsiveness was measured by means of a standard methodology with methacholine (Provocholine, Methapharm, Ontario, Canada).¹⁴ The test was performed at least 4 hours after the last use of a short-acting bronchodilator. eNO was measured with the NIOX system (Aerocrine AB, Stockholm, Sweden).^{14,21} Skin prick tests were

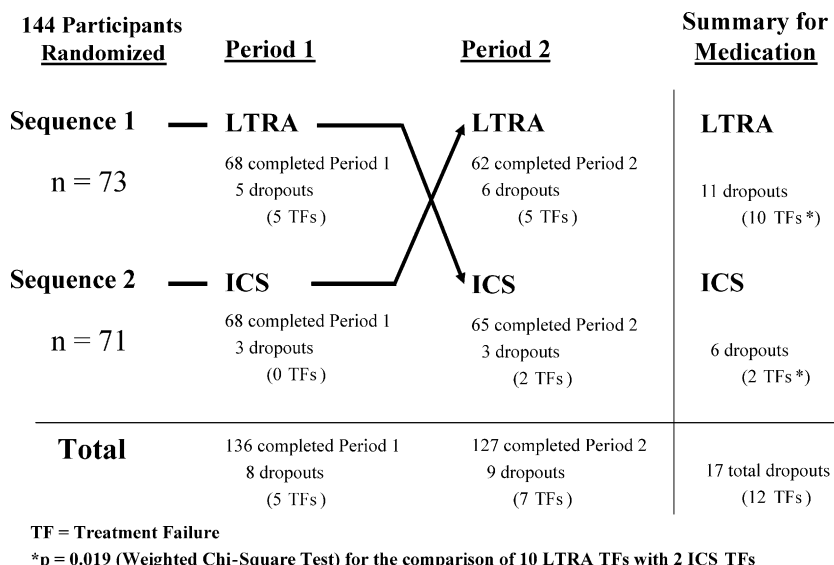


FIG 1. Study cohort and enrollment disposition for each period and sequence. Treatment failure was defined as an asthma exacerbation that required systemic steroid therapy. A weighted χ^2 test is applied to test for differences in treatment failure rates for the 2 medications, weighting by the sample size in each period. Not all children who completed visit 6 had complete data for FEV₁.

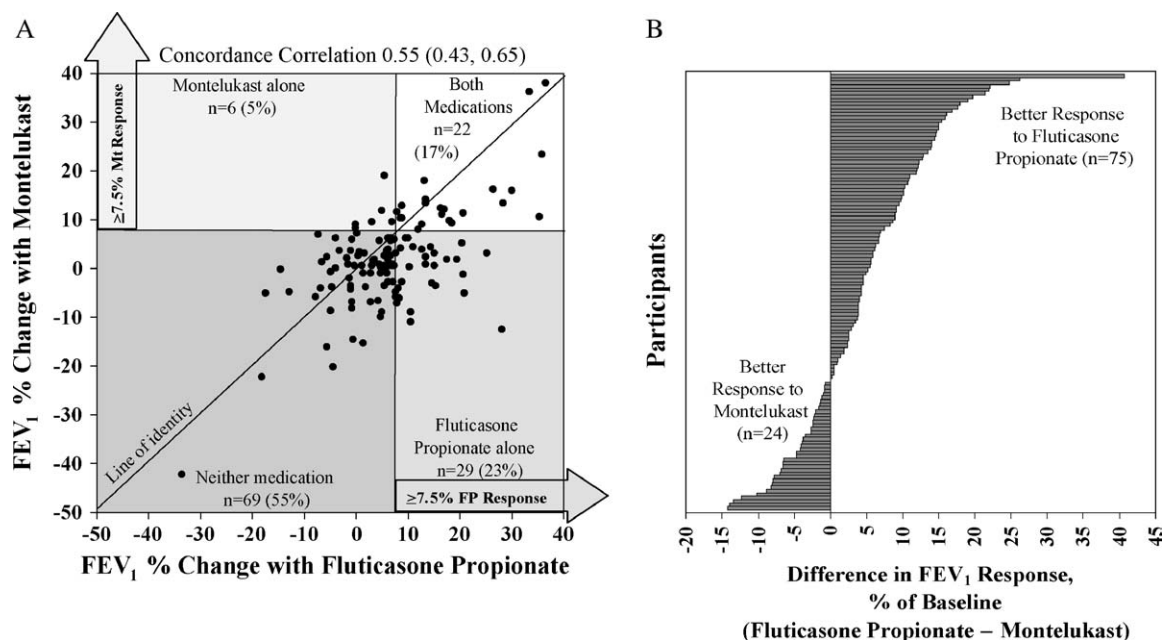


FIG 2. A, Variability of response and differential response to fluticasone and montelukast, as measured by change in FEV₁. Four regions show categories of response, defining a favorable response as 7.5% or greater. FP, Fluticasone propionate; Mt, montelukast. The line of identity is designated, with patients favoring montelukast falling above the line, and those favoring fluticasone falling below the line. The concordance correlation with 95% CIs is displayed. **B,** Difference in FEV₁ response between fluticasone propionate and montelukast for individual participants. Each line designates a single participant.

performed by using the Multitest II system (Lincoln Diagnostics, Decatur, Ill) with a core battery of aeroallergens.^{14,22,23}

Sample size and analyses

The target sample size of 140 randomized participants provided 90% statistical power for detecting a significant correlation between

the study medications for a change in prebronchodilator FEV₁. An effect size of ± 0.2 was used for the Kendall correlation coefficient (although concordance correlation coefficients, which are suited for the measurement of agreement beyond a simple linear relationship,²⁴ are presented), and an allowance was made for a 15% dropout rate.

TABLE I. Median characteristics (quartile 1, quartile 3) of patients with improvement in FEV₁ of 7.5% or greater for both, either, or neither fluticasone and montelukast medications

Baseline characteristic	Response to both fluticasone propionate and montelukast, n = 22 (17%)	Response to fluticasone propionate alone, n = 29 (23%)	Response to montelukast alone, n = 6 (5%)	Response to neither medication, n = 69 (55%)
Prebronchodilator FEV ₁ % predicted	90 (82, 97)*	88 (80, 100)*	94 (91, 99)	99 (92, 108)
Prebronchodilator FEV ₁ /FVC (%)	78 (70, 82)*	76 (72, 82)*	81 (76, 85)	83 (80, 87)
Maximum bronchodilator response – % change in FEV ₁	15 (10, 22)	15 (11, 21)	15 (10, 16)	14 (9, 18)
Methacholine PC ₂₀ (mg/mL)	0.8 (0.4, 1.9)	0.5 (0.3, 2.2)*	2.5 (0.9, 4.3)	1.6 (0.5, 4.1)
eNO (ppb)	34 (17, 53)	54 (19, 90)*	26 (21, 27)	23 (10, 41)
Blood total eosinophil count, absolute (cells/mm ³)	368 (184, 476)	375 (167, 657)*	207 (120, 504)	228 (130, 389)
Serum ECP (μg/L)	17 (9, 23)	23 (17, 37)*	13 (7, 32)	14 (8, 22)
Serum IgE (kU/L)	244 (70, 568)	303 (123, 469)*	140 (81, 166)	120 (39, 299)
uLTE ₄ (pg/mg creatinine)	121 (100, 139)*	113 (79, 161)	145 (115, 154)	90 (65, 124)
Asthma-free days per week	1.3 (0.0, 4.4)	1.2 (0.0, 3.5)	3.2 (0.0, 4.7)	1.2 (0.0, 3.5)
Bronchodilator use per week (for low peak flow or symptoms)	5.1 (2.0, 10.0)	6.0 (2.0, 10.0)	1.4 (0.0, 7.0)	4.0 (0.0, 11.2)
Age (y)	10 (7, 13)	12 (10, 14)	9 (7, 9)*	12 (8, 14)
Duration of asthma (y)	7 (5, 9)	9 (3, 11)	4 (1, 4)*	7 (5, 10)

Sample sizes might vary slightly across baseline characteristics because of missing data. The following variables were logarithmically transformed (base 2) for analysis: methacholine PC₂₀, eNO, blood TEC (absolute), serum ECP, serum IgE, and uLTE₄.

*Groups differ significantly from the “neither” group when comparing the odds ratios resulting from nominal logistic regression analysis.

The primary outcome measure was percentage change in pre-bronchodilator FEV₁ from baseline to the end of each treatment period. The study design contained no placebo washout periods at the request of the institutional review boards at 2 of the clinical centers. Therefore the first 4 weeks of each treatment period served as pseudo washout periods and were not included in the statistical analyses. Only individuals who completed both treatment periods were included in the analysis because the study was not designed with the intention to conduct an intent-to-treat analysis. A mixed-effects linear model was applied to account for period and sequence effects within the repeated-measurements feature of the crossover design for FEV₁ response. Restricted maximum likelihood estimation was applied to estimate all of the model parameters by using the PROC MIXED of SAS 8.2 (SAS Institute, Inc, Cary, NC). The FEV₁ values were corrected in further analyses for a small sequence effect (–0.14%) and a moderate and statistically significant period effect (–1.22%) for each of the 2 treatments.

The continuous responses to fluticasone and montelukast were examined separately and as a difference (fluticasone response minus montelukast response). These outcomes and the baseline characteristics were also dichotomized to obtain odds ratio estimates with 95% CIs. FEV₁ of 7.5% or greater was chosen as the effect size to determine a clinically meaningful response; this response was approximately one half the median maximum observed change after albuterol administration and greater than the 5% increase in short-term responses to ICSs reported in a similar population.²⁵ Cut points for dichotomous predictors were selected from the median value of the predictor associated with a 5% to 10% increase in FEV₁. Nominal logistic regression was applied to determine characteristics associated with response to fluticasone alone, montelukast alone, or both medications compared with response to neither medication. The set of potential predictors included asthma characteristics, pulmonary function, and biomarkers. Several variables were logarithmically transformed with base 2: PC₂₀ because of doubling doses in the methacholine challenge procedure and biomarkers because of skewed distributions.

Rates of dropout caused by asthma exacerbations that required systemic corticosteroids were compared by using a weighted χ^2 test, weighting by the sample size in each period, to account for the fact that dropouts in period 1 did not receive both treatments. Categorical data analyses that included 9 dropouts who had data in period 1 and for whom nonresponse was assumed for period 2 yielded essentially identical results.

The continuous and dichotomous responses were examined through PROC REG and PROC LOGISTIC of SAS 8.2, respectively, both univariably and multivariably by using a stepwise selection process; the multivariable models are not presented. Microsoft PowerPoint 2000 and SPLUS 2000 were used for graphic displays of the results. A 2-sided *P* value of less than .05 was considered significant.

RESULTS

Study cohort

Of 144 participants enrolled in the study, 126 successfully completed both treatment arms for the primary end point, with 33% in the youngest age group (6–9 years), 48% minorities, and 41% female patients (see Table E1 in the Journal's Online Repository at www.mosby.com/jaci).¹⁴ Seventeen (12%) participants did not complete the study (Fig 1); 12 had asthma exacerbations requiring treatment with systemic corticosteroids, and these were considered treatment failures. Two of these treatment failures occurred during the fluticasone treatment period, and 10 occurred during montelukast therapy (*P* for difference = .019, accounting for incomplete treatment exposure). Adherence to both fluticasone and montelukast administration was comparable. For those who completed treatment (n = 126), mean (SD) adherence for fluticasone

TABLE II. Univariable regression analysis for continuous outcomes FEV₁ response for fluticasone propionate, montelukast, and the difference (fluticasone — montelukast) between the 2 medications

Baseline predictor	Outcome variable	Parameter estimate	SE	P value
Bronchodilator use per week: For each unit increase in bronchodilator use at baseline, the difference in response (FP – Mt) is increased by 0.23 percentage points on average. (Five additional puffs per week of albuterol at baseline increases the difference by 1.15 percentage points on average.)	FEV ₁ % change, FP	0.11	0.11	.323
	FEV ₁ % change, Mt	–0.12	0.10	.253
	Difference (FP – Mt)	0.23	0.09	.015
Asthma-free days per week	FEV ₁ % change, FP	–0.53	0.41	.199
	FEV ₁ % change, Mt	0.14	0.38	.710
	Difference (FP – Mt)	–0.67	0.34	.053
Prebronchodilator FEV ₁ % predicted: For each percentage point increase in baseline FEV ₁ % predicted, the FP response decreases by 0.32 percentage points on average, and the Mt response decreases by 0.20 percentage points on average. However, there is also a significant effect for the difference so that for every unit increase in baseline FEV ₁ % predicted, the difference in response (FP – Mt) is decreased 0.12 percentage points on average. (An increase of 5 percentage points in baseline FEV ₁ % predicted corresponds to an average decrease in the difference by 0.60 percentage points.)	FEV ₁ % change, FP	–0.32	0.07	< .001
	FEV ₁ % change, Mt	–0.20	0.06	.002
	Difference (FP – Mt)	–0.12	0.06	.050
Prebronchodilator FEV ₁ /FVC (%): For each percentage point increase in baseline FEV ₁ /FVC, the FP response decreases by 0.59 percentage points on average, and the Mt response decreases by 0.28 percentage points on average. However, there is also a significant effect for the difference so that for every unit increase in baseline FEV ₁ /FVC, the difference in response (FP – Mt) is decreased 0.31 percentage points on average. (An increase of 5 percentage points in baseline FEV ₁ /FVC corresponds to an average decrease in the difference by 1.55 percentage points.)	FEV ₁ % change, FP	–0.59	0.11	< .001
	FEV ₁ % change, Mt	–0.28	0.11	.012
	Difference (FP – Mt)	–0.31	0.10	.002
Maximum bronchodilator response – % change in FEV ₁ : For each unit increase in bronchodilator responsiveness at baseline, the difference in response (FP – Mt) is increased by 0.20 percentage points on average. (An increase of 5 additional percentage points of reversibility baseline corresponds to a 1.00 percentage point increase in the difference in responses.)	FEV ₁ % change, FP	0.18	0.10	.069
	FEV ₁ % change, Mt	–0.02	0.09	.844
	Difference (FP–Mt)	0.20	0.08	.017
Methacholine PC ₂₀ (mg/mL)†: For each doubling of methacholine PC ₂₀ , the FP response decreases by 1.30 percentage points on average. Additionally, for each doubling of methacholine reactivity at baseline, the difference in response (FP – Mt) is decreased by 1.13 percentage points on average.	FEV ₁ % change, FP	–1.30	0.49	.009
	FEV ₁ % change, Mt	–0.17	0.46	.713
	Difference (FP – Mt)	–1.13	0.39	.005
eNO (ppb)†: For each doubling of eNO at baseline, the difference in response (FP – Mt) is increased by 1.84 percentage points on average.	FEV ₁ % change, FP	1.03	0.74	.168
	FEV ₁ % change, Mt	–0.81	0.70	.250
	Difference (FP – Mt)	1.84	0.61	.003
Blood TEC (cells/mm ³)†	FEV ₁ ¹ % change, FP	1.58	0.80	.051
	FEV ₁ % change, Mt	0.46	0.74	.537
	Difference (FP – Mt)	1.13	0.68	.099
Serum ECP (μg/L)†: For each doubling of ECP, the FP response increases by 2.59 percentage points on average. Additionally, for each doubling of ECP at baseline, the difference in response (FP – Mt) is increased by 2.26 percentage points on average.	FEV ₁ % change, FP	2.59	0.79	.001
	FEV ₁ % change, Mt	0.33	0.74	.658
	Difference (FP – Mt)	2.26	0.66	.001
Serum IgE (kU/L)†: For each doubling of IgE, the FP response increases by 1.06 percentage points on average.	FEV ₁ % change, FP	1.06	0.46	.022
	FEV ₁ % change, Mt	0.57	0.42	.176
	Difference (FP – Mt)	0.49	0.39	.213
uLTE ₄ (pg/mg creatinine)†	FEV ₁ % change, FP	2.29	1.42	.109
	FEV ₁ % change, Mt	1.85	1.27	.147
	Difference (FP – Mt)	0.44	1.27	.731
Age	FEV ₁ % change, FP	0.05	0.29	.865
	FEV ₁ % change, Mt	–0.28	0.26	.280
	Difference (FP – Mt)	0.33	0.24	.171
Age at onset of asthma	FEV ₁ % change, FP	–0.09	0.26	.728
	FEV ₁ % change, Mt	–0.25	0.24	.297
	Difference (FP – Mt)	0.16	0.22	.480

TABLE II. (Continued)

Baseline predictor	Outcome variable	Parameter estimate	SE	P value
Duration of asthma	FEV ₁ % change, FP	0.12	0.25	.639
	FEV ₁ % change, Mt	0.01	0.22	.955
	Difference (FP – Mt)	0.10	0.21	.619
Female sex: Female patients respond to Mt 3.91 percentage points more than male patients on average.	FEV ₁ % change, FP	1.52	1.96	.439
	FEV ₁ % change, Mt	3.91	1.74	.026
	Difference (FP – Mt)	–2.39	1.64	.146
Minority: The difference in response (FP – Mt) for minorities is 4.29 percentage points less than for nonminorities on average.	FEV ₁ % change, FP	–2.15	1.93	.266
	FEV ₁ % change, Mt	2.14	1.74	.221
	Difference (FP – Mt)	–4.29	1.58	.008
Hispanic	FEV ₁ % change, FP	0.64	2.24	.776
	FEV ₁ % change, Mt	–2.49	2.02	.219
	Difference (FP – Mt)	3.13	1.87	.096
Body mass index (kg/m ²)	FEV ₁ % change, FP	–0.15	0.20	.434
	FEV ₁ % change, Mt	0.12	0.18	.492
	Difference (FP – Mt)	–0.27	0.16	.094
No. of positive aeroallergen skin test results (of 8)	FEV ₁ % change, FP	0.62	0.43	.154
	FEV ₁ % change, Mt	0.03	0.39	.947
	Difference (FP – Mt)	0.59	0.36	.104

FP, Fluticasone propionate; Mt, montelukast.

* $P \leq .05$.†Analyzed by using a Log₂ transformation.

by Diskus counter was 94% (14) and 89% (15) for treatment periods 1 and 2, respectively. For montelukast, adherence was 97% (24) by tablet count and 92% (29) by eDEM for treatment period 1 and 93% (22) by tablet count and 86% (17) by eDEM for treatment period 2.

Distribution of responses

There was agreement in the responses to the 2 medications at the end of the 8-week treatment periods, with a concordance correlation of 0.55 (95% CI, 0.43–0.65; $n = 126$ participants) but with substantial variability between participants (Fig 2, A). Overall, the mean (SE) FEV₁ percentage of improvement was 6.8% (0.96) for fluticasone and 1.9% (0.87) for montelukast. The difference in the response for the 2 medications (fluticasone minus montelukast) for each individual participant is summarized in Fig 2, B, yielding a mean difference in the responses of 4.9% (SE, 0.81; $P < .001$). For fluticasone, FEV₁ improved in 29% of the participants by 5% to 10%, and in 30% by 10% or greater; for montelukast, FEV₁ improved in 17% by 5% to 10% and in 16% by 10% or greater. Defining response as FEV₁ of 7.5% or greater, 17% responded to both treatments, 23% responded to fluticasone alone, 5% responded to montelukast alone, and 55% responded to neither treatment (Table I). The group that responded to both medications had at baseline significantly higher uLTE₄ levels and lower prebronchodilator FEV₁ percent predicted and FEV₁/forced vital capacity (FVC) values compared with those of the group responding to neither medication. Those who responded to fluticasone alone had at baseline significantly higher eNO levels, TECs, ECP levels, and IgE levels and lower prebronchodilator FEV₁ percent predicted, prebronchodilator FEV₁/FVC, and methacholine PC₂₀ values than those who responded to neither

medication. Those who responded to montelukast alone were significantly younger (median, 9 years) and had shorter durations of asthma (median, 4 years) than those who responded to neither medication.

Predictors of response to each treatment and differential response

Univariable regression analysis for continuous outcomes indicated that significant baseline predictors of greater response to fluticasone included lower prebronchodilator FEV₁ percent predicted, lower prebronchodilator FEV₁/FVC ratio, lower methacholine PC₂₀ value, higher ECP level, and higher IgE level. For montelukast, greater response was associated with lower prebronchodilator FEV₁ percent predicted and FEV₁/FVC ratio, as well as female sex (Table II). The difference in response (fluticasone minus montelukast) was associated with lower prebronchodilator FEV₁ percent predicted and FEV₁/FVC ratio, lower methacholine PC₂₀ value, higher bronchodilator use, higher FEV₁ response to bronchodilator, higher eNO level, higher ECP level, and non-minority race (Table II). Several measures of airway inflammation (methacholine PC₂₀ value, FEV₁ response to bronchodilator, eNO level, and ECP level) remained significant, even after controlling for baseline FEV₁/FVC ratios (data not shown), demonstrating their independence from baseline lung function as predictors of the difference in response between fluticasone and montelukast.

Multivariable regression analysis (stepwise selection with $P < .10$ for each regressor) for the difference in medication response (fluticasone minus montelukast) resulted in a model containing baseline prebronchodilator FEV₁/FVC ratio (parameter estimate [PE] [SE] = –0.22 [0.10], $P = .0266$), baseline log₂ ECP value (PE [SE] = 1.80 [0.63], $P = .0049$), body mass index (PE

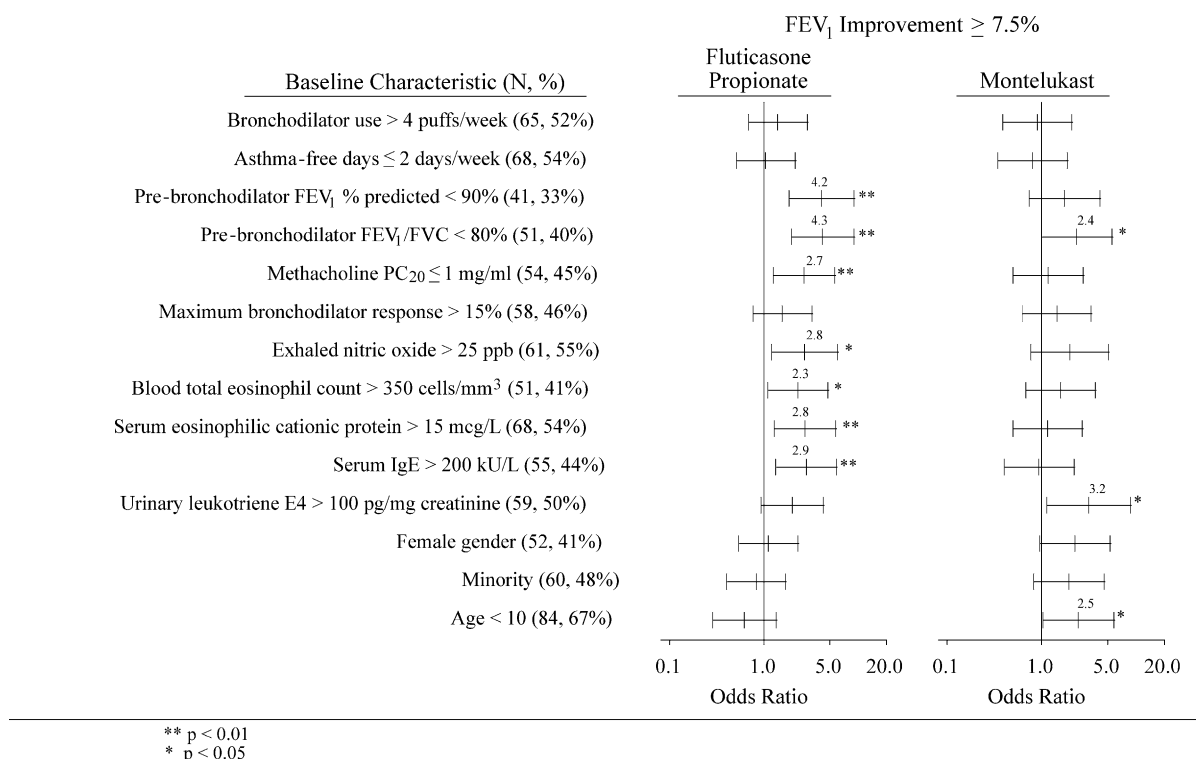


FIG 3. Univariable odds ratios for the odds of response with selected markers compared with the odds of response without the marker, where response for improvement in FEV₁ of 7.5% or greater is shown separately for each medication. Horizontal lines represent 95% CIs. The odds ratios are shown on a logarithmic scale.

[SE] = -0.33 [0.15], $P = .0246$), and log₂ PC₂₀ value (PE [SE] = -0.68 [0.39]; $R^2 = 0.19$). If ECP, which is a measurement that is less readily available to clinicians than others, is excluded as a potential explanatory variable, baseline asthma-free days and age replace ECP in the model ($R^2 = 0.18$). As expected, some of the regressors that displayed statistically significant relationships with the difference in medication response in Table II do not appear in the multivariable model because of the correlations among the regressors.

Further univariable analysis with dichotomized predictors revealed that significant baseline predictors of a response to fluticasone of 7.5% or greater included prebronchodilator FEV₁ percent predicted of less than 90%, FEV₁/FVC ratio of less than 80%, methacholine PC₂₀ value of 1 mg/mL or less, eNO value of greater than 25 ppb, TEC of greater than 350 cells/mm³, ECP level of greater than 15 μg/L, and IgE level of greater than 200 kU/L; predictors for a response to montelukast included prebronchodilator FEV₁/FVC ratio of less than 80%, uLTE₄ level of 100 pg/mg creatinine or greater, and age of less than 10 years (Fig 3).

DISCUSSION

In this study we found wide variability in the pulmonary responses to 2 asthma control medications in a population

of children with mild-to-moderate persistent asthma but also significant concordance of response (Fig 2, A); that is, a large proportion of the cohort had similar responses to each of the 2 medications. We also identified a group of children with increased markers associated with allergic airway inflammation who have a significantly greater response to fluticasone than to montelukast.

The children in our study were treated consecutively with an ICS and an LTRA in a crossover design. Both of these classes of medicines are effective controllers of asthma symptoms, with ICSs showing better mean improvement in both pulmonary function and symptoms compared with LTRAs.²⁶ We found that FEV₁ responses to these medications were significantly concordant, and more than one half (55%) of all participants responded to neither medication, as defined by improvement in FEV₁ of 7.5% or greater (Fig 2, A, and Table I). These participants were characterized by higher baseline pulmonary function and lower levels of markers of allergic inflammation but had asthma-free days during the characterization period that were not significantly different from the other groups. As such, this group might represent a specific asthma phenotype with unaltered pulmonary function and no evidence of allergic airway inflammation but with frequent symptom days. This subgroup merits further evaluation.

Of particular interest were the factors that predicted responses to one medication but not to the other. The

group that responded to fluticasone alone (23%) had lower pulmonary function and methacholine PC₂₀ values and higher eNO levels, TECs, IgE levels, and ECP levels at baseline when compared with participants who responded to neither medication (Table I). Several recent studies have demonstrated a strong correlation between eNO levels and sputum eosinophil counts²⁷⁻³⁰ in patients with asthma, and this association was most marked in corticosteroid-naïve patients. Our findings thus suggest that children with higher levels of eosinophilic airway inflammation might respond to ICSs but not to LTRAs. The group that responded to montelukast alone, although small in proportion (5%), was younger in age and had a shorter duration of disease. Perhaps leukotriene-driven inflammation is an important feature of asthma in young children, or perhaps this represents a specific phenotype of the disease. Children who responded to both medications (17%) had significantly lower pulmonary function and higher uLTE₄ levels at baseline than those who responded to neither medication (Table I). These data reveal an asthma phenotype with impaired lung function and overexpressed leukotriene production that is responsive to both ICSs and LTRAs.

We conducted further analysis to identify predictors for the differential response of the 2 medications. Univariable regression analyses for continuous outcomes identified baseline parameters, favoring a greater differential response for fluticasone over montelukast (Fig 2, B). These included decreased pulmonary function and increased FEV₁ response to a bronchodilator, airway hyperresponsiveness, and markers of allergic inflammation (eNO and ECP; Table II). Also, in assessing determinants of responses to each medication separately, we confirmed and extended the findings reported in adults,⁸ suggesting that improvement in FEV₁ after treatment with fluticasone is not only associated with high eNO levels but also increased TECs, ECP levels, and IgE levels in children (Fig 3). We also showed that an increased likelihood of response to montelukast is associated with higher uLTE₄ levels (Fig 3). The differential response to the 2 medications is consistent with the observation that ICSs have multiple targets for intervention, whereas LTRAs are more selective. Overbeek et al³¹ recently reported on the comparative effect of fluticasone and montelukast on measures of inflammation obtained from biopsy and serum samples from adults with mild asthma. Although neither medication significantly reduced activated T cells or eosinophils, the ICS significantly reduced mast cells on biopsy analysis, as well as serum ECP levels, compared with the LTRA.

The main limitation of our study was the reliance on a single FEV₁ measurement at the 8-week point of each treatment period. Although there was no placebo period in our crossover design, available data indicated that a 4-week period was sufficient to allow washout of the medication from the first treatment period. Studies in which the treatment periods are extended beyond 8 weeks could help determine whether our findings persist over longer periods of time and are independent of seasonal variability in asthma control.

In summary, although there is variability in response to ICSs and LTRAs, we did identify characteristics of patients that should guide the clinician in the choice of asthma control medication. Children who have reduced pulmonary function or high levels of markers indicating allergic inflammation should receive ICS therapy, whereas those without these features could receive a therapeutic trial of either ICS or LTRA with an assessment of response. Our findings suggest that asthma therapy might soon move from the current approach based on mean responses in populations to one in which the treatment that is most likely to expeditiously achieve a favorable response is identified for each individual patient on the basis of her or his phenotypic and possibly genotypic characteristics.

REFERENCES

1. National Asthma Education and Prevention Program report: guidelines for the diagnosis and management of asthma update on selected topics—2002. *J Allergy Clin Immunol* 2002;110(suppl):S141-219.
2. Schwartz HJ, Lowell FC, Melby JC. Steroid resistance in bronchial asthma. *Ann Intern Med* 1968;69:493-9.
3. Lee TH, Brattsand R, Leung DYM. Corticosteroid action and resistance in asthma. *Am J Respir Cell Mol Biol* 1996;93(suppl):S1-S79.
4. Sher ER, Leung DYM, Surs W, Kam JC, Zieg G, Kamada AK, et al. Steroid-resistant asthma. Cellular mechanisms contributing to inadequate response to glucocorticoid therapy. *J Clin Invest* 1994;93:33-9.
5. Leung DYM, Bloom JW. Update on glucocorticoid action and resistance. *J Allergy Clin Immunol* 2003;111:3-22.
6. Malmstrom K, Rodriguez-Gomez G, Guerra J, Villaran C, Pineiro A, Wei LX, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. *Ann Intern Med* 1999;130:487-95.
7. Zhang J, Yu C, Holgate ST, Reiss TF. Variability and lack of predictive ability of asthma end-points in clinical trials. *Eur Respir J* 2002;20:1102-9.
8. Szeffler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002;109:410-8.
9. Palmer LJ, Silverman ES, Weiss ST, Drazen JM. Pharmacogenetics of asthma. *Am J Respir Crit Care Med* 2002;165:861-6.
10. Israel E, Chervinsky PS, Friedman B, van Bavel J, Skalky CS, Ghanam AF, et al. Effects of montelukast and beclomethasone on airway function and asthma control. *J Allergy Clin Immunol* 2002;110:847-54.
11. Meyer KA, Arduino JM, Santanello NC, Knorr BA, Bisgaard H. Response to montelukast among subgroups of children aged 2 to 14 years with asthma. *J Allergy Clin Immunol* 2003;111:757-62.
12. Simons FER, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G, et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr* 2001;138:694-8.
13. Simons FER, Menton J, Leff JA. New drug treatment for asthma: clinical versus statistical significance. *J Pediatr* 2002;140:484-5.
14. Strunk RC, Szeffler SJ, Phillips BR, Zeiger RS, Chinchilli VM, Larsen G, et al. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. *J Allergy Clin Immunol* 2003;112:883-92.
15. Vathenen AS, Knox AJ, Wisniewski A, Tattersfield AE. Time course of change in bronchial reactivity with an inhaled corticosteroid in asthma. *Am Rev Respir Dis* 1991;143:1317-21.
16. Gershman NH, Wong HH, Liu JT, Fahy JV. Low- and high-dose fluticasone propionate in asthma: effects during and after treatment. *Eur Respir J* 2000;15:11-8.
17. Laviolette M, Malmstrom K, Lu S, Chervinsky P, Pujet J-C, Peszek I, et al. For the Montelukast/Beclomethasone additivity group. Montelukast added to inhaled Beclomethasone in treatment of asthma. *Am J Respir Crit Care Med* 1999;160:1862-8.
18. Shapiro G, Bronsky EA, LaForce CF, Mendelson L, Pearlman D, Schwartz RH, et al. Dose-related efficacy of budesonide administered via

- a dry powder inhaler in the treatment of children with moderate to severe persistent asthma. *J Pediatr* 1998;132:976-82.
19. Pocock SJ. Clinical trials: a practical approach. New York: John Wiley & Sons Ltd; 1983. p.84-86.
 20. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152:1107-36.
 21. Silkoff PE, Wakita S, Chatkin J, Ansarin K, Gutierrez C, Caramori M, et al. Exhaled nitric oxide after beta2-agonist inhalation and spirometry in asthma. *Am J Respir Crit Care Med* 1999;159:940-4.
 22. Childhood Asthma Management Program. Childhood Asthma Management Program allergy and skin test manual, version 2.0. Springfield (VA): National Technical Information Service; 1994.
 23. Mitchell H, Senturia Y, Gergen P, Baker D, Joseph C, McNiff-Mortimer K, et al. Design and methods of the National Cooperative Inner-City Asthma Study. *Pediatr Pulmonol* 1997;24:237-52.
 24. Lin L. A concordance correlation coefficient to evaluate reproducibility. *Biometrics* 1989;45:255-68.
 25. The 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.
 26. Busse W, Raphael GD, Galant S, Kalberg C, Goode-Sellers S, Srebro S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol* 2001;107:461-8.
 27. Jatakanon A, Lim S, Kharitonov SA, Chung KF, Barnes PJ. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. *Thorax* 1998;53:91-5.
 28. Berlyne GS, Parameswaran K, Kamada D, Elthimiadis A, Hargreave FE. A comparison of exhaled nitric oxide and induced sputum as markers of airway inflammation. *J Allergy Clin Immunol* 2000;106:638-44.
 29. Piacentini GL, Bodini A, Costella S, Vicentini L, Mazzi P, Sperandio S, et al. Exhaled nitric oxide and sputum eosinophil markers of inflammation in asthmatic children. *Eur Respir J* 1999;13:1386-90.
 30. Covar R, Spahn JD, Martin R, Silkoff PE, Sundstrom DA, Murphy J, et al. Safety and application of induced sputum analysis in childhood asthma. *J Allergy Clin Immunol* 2004;114:575-82.
 31. Overbeek SE, O'Sullivan S, Leman K, Mulder PGH, Hoogsteden HC, Prins J-B. Effect of montelukast compared with inhaled fluticasone on airway inflammation. *Clin Exp Allergy* 2004;34:1388-94.

APPENDIX

The members of the Childhood Asthma Research and Education Network for this study included the following:

Clinical centers:

National Jewish Medical and Research Center, Denver, Colo: Stanley J. Szeffler, MD (Principal Investigator); Gary Larsen, MD (Co-Investigator); Joseph Spahn, MD (Co-Investigator); Ronina Covar, MD (Co-Investigator); Andrew Liu, MD (Co-Investigator); D Sundström (Coordinator); Amy Grumann, RN (Coordinator); Melanie Phillips (Coordinator); Michael White (Research Assistant).

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); James E. Gern, MD (Consultant); David B. Allen, MD (Consultant); Kristen Blotz, RN (Coordinator); Sarah Garibay, RN (Coordinator); Kelly Miller (Coordinator); Rick Kelley (Pulmonary Function Manager); Luke Weasler (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); Michael Schatz, MD (Co-Investigator); Noah J. Friedman, MD (Co-Investigator); Sandra C. Christiansen, MD (Co-Investigator); Alfredo A. Jalowayski, PhD (Co-Investigator); Hal Hoffman, MD (Co-Investigator); Kathleen Harden, RN (Coordinator); Catherine Nelle, RN (Coordinator); Eva Rodriguez, RRT; Elaine Jensen; Linda Galbreath.

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); Cindy Moseid (Secretary).

Arizona Respiratory Center, University of Arizona, College of Medicine, Tucson, Ariz: Fernando D. Martinez, MD (Principal Investigator); Wayne J. Morgan, MD (Co-Investigator); Theresa W. Guilbert, MD (Co-Investigator); John D. Mark, MD (Co-Investigator); and Mark A. Brown, MD; James Goodwin, PhD (Coordinator); Melisa Celaya (Coordinator); Anna Valencia (Coordinator); Janet Lawless, RN (Coordinator); Shelley Radford, RT; 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 National Heart, Lung, and Blood Institute Division of Lung Diseases); Virginia Taggart, MPH (National Heart, Lung, and Blood Institute Project Scientist); Gail Weinmann, MD (Executive Secretary, DSMB); Gang Zeng, PhD.

Data Coordinating Center, Penn State University College of Medicine, Hershey, Pa: Vernon M. Chinchilli, PhD (Principal Investigator); David Mauger, PhD (Co-Investigator); Timothy Craig, DO (Co-Investigator); Ian Paul, MD (Co-Investigator); Gavin Graff, MD (Co-Investigator); Brenda Phillips (Scientific Coordinator); Jessica Beiler (Scientific Coordinator); Sue Boehmer (Scientific Coordinator); Loretta Doty (Project Coordinator); Anne-Marie Dyer; Lindsay Texter; Jim Schmidt; Patsy Rawa; Linda Ferrari; Sherrie Whisler; Brenda Beers; Linda Miller; Judy Potteiger; Lori Schell; Holly Hess; Vanessa Simmons; Thuy Tran; Lincoln Milner; Brian Moore; Andrew Sutton.

Committees:

Data and Safety Monitoring Board: Thomas F. Boat, MD (Chair), Children's Hospital Medical Center,

Cincinnati, Ohio; William C. Bailey, MD, The University of Alabama at Birmingham, Birmingham, Ala; Mary Kay Garcia, PhD, RN, CPNP; Carolyn M. Kerckmar, 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; 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; Mark Liu, MD, Johns Hopkins Asthma and Allergy Center, Baltimore, Md.

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

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

Quality Control Committee: Robert S. Zeiger, MD, PhD, (Chair); Vernon M. Chinchilli, PhD; Robert C. Strunk, MD; Theresa Guilbert, MD; Dave Mauger, PhD; Stanley Szeffler, MD; Brenda Phillips, MS; D. Sundström; James Schmidt, BS.

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

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

Pharmaceutical Suppliers:

GlaxoSmithKline, Inc, Research Triangle Park, NC; Merck & Co, Inc, West Point, Pa, donated the drugs and placebo fluticasone propionate and montelukast, respectively.

Equipment Support:

Lincoln Diagnostics (Multi-Test II kits, donated), Decatur, Ill; Monaghan Medical (Aerochamber and masks), Plattsburgh, NY; MEMS, Medication Event Monitoring Systems, AARDEX, Zug, Switzerland; Aerocrine, Inc, Chicago, Ill; VIASYS Healthcare GmbH, Hoechst, Germany.