Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med 2006;354:1985-97.

Additional Methods-electronic

Treatments

Montelukast (4 mg orally at bedtime; Singulair, Merck & Co., West Point, PA) was added to the study medication if the child developed persistent symptoms or required 4 courses of oral steroids in a 12-month period. If symptom control was inadequate on montelukast or the child required hospitalization, open-label fluticasone propionate (110 mcg/puff 1 puff BID via metered-dose inhaler and Aerochamber and mask) was added. If control was not achieved, addition of other medications by physician discretion was allowed. The addition of these medications was based on step-up protocols, and all supplementary medications were tapered after 2 month treatment-courses based on defined parameters[16]. Treatment failure status was assigned if the child had 2 hospitalizations in a 12-month period or, at anytime, if a hypoxic seizure or an intubation due to an exacerbation occurred [16].

Skin Prick Test Methods and specific allergens.

Allergy skin tests were done to 8 common aeroallergens at all the clinical centers (mixtures for house-dust mite [Dermatophagoides pteronyssinus and D farinae], cockroach [American and German], dog [mixed breeds], cat [standardized], mold [mix #1], grass [standardized Southern mix], tree [eastern 8 tree mix], and weed [national mix] [Greer Laboratories, Lenoir, NC]), and 3 foods milk [cow], egg [chicken, whole], and peanut [Greer Laboratories, Lenoir, NC]) using the Multi-test IIâ (provided by Lincoln Diagnostics, Decator, IL) prick

technique. The St. Louis center tested the following additional allergens: red oak, aspergillus fumigatus, and short ragweed [Greer Laboratories, Lenoir, NC]. A test was considered positive if the prick test resulted in a wheal with a mean diameter (mean of maximum and 90° midpoint diameters) that was at least 3 mm greater than a saline control.

Forced impulse oscillometry.

Impulse oscillometry (IO) was performed using the Jaeger Masterscreen IO System (VIASYS Healthcare GmbH, Hoechberg, FRG) and was performed prior to spirometry with at least 3 forced oscillation measurements being obtained. For each measurement, participants wore nose clips and breathed normally for 30 seconds while a parent or guardian gently held the sides of the face to decrease the shunt capacitance of the cheeks. The instrument was calibrated prior to measurement with a 3-liter syringe and during measurement applied a pressure step wave every 250 milliseconds through a loudspeaker to the airway opening via a size-appropriate mouthpiece. Throughout data acquisition, pressure and flow traces were graphically displayed in real time. Measurements were accepted when the tracings showed stable, uninterrupted tidal breathing during data acquisition for a maximum of 30 and a minimum of 15 seconds and four tidal breaths. This yielded a total of 60 to 120 impulses from which impedance parameters could be calculated at discrete frequencies from 5 to 35 Hz. Measurements were rejected if disturbed by tongue position obstructing the mouthpiece, coughing, breath-holding, swallowing, or

vocalization. The impedance parameters from 3 acceptable data epochs were averaged. The value of resistance at 10Hz (R10) was monitored to assess repeatability of the 30 seconds of data collection. The coherence function at 10 Hz had to be 0.80 or greater while values of R10 had to be within a 20% range (calculated from the largest value for R10). All tests were reviewed independently to ensure that those tests not meeting these criteria were not included in the analysis.

Impulse oscillometry assesses the impedance of the respiratory system (Z_{RS}) and allows calculation of the contribution of resistance (R_{RS}) and reactance (X_{RS}) to the total Z_{RS}. Resistance can be calculated from pressure and flow signals where pressure is in phase with flow while reactance computation involves pressure 90 degrees out of phase with flow. Reactance at low frequencies reflects the visco-elastic properties of the respiratory system and will be more negative with greater magnitude in patients with airway dysfunction[20-22]. Parameters included in this analysis included the resistance (R5) and reactance (X5) at 5 Hz. In addition, the resonant frequency (f-res) was recorded. This is the frequency at which reactance is zero.

Statistical Analyses

Multivariable Poisson regression modeling was used to analyze outcome measures expressed as rates: exacerbations requiring corticosteroid bursts, unscheduled physician visits, hospitalizations, montelukast use and supplemental ICS use. In addition to treatment group assignment these models

included covariates as specified for the primary outcome analysis: age at randomization, sex, race or ethnic group based on parental report (Non-Hispanic White vs. All Others), clinical center, aeroallergen skin test reactivity (yes/no), total months of asthma-like symptoms at baseline, severity of symptoms at baseline (episode-free days during the run-in period), % eosinophils, and eczema (yes/no). Rate estimates from these models were reported as number of occurrences per 100 child-years. 95% confidence interval endpoints for rate estimates were calculated as the antilog of Wald-based 95% confidence interval endpoints associated with the model predictions (Poisson regression models are a class of more general log-linear regression models). Therefore, the 95% confidence intervals reported here are asymmetric with respect to the rate estimates.

Multivariable linear regression modeling was used to analyze continuous outcomes: reactance measured via impulse oscillometry and growth assessment. These models included treatment group assignment and covariates as described above. Growth was characterized by two different measures: change in height from baseline in centimeters, and velocity in centimeters per year. A velocity outcome was calculated for each participant at each study visit, not including the first or the last. This was defined as the slope estimated from the regression of height on time using three consecutive visits. For example, the velocity for a participant at 20 months was calculated from the three height measurements at 16, 20 and 24 months. Consequently, velocity was undefined at the baseline and

final visits. The velocity outcomes across participants were then used as the response variable in the multivariable linear regression models.

Kaplan-Meier survival estimates were used to characterize the time-to-event outcomes: first prednisolone burst, second prednisolone burst and supplementary controller. Statistical significance of treatment group differences was assessed using the log-rank test. For the survival analyses restricted to the observation year, events occurring during the treatments years were ignored. That is, the time-to-event clock was “reset” at the beginning of the observation year. Survival analyses over the entire 3-year period ignored the change in treatment occurring at the end of the treatment period. Therefore, the Kaplan-Meier curves (displayed in Figure 3) over the period 24-36 months are not directly comparable to the 24-36 month portion of the Kaplan-Meier curves over the entire 36 months. ANCOVA and regression analyses were carried out using the SAS statistical software system version 8.2 (SAS Institute Inc, Cary, NC). Kaplan-Meier analyses were carried out using the S-Plus statistical software system version 6.2 (Insightful Corp, Seattle, WA). All statistical tests were carried out at the two-sided 0.05 significance level.

Table 1-electronic. Modified Asthma Predictive Index from[17], pubished with permission by Elsevier.

Modified* Versus Original Asthma Predictive Index (Castro-Rodriguez[3])

1. A history of 4 or more wheezing episodes with at least one physician diagnosed

2. In addition, the child must meet at least one of the following major conditions or at least 2 of the following minor conditions

Modified Asthma Predictive Index	**Original Asthma Predictive Index**
Major Criteria	**Major Criteria**
Parental history of asthma	Parental history of asthma
MD-diagnosed atopic dermatitis	MD-diagnosed atopic dermatitis
Allergic sensitization to at least one aeroallergen	
Minor Criteria	**Minor Criteria**
Allergic sensitization to milk, egg, or peanuts	**MD-diagnosed allergic rhinitis**
Wheezing unrelated to colds	Wheezing unrelated to colds
Blood eosinophils above 4%	Blood eosinophils above 4%

***Differences in indices are bolded**

Appendix

The members of the CARE Network as of February 2005 are as follows:

Clinical Centers:

National Jewish Medical and Research Center, Denver: Stanley J. Szefler, MD (Principal Investigator); Gary Larsen, MD (Co-Investigator); Joseph Spahn, MD (Co-Investigator); Ronina Covar, MD (Co-Investigator); Andrew Liu, MD (Co-Investigator);
Neal Jain, MD (Study Physician); Harvey Leo, MD (Study Physician); Beth Macomber, MD (Study Physician); Chris Mjaanes, MD (Study Physician); Ben Song, MD (Study Physician); D Sundstrom (Coordinator); Amy Grumann, RN (Coordinator); Melanie Phillips (Coordinator); Michael White (Research Assistant); Jay Markson, MD (Referring Pediatrician); Jeffrey Barter, MD (Referring Pediatrician); Gayle Spears, PA-C (Referring Physician Assistant); Kate Morgan (Coordinator); Katie Patterson (Coordinator); Keith Breese (Coordinator).

University of Wisconsin, Clinical Science Center, Madison: 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); Holly Eversoll, RN (Coordinator); Alana Clark (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: 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); Michael S. Kaplan, MD (Co-Investigator); Hal Hoffman, MD (Co-Investigator); Kathleen Harden, RN (Coordinator); Catherine Nelle, RN; Eva Rodriguez, RRT; Linda Galbreath; Elaine Jensen.

*Washington University School of Medicine, St. Lou*is: 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, T*ucson: Fernando D. Martinez, MD (Principal Investigator); Theresa W. Guilbert, MD (Co-Investigator); Wayne Morgan, 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; William Hall, RT. Special thanks to El Rio Health Center.

Resource Centers:

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

Project Office, National Heart, Lung and Blood Institute, *Bethesda, Maryland:* James Kiley, PhD, (Director of the NHLBI Division of Lung Diseases); Virginia Taggart, MPH (NHLBI Project Scientist); Gail Weinmann MD; Gang Zheng, PhD.

Data Coordinating Center, Penn State University College of Medicine, Hershey, Pennsylvania: Vernon M. Chinchilli, PhD (Principal Investigator); Elizabeth Mauger, PhD (Co-Investigator, 2000 – June 2001)); David Mauger, PhD (Co-Investigator); Timothy Craig, DO (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; 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 (June 2000 - January 2002); Holly Hess (June 2000 - February 2002); Vanessa Simmons.

Committees:

Data and Safety Monitoring Board: Thomas F. Boat, MD (Chair), Children's Hospital Medical Center, Cincinnati, OH; William C. Bailey, MD, The University of Alabama at Birmingham, Alabama; Mary Kay Garcia, PhD, RN, CPNP; Carolyn M. Kercsmar, MD,Case Western Reserve University, Cleveland, OH; 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, WA; Paul O'Byrne, MD, St. Joseph's Hospital, Hamilton, ON; Mark Liu, MD, Johns Hopkins Asthma and Allergy Center, Baltimore, MD.

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

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Pharmaceutical Suppliers:

GlaxoSmithKline, Inc., Research Triangle Park, North Carolina (fluticasone, albuterol); Muro Pharmaceutical, Inc., Tewksbury, Massachusetts (prednisolone); Merck & Co., Inc., West Point, Pennsylvania (montelukast); Schering- Plough Corporation, Kenilworth, New Jersey (albuterol).

Equipment Support:

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