Childhood Asthma Research and Education (CARE) Network

Pediatric **A**sthma **C**ontroller **T**rial

(P A C T)

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I. PRINCIPAL HYPOTHESIS TO BE TESTED

Proposed Null Hypothesis: In children with mild-moderate persistent asthma as defined by symptoms and positive methacholine challenge, treatments for 12 months with:

1. an inhaled corticosteroid (ICS)
2. an ICS @ 50% dose combined with a long-acting beta-agonist (LABA)
3. an oral leukotriene receptor antagonist (LTRA)

do not differ in their effects on asthma control, as measured by the percentage of days without asthma.

ADDITIONAL HYPOTHESES TO BE TESTED

- The number of asthma exacerbations during the 12 months of treatment requiring open-label oral corticosteroids does not differ among the three treatment groups.
- The time to the first asthma exacerbation requiring open-label oral corticosteroids does not differ among treatment groups.
- The three treatments do not differ in their effects on indicators of airway obstruction at the end of 12 months (compared to baseline) as reflected by the change in: a.m. peak expiratory flow (PEF), FEV_1, resistance and reactance (impulse oscillometry), and FEV_1 after repeated treatment with albuterol.
- The three treatments do not differ in their effects on other indicators of asthma control at the end of 12 months including: methacholine PC_{20} FEV_1, exhaled nitric oxide (ENO), PEF variability, and percentage of rescue-free days, albuterol-free days and episode-free days.
- The asthma-specific quality of life (QOL) does not differ among the three treatment groups.
- The sum of direct asthma costs (medications taken “as needed”, unscheduled office visits, ED/UC visits, hospitalizations) and indirect asthma costs (days lost from school or parent lost days from work) does not differ among the three treatment groups.
- The rate of adverse drug reactions at the end of 12 months does not differ among the three treatment groups.
- Study medication adherence during the 12 months of treatment does not differ among the three groups.
- Asthma control over the 12-month treatment period, as measured by a weighted scoring of symptoms, beta-agonist use, and FEV_1, does not differ among the three treatment groups.
- The subject’s asthma phenotype and genotype for selected markers cannot be linked to clinical response to a specific treatment regimen.
- The response to the initial 6 weeks of therapy, (as measured by Δ FEV_1, Δ ENO, Δ PEF variability) will not predict asthma control during the 12 months of therapy.

II. BACKGROUND AND RATIONALE

A. Introduction

Asthma is the most common chronic disease of childhood, affecting nearly 5 million children in the United States. Children with asthma account for almost 3 million physician visits and 200,000 hospitalizations each year. To care for these children, parents take time away from work. The annual health care cost for treating children with asthma is approaching $2 billion, and another $1 billion is estimated for the indirect costs associated with caring for these

children.[1] Due to the morbidity and potential mortality of childhood asthma, evidence-based treatment guidelines are essential to direct the clinician to successful management.

The NHLBI Expert Panel Report 2 "Guidelines for the Diagnosis and Management of Asthma" was published in 1997,[2] in order to provide guidelines for both adults and children with asthma. An expert panel reviewed the available literature and provided recommendations for treatment of different disease severities: intermittent, mild persistent, moderate persistent, and severe persistent. For children over 5 years of age with mild persistent asthma, daily medication with an anti-inflammatory-either inhaled steroid (low dose) or cromolyn 1-2 puffs tid-qid or nedocromil 1-2 puffs bid-qid was recommended. Sustained-release theophylline was acknowledged as an alternative, but not preferred, therapy. Leukotriene modifying agents were included as agents to be considered for those ≥ 12 years old, although the panel felt their position in therapy was not fully established.

If the NAEPP were to be reconvened today, both the availability of newly marketed therapeutic agents and the results of several major clinical trials would likely modify these 1997 recommendations. The CAMP trial, published in 2000,[3] determined that inhaled budesonide improved bronchial responsiveness and provided better asthma control than nedocromil in 5-12 year-old children with mild-to-moderate asthma. The SOCS (salmeterol or ICS) trial,[4] published in 2001, documented that patients with persistent asthma, well controlled by low doses of triamcinolone, cannot be switched to salmeterol monotherapy without risk of clinically significant loss of asthma control.

Paradigm-shifting studies by Greening,[5] Woolcock,[6] and Pauwels,[7] concluded that the addition of long-acting beta-agonists to a fixed dosage of ICS improves asthma control more than increasing dosages of ICS. The SLIC (salmeterol ± ICS) trial,[8] also published in 2001 as a companion to SOCS, documented that in patients with persistent asthma who were sub optimally controlled by triamcinolone therapy alone but whose asthma symptoms improved after the addition of salmeterol, a substantial reduction (50%) in triamcinolone dose could be achieved without a significant loss of asthma control. However, total elimination of triamcinolone therapy resulted in a significant deterioration in asthma control and, therefore, could not be recommended. The SLIC study did suggest both a potential additive and an ICS-sparing role for a long-acting beta-agonist in asthmatic patients inadequately controlled with ICS alone. Therefore, the SLIC trial, coupled with pivotal trials conducted by Kavuru,[9] Shapiro,[10] and Aubier,[11] justify the marketing of a fixed combination ICS (fluticasone) and LABA (Salmeterol) (Advair®). This combination product might be of particular benefit to children 6-14 years of age, since it has the potential of minimizing cumulative ICS dose exposure and improving medication adherence.

In children, however, the ability of LABAs to provide better overall asthma control in combination with an ICS greater than that achieved with the same or even higher doses of an ICS has not been as consistently demonstrated as in adults.[31] Although these published results have been criticized for the relatively "good control" status of the children at the time of study enrollment, they raise the issue of potential differences between children and adults regarding response to various controller medications either alone or in combination. More importantly, these observations indicate that results obtained in clinical trials with adult patients may not be extrapolated to children.

As a novel class of asthma therapy, the LTRAs were too new to establish themselves in the EPR2 guidelines (montelukast was not even available on the market at the time). However, subsequent efficacy trials in children 5-12 years of age and safety trials in children as young as

2-5 years of age are now available. Such safety information is critical, because in spite of the reassuring safety data with low-dose ICS, both the asthma community and primary care providers have asked the question "Can LTRAs be used as first-line therapy, instead of ICS?" Unfortunately, there are no substantive treatment data in children with truly mild asthma thereby limiting our ability to make appropriate comparisons. The obvious advantage of the use of the LTRAs, compared to an ICS, is the oral dosage form and once-twice daily drug administration. Both of these aspects of delivery can enhance long-term adherence. However, the LTRAs can only be considered a first-line choice in the management of mild-moderate persistent asthma in children if the asthma control achieved with these agents is comparable to that achieved by ICS alone or ICS/LABA combinations.

Thus, these various issues underscore the value and need of a dispassionate group of investigators (the CARE Network) to adequately answer the important question: What is the first line treatment of choice in children with mild-moderate persistent asthma?

B. Specific Aims

1. To determine what is the first line choice in controller therapy (inhaled ICS alone, inhaled ICS in combination with inhaled LABA, or an LTRA) for children with mild-moderate persistent asthma, as defined by measures of asthma control.
2. To determine whether three different controller therapies differ in their effect on indicators of airway obstruction over 12 months of treatment.
3. To determine whether these three different controller therapies differ in their adherence patterns, asthma-specific QOL assessments, and adverse event/safety profiles over 12 months of treatment.
4. To determine whether the initial response to 6 weeks of therapy predicts long-term response, as measured by days without asthma and asthma exacerbation rates over 12 months of treatment.
5. To profile patients who are responders and non-responders to each of the treatment regimens.
6. To examine whether the patient's asthma phenotype and genotype for selected markers can be linked to a specific therapeutic response in this carefully characterized patient population of children with $FEV_1 \geq 80\%$, yet symptoms of mild-moderate asthma.

C. Rationale for Selection of Study Population

The PACT protocol is designed to enroll 6-14 year-old subjects with persistent asthma of mild-moderate severity, based primarily on the criteria of symptom frequency. Our intent is to also limit enrollment to children with predicted FEV_1 values of ≥ 80%. There is a paucity of treatment data in this mild-moderate subset, especially in the pediatric population. Most of the FDA-pivotal trials of asthma controller medications and/or comparator trials of controllers have enrolled subjects with asthma in the 50-80% predicted FEV_1 category, coupled with bronchodilator reversibility criteria of ≥ 12%. Such entry criteria result in mean FEV_1 values at baseline of 65-70% predicted, clearly a more moderate-severe subset.

Results from the CAMP trial, as well as other data from CARE investigators, suggest that asthma in children is most accurately classified by symptom frequency and medication usage rather than by lung function criteria. This data is summarized below.

Zeiger et al[12], on behalf of the CAMP Research Group, evaluated the relationships between duration of asthma and asthma severity among children enrolled in CAMP. Children were eligible for CAMP if they had evidence of 1 or more of the following historical findings for at least

6 months in the year before interview: (1) asthma symptoms at least 2 times per week, (2) at least 2 uses per week of an inhaled bronchodilator, or (3) daily use of asthma medication. The baseline characteristics of the CAMP study cohort (n = 1041) are outlined in this table.

Selected Baseline Characteristics of the CAMP Study Cohort

Characteristic	No. of Patients	Mean, median (SD) or % of patients
Sx ≥ 2 times weekly %	1041	87.3%
Assessed severity of asthma (% moderate)	1041	52.2%
Daily Sx during 28-day screening period	1037	0.6, 0.5 (0.3)
Inhaled β-agonists ≥ 2 times weekly	1039	75.1%
Daily albuterol puffs for Sx during 28-day screening period	1037	1.5, 1.1 (1.4)
$PC_{20}FEV_1$ (mg/ml)	1038	2.08, 1.08 (2.47)
Prebronchodilator FEV_1 (% predicted)	1039	93.9, 94.0 (14.3)
Postbronchodilator FEV_1 (% predicted)	1039	102.8, 102.8 (12.7)

Only a small minority of the CAMP enrollees had an FEV_1 < 80% predicted and even fewer had FEV_1 values as low as 70%, yet half had symptoms consistent with moderate persistent asthma.

Jenkins et al[13] have evaluated 260 steroid-dependent asthmatics referred to National Jewish Medical and Research Center over a 6-year period. Adults accounted for 53.1% (n = 138) of the cohort, and children the remainder (n = 122). Lung function studies were disparate between adults and children. Children had greater air trapping (RV 255 $\pm$ 9.9% vs. 195 $\pm$ 8.1% for adults, $p<0.0001$) but less airflow obstruction (FEV_1 74.5 ± 2.1% vs. 57.7 ± 1.9% for adults, $p<0.0001$). Of note, 41% of children vs. 3% of adults in this cohort had FEV_1's ≥ 80% and only 28% of children vs. 54% of adults had FEV_1 values of ≤ 60% predicted. The authors concluded that only 28% of their asthmatic children would have been classified as severe, over 40% would be considered mild persistent based on the NAEPP FEV_1 criteria, and that it may be time for a reappraisal of lung function values in childhood asthma as indicators of disease severity.

Bacharier et al[14] report the results of a cohort of 5-18 year-old children (n = 195) with asthma seen in 2 academic center outpatient asthma clinics (the St. Louis and Madison CARE Centers). Questionnaires regarding asthma medication use and symptom frequency over the preceding 2 and 4 weeks, respectively were administered to the parents. Spirometry was performed on all children. Classification of asthma severity by medication use resulted in 11.9% being classified as mild intermittent (MI), 28.7% as mild persistent (MiP), 21.6% as moderate persistent (MoP), and 37.8% as severe persistent (SP). Symptom frequency classified 42.6% as MI, 28.2% as MiP, 15.4% as MoP, and 13.9% as SP. The percentage of patients and their lung function measures, based upon the level of severity determined by the higher of symptom-determined severity or medication-determined severity, are shown in this table.

Severity Level	Percentage of patients	FVC % pred mean (SD)	FEV_1% pred mean (SD)	FEV_1/FVC (%) mean (SD)
MI	6.2%	99.3 (11.5)	90.1 (12.4)	83.7 (7.8)
MiP	27.7%	101.2 (11.1)	95.2 (11.7)	85.5 (7.9)
MoP	23.6%	100.4 (14.1)	90.2 (15.3)	82.2 (10.0)
SP	42.6%	99.3 (12.9)	83.8 (15.1)	77.6 (9.5)

NAEPP Guidelines suggest that an FEV_1 of ≥ 80% predicted corresponds to MI or MiP asthma, that an FEV_1 of >60 and <80% predicted corresponds to MoP asthma, and an FEV_1 ≤60% predicted corresponds to SP asthma. These results do not support this classification scheme in children. In this study, FEV_1 poorly differentiated patients between the 4 severity levels. In addition, even patients with SP asthma had a mean FEV1 > 80% predicted and, with the exception of SP, the mean FEV_1/FVC was within the reference 95% confidence limits. While treatment algorithms in the Guidelines apply to patients not receiving controller medications, these patients were attending subspecialty asthma clinics and were receiving controller medications for asthma. Overall, these results suggest that asthma in children is most accurately classified by symptom frequency and medication usage rather than by lung function criteria.

These three data sets provide the rationale for our selection of study population.

D. Rationale for Selection of Medications

1. Inhaled Corticosteroid (200 mcg fluticasone or 400 mcg budesonide or equivalent ICS daily dose).

The NAEPP guidelines for the treatment of asthma state that ICS are the most potent and effective anti-inflammatory therapy currently available for the treatment of mild, moderate, or severe persistent asthma.[2] ICS reduce asthma symptoms and exacerbations, improve lung function, and decrease airway inflammation and bronchial hyper reactivity. Delayed introduction of ICS may result in reduced improvement in lung function and airways hyper responsiveness compared with the early use of ICS.[15-20] Thus, early introduction of ICS may have the potential to impede airway remodeling and airway damage.[15-20] ICS have also been associated with a significant protective effect on the risk for hospitalization and ER visits in children with asthma.[21] The regular use of low-dose ICS is associated with a decreased risk of death from asthma in a population-based cohort of subjects 5-44 years of age.[22]

Because of these beneficial effects of ICS on the consequences of asthma, coupled with outcomes of the CAMP trial,[3] low dose ICS is a logical and important treatment arm for PACT. The daily dose of ICS will be 200 mcg fluticasone or 400 mcg budesonide or equivalent, selected on the basis of published safety data.[3, 23-25]

2. Inhaled corticosteroid at 50% daily dose in combination with long-acting beta-agonist.

The efficacy of adding LABA to ICS therapy versus increasing the dose of ICS therapy in patients in whom low- to moderate doses of ICS therapy alone provided insufficient asthma control has been evaluated in a number of adult asthma trials,[5,6,7] as well as a meta-analysis.[26] All are in agreement that improvement in pulmonary function and asthma symptoms is greater with low-dose ICS plus an LABA than with higher dose ICS therapy.

Despite concerns to the contrary, ICS/LABA combinations have not been implicated in contributing to worsening asthma or in magnifying the problems associated with asthma

exacerbations.[7,27,28] Lower exacerbation rates were observed with combination treatment in patients with both mild-to-moderate airway obstruction (60-95% predicted) and severe obstruction at baseline. Furthermore, an analysis of the time to first exacerbation revealed that fluticasone propionate (FP) plus salmeterol was significantly (p=0.049) more protective than higher dose FP therapy.[28] A complete review of the clinical trials with Advair®, scientific rationale for the combination, and adverse events/safety profile have been published by Nelson.[29]

Much less data is available on the use of ICS/LABA combinations in strictly mild disease, in the pediatric population, or as first-line comparator trials with other controllers, e.g. LTRAs. The Optima Study[30] evaluated the effects of adding formoterol to low dose budesonide for 1 year in patients with mild persistent asthma who were taking a low dose of ICS ($\leq$ 400 mcg/day). The 1272 ICS treated patients (mean baseline FEV_1 86.54%) were assigned to twice daily treatment with 100 mcg budesonide, or 100 mcg budesonide plus 4.5 mcg formoterol, or 200 mcg budesonide, or 200 mcg budesonide plus 4.5 mcg formoterol. The main outcome variables were the time to the first severe asthma exacerbation and poorly controlled asthma days. The addition of formoterol either to a lower or higher dose of budesonide reduced the risk for the first asthma exacerbation (RR= 0.57, 95% CI= 0.46, 0.72) and the rate of poorly controlled asthma days (RR= 0.70, 95% CI= 0.6, 0.82). Adding formoterol 4.5 mcg bid to budesonide 100 mcg bid resulted in fewer severe exacerbations and poorly controlled days compared with increasing the dose of budesonide to 200 mcg bid.

Limited data on the efficacy of ICS/LABA combination therapy are available in children. The Dutch Paediatric Asthma Study Group[31] compared the effects of one year of treatment with beclomethasone (BDP) 200 mcg bid, the same dose of BDP together with salmeterol 50 mcg bid, and BDP 400 mcg bid. One hundred seventy-seven children, 6-16 years of age, with moderate asthma were enrolled. Important entry criteria included: (1) FEV_1 55-90% predicted; (2) FEV_1 reversibility $\geq$ 10%; (3) positive methacholine challenge; (4) use of ICS 200-800 mcg daily for at least 3 months. Qualified children were at first treated for 6 weeks with BDP 200 mcg bid as part of a run-in period. At the end of the run-in period, the pre-bronchodilator FEV_1 %-predicted was about 88 $\pm$ 12% and the post bronchodilator FEV_1 %-predicted was 103 $\pm$ 12%. The authors concluded that there were no significant differences between the 3 groups in FEV_1, PD_{20}, symptom scores, or exacerbation rates after 1 year. In their discussion, the authors conjecture that the differences in outcomes of this pediatric study differed from the published adult studies[5,6] due to inclusion criteria. In contrast with the Verberne study,[31] in which inclusion criteria were based on airway caliber and airway responsiveness, the inclusion criteria of both adult studies[5,6] were based on symptom scores in the run-in period prior to randomization and PEF variability. Thus, a more symptomatic patient population was enrolled.

Since the publication of the Verberne study,[31] the positioning of the LABA in the management of childhood asthma has been debated.[32,33] Bisgaard[32] highlights concern for the development of tolerance with reduced bronchodilation and bronchoprotection, reported in some trials with regular LABA therapy. Verberne and de Jongste[33] argue that future clinical trials with different therapeutic regimens with LABA in children are necessary before changing current recommendations. Further, these authors recommend that such trials should incorporate direct or indirect measures of airway inflammation, symptoms, peak flows, and lung function tests.

Calhoun et al[34] have recently reported on a trial evaluating Advair Diskus® 100/50 versus montelukast as first line maintenance therapy for asthma. Subjects were 15 years of age and older, with baseline FEV_1 50-80% predicted, and baseline albuterol use of 4-5 puffs/day.

Patients treated with Advair® had a significantly greater improvement in FEV_1 compared with montelukast 10mg at all time points in the 12-week trial. Positive changes in FEV_1 and PEF a.m. were observed in both milder asthma ($FEV_1 \geq 70\%$ at baseline) and moderate asthma ($FEV_1 \leq 70\%$ at baseline). Significantly fewer patients treated with Advair® had an asthma exacerbation compared with patients treated with montelukast (0% vs. 5%, p=0.001). Both symptom-free days and rescue-free days favored Advair® (p<0.001).

The clinical trial data in adults, the potential value of a fixed combination of ICS/LABA in improving medication adherence,[35] and the ICS sparing effects of LABA,[8] all contribute to the rationale of selecting an ICS (50% dose)/LABA combination for PACT. This arm of the PACT study may be even more important in light of the recently published study by Israel et al[36] documenting a dose-related loss of bone at the hip in premenopausal women treated with triamcinolone acetonide. Further, there are ongoing concerns about the position of ICS/LABA combinations in the management of childhood asthma, no comparative first-line treatment trials in children with mild-moderate persistent disease, and requests from the asthma community for such trials. PACT is designed to answer many of these questions.

3. Leukotriene Receptor Antagonists

Bisgaard[37] recently reviewed the role of leukotrienes in asthma airway inflammation and the evidence for the effect of leukotriene modifiers from randomized controlled trials with a view to their potential role in pediatric asthma management. The rationale for including an LTRA in the PACT protocol is nicely articulated by one of Bisgaard's conclusions, "There are no LTRA pediatric studies addressing asthma control in children with mild persistent symptoms."

Subjects in most of the published LTRA Phase III trials in adults and children had moderate to severe asthma; several reviews of these trials are available in the literature.[37-40] Most of these trials were 6-12 weeks in duration and enrolled subjects with FEV_1 values between 40-85 %-predicted and $\geq$ 12% bronchodilator reversibility. In these studies, the LTRAs proved to be modestly effective.[37] In the sole pivotal trial in children 6-14 years of age with persistent asthma (mean baseline $FEV_1 = 72 \pm 9$ %-predicted), Knorr et al[41] evaluated the use of montelukast 5mg daily compared with placebo for 8 weeks. Children taking montelukast had a significantly greater improvement in FEV_1 from baseline compared with those taking placebo. (8.2% vs. 3.58 %, p<0.05). In addition, montelukast-treated children had statistically significant improvements in beta-agonist use, asthma exacerbations, quality of life, a.m. PEF, and global evaluations.

More recently, Knorr et al[42] published the results of a multinational, double-blind trial of 689 preschool-aged children (2-5 years) randomly assigned to 12 weeks of treatment with placebo or 4mg of montelukast. Patients had a history of physician-diagnosed asthma requiring use of beta-agonist and a pre-defined level of daytime asthma symptoms. The primary objective of this study was to determine the safety profile of montelukast in this young cohort and secondarily, to study the effect of montelukast on exploratory measures of asthma control. The authors concluded that statistically significant improvements in multiple parameters of asthma control were produced by montelukast, compared with placebo, including: daytime asthma symptoms; overnight asthma symptoms; the percentage of days with asthma symptoms; the need for beta-agonist or oral corticosteroids; physician global evaluations; and peripheral blood eosinophils.

This recently published Knorr analysis[42] in 2-5 year olds, coupled with the tolerability data in adults and children $\geq$6 years of age enrolled in the controlled and extension trials with montelukast,[43] provide reassuring safety data for the inclusion of an LTRA in PACT. This data is summarized in Table 1.

Because few studies have specifically evaluated LTRA therapy in mild persistent asthma, Barnes et al[44] used a sub-group analysis to investigate the effects of montelukast on adult patients on the milder end of the asthma severity spectrum. These investigators identified seven, double-blind, randomized, placebo-controlled trials of adults with mild-moderate persistent asthma treated with montelukast. Subsets of patients with baseline FEV_1 >80% and >75% predicted or further restricted by less than daily rescue beta-agonist use were included as four cohorts. Pooled results demonstrated a treatment effect for montelukast over placebo in all cohorts, for all endpoints. There was significant improvement in FEV_1 in montelukast-treated patients (7-8% over baseline) compared with placebo (1-4% over baseline) for all cohorts; $p \leq 0.02$. The percentage of rescue-free days increased more with montelukast (22-30%) than with placebo (8-13%). Barnes et al[44] conclude that montelukast produced improvements in parameters of asthma control in patients with milder persistent asthma that should be confirmed in additional prospective trials. PACT is exactly such a trial.

E. Study Medication Decision

The CARE Steering Committee invited all manufacturers of inhaled corticosteroid and leukotriene receptor antagonist appropriate for this protocol (Astra-Zeneca, Glaxo-Smith-Kline, and Merck) to provide active drug and matching placebo for the PACT study. Astra-Zeneca offered budesonide (HFA MDI 80 mcg/puff administered 2 puffs bid) for the ICS arm, budesonide-formoterol combination (HFA MDI 40 mcg-4.5 mcg/puff administered 2 puff bid) for the ICS/LABA arm, and matching placebo MDI. Glaxo-Smith-Kline offered fluticasone (diskus 100 mcg bid) for the ICS arm, fluticasone-salmeterol combination (diskus 100 mcg-50 mcg morning) and salmeterol (diskus 50 mcg evening) for the ICS/LABA arm, and matching placebo diskus.

The CARE Steering Committee, in conjunction with the NHLBI, carefully reviewed these offers and unanimously determined to use montelukast, fluticasone, and fluticasone-salmeterol combination plus salmeterol. Several issues factored into the decision to choose fluticasone/salmeterol over budesonide/formoterol. Neither of the budesonide/formoterol formulations are currently FDA approved, which would necessitate filing two complex INDs and might raise concern with IRBs. In contrast, the fluticasone/salmeterol formulations are currently FDA approved and would require filing one relatively simple IND for once-daily dosing of the fluticasone-salmeterol combination. Because drug acquisition will determine the starting date for PACT, consideration was also given to the fact that the fluticasone/salmeterol formulations would be made available 2 months earlier than the budesonide/formoterol formulations.

F. Rationale for Selection of Study Outcomes

The primary outcome measure for PACT is the percentage of days without asthma during the 12-month treatment period. A day without asthma is defined as no albuterol rescue use (pre-exercise treatment permitted), no use of oral steroids for asthma, no use of non-study asthma medications, no daytime asthma symptoms, no nighttime awakenings due to asthma, no unscheduled primary care provider visits for asthma, no emergency room visits or hospital admissions for asthma, and no missed school due to asthma. This outcome measure was selected because it is relevant to both patients/families and healthcare providers, and in the primary care sector may be the main parameter that guides childhood asthma management. Most children with mild-moderate persistent asthma are not managed by asthma specialists, and therefore do not routinely have pulmonary function measured. In addition, percentage of days without asthma is a continuous variable and there is reasonable literature evidence, in

comparable patient populations, to guide PACT sample size calculations. Importantly, it is reasonable to expect that all 3 of the selected PACT treatment regimens will increase the percentage of days without asthma in children with mild-moderate persistent asthma, as defined in this protocol.

Asthma exacerbation rates and the time to the first exacerbation of asthma is an important secondary outcome for PACT. Since PACT is 12 months in duration, the ability of the 3 treatments to prevent exacerbations due to allergens or upper respiratory infections can be evaluated. This robust outcome also has pharmacoeconomic implications. The occurrence of asthma exacerbations, serious enough to warrant prednisone, is associated with asthma morbidity (missed school days, missed work days by parents, UC/ED visits, hospitalizations) and potential mortality. Healthcare utilization outcomes will be assessed in PACT.

Traditional measures of pulmonary function (spirometry) and more innovative approaches (impulse oscillometry) will be important secondary outcomes in PACT. These measurements will be performed serially in PACT both before and after bronchodilators. Fuhlbrigge's[45] recent data suggests that the strong association between FEV_1 percent-predicted and risk of asthma attack over a subsequent year supports an emphasis on objective measures of lung function in assessment of risk factors for adverse asthma outcomes. The available literature indicates that each of the control medications selected for PACT improve pulmonary function, especially when administered over an extended treatment period.

In the last ten years, new tools for measuring response to asthma therapies have become available. These include potential markers of inflammation such as total eosinophil count, plasma eosinophilic cationic protein (ECP), induced sputum cytology, and exhaled nitric oxide. However, these markers are not readily available to the clinician. Current knowledge regarding these outcome measures and their potential applications to assessing response to therapy are summarized below. Information is now needed to determine how these measurements can be applied to clinical care in order to advance the general management of asthma.

The blood eosinophil count as a marker of disease severity was among the first described more than 20 years ago[46] when elevated circulating eosinophil counts were noted among asthmatics. In addition, a significant inverse correlation between the eosinophil count and pulmonary function has been noted. More recently, the eosinophil granule protein, ECP, has been identified as a potential marker of airway inflammation in that elevated ECP levels have been demonstrated in sputum, bronchoalveolar lavage fluid (BALF), and serum of asthma patients.[47] In addition, the late-phase asthmatic response following allergen challenge is associated with BALF eosinophilia and increases in ECP levels.[48] Serum ECP levels also correlate with asthma severity[49] and a fall during glucocorticoid therapy.[50] Lastly, in at least one study, serum ECP levels correlated with BALF levels.[50]

A number of studies have demonstrated elevated levels of exhaled nitric oxide (ENO) among patients with asthma.[51-53] In addition, both oral and inhaled glucocorticoid therapy, as well as oral montelukast therapy, result in significant reductions in ENO concentrations.[54-57] A study by Lanz et. Al.[58] found ENO levels to be significantly elevated in children with acute asthma compared to atopic or nonatopic controls with a significant reduction in ENO concentration following a course of glucocorticoid therapy. These findings, plus the ease of collection, make this a very attractive marker of inflammation in childhood asthma.

In a manner similar to another CARE-generated protocol CLIC (characterizing the response to a leukotriene receptor antagonist and an inhaled corticosteroid), methacholine challenge, allergen skin test sensitivity, total eosinophil count, serum ECP, exhaled nitric oxide, asthma history,

family history, and assessment of asthma severity will be used to characterize the asthma phenotype of the patient prior to beginning treatment.

III. PROTOCOL OVERVIEW

A 12-month treatment protocol is proposed. After a 2-4 week assessment/characterization run-in period, 6-14 year-old children who meet NAEPP criteria for mild-moderate persistent asthma specifically based on symptom criteria and a positive methacholine challenge and $FEV_1 \geq 80\%$ will be assigned to one of three active treatment arms for 12-months:

1. active ICS (100 mcg fluticasone bid)
2. combination of active ICS @ 50% dose (100 mcg fluticasone)/active LABA (50 mcg salmeterol) qd plus active LABA (50 mcg salmeterol qd)
3. active LTRA (montelukast 5 mg qd)

In addition to active drug, arms 1 and 2 will receive placebo LTRA capsules. Similarly, arm 3 will receive placebo diskus inhaler devices.

Two types of subjects will be recruited for this study: 1) subjects who are naïve to controller therapy for 2-4 weeks prior to the screening visit (dependent on the specific type of controller medication as further defined in the exclusion criteria) and 2) subjects who are controlled on an asthma controller for at least 4 weeks prior to the screening visit (as further defined in the exclusion criteria) whose symptoms are consistent with NAEPP guidelines[2] for step-down therapy. Subjects who enter the study naïve to controller therapy and meet eligibility criteria will enter a 2-week run-in period. Subjects who are controlled on an asthma controller and meet eligibility criteria will enter a 2-4 week run-in period. The length of the run-in period will depend on the severity of the subject's symptoms.

Subjects in all three treatment groups will be supported and managed with rescue algorithms of beta-agonists, and/or short courses of prednisone for asthma exacerbations in a manner consistent with the NAEPP guidelines.[2] The need for more than 2 courses of prednisone during the course of the 12-month treatment period will result in assignment of treatment failure status and continued treatment with an appropriate open-label therapy.

Treatment assignment will be made by a double-blind randomized parallel group design, stratified by CARE clinical center. Within each center, a blocked randomization scheme will be invoked in order to ensure balance across treatment arms with respect to the following blocking factors: bronchodilator response (<12% or ≥12%), race (caucasian or non-caucasian), and methacholine PC_{20} (<2 or ≥2 mg/ml).

The protocol can be viewed as consisting of two phases: a run-in period of 2-4 weeks and a double-blinded treatment period of 12 months. The 2-4 week run-in period will confirm essential enrollment criteria and provide baseline characterization tests. This will allow time for the parent and child to determine their interest in a 12-month study, to observe the subject and verify asthma severity, to assess adherence, to minimize the risk of dropouts during the study, and to train the child in the necessary procedures in order to obtain the most reliable data.

In the run-in period, subjects will make several visits to the study center. The purposes of these visits are (1) to determine that the subjects have mild-moderate persistent asthma by symptom criteria, have normal lung function ($FEV_1 \geq 80\%$ predicted), and qualify for study inclusion; and (2) to obtain baseline data on the outcome variables and to characterize subjects in a manner

similar to the CLIC protocol. The run-in period is purposefully short in duration (to minimize time without controller therapy) and subjects will be allowed to use albuterol prn and will have careful daily symptom and peak flow monitoring.

In the active treatment period, subjects will be randomized to one of the three treatment arms and will be seen at 6-12 week intervals. Interim telephone calls will also be scheduled. Details of the run-in and treatment phases are described below (Figure 1).

Figure 1: Study Schematic

Run-In Phase

Albuterol prn

Morning and Evening Placebo Diskus

Evening Placebo Capsule

Treatment Phase

	Morning Diskus	Evening Diskus	Evening Capsule
1	Fluticasone	Fluticasone	Placebo
2	Fluticasone/ Salmeterol	Salmeterol	Placebo
3	Placebo	Placebo	Montelukast

Randomize to Treatment Group ⇳

Visit	1	2	3	4	5	6	7
Week	- (2-4) *	0	6	12	24	36	48
Telephone Calls				18	30	42	
Informed Consent	+						
Genetics (optional at visit 2 or 7)		+					+
CBC		+					+
ECP		+					+
Serum IgE		+					+
Allergen Skin Test		+					
Urinary Leukotrienes		+					+
Pregnancy Test	+	+					+
Height by Stadiometry	+	+	+	+	+	+	+
Exhaled Nitric Oxide	+	+	+	+	+	+	+
FO/FEV_1 with BD				+	+		
FO/FEV_1	+	+	+			+	+
Max BD	+ **		+			+	
Methacholine		+					+
Health Utilization Review		+	+	+	+	+	+
Review Symptom Diary		+	+	+	+	+	+
ACQ/MATAQ		+	+	+	+	+	+
Home Environment Ques.		+					+
Activities/Sports Ques.		+		+	+	+	+
Dispense Drug	+	+		+	+	+	
Electronic Peak Flow Meter	Dispense						Collect

ACQ = Asthma Control Questionnaire
CBC = Total Blood Count / Total Eosinophil Count
ECP = Serum Eosinophil Cationic Protein
MaxBD = Maximum Bronchodilator Response
FO/FEV_1 = Forced Oscillation and Spirometry
w/BD = with Bronchodilator
MATAQ = Modified Asthma Therapy Questionnaire

***** Participants entering on controller therapy will be randomized 2-4 weeks after enrollment depending on symptoms. Those entering off therapy will be randomized 2 weeks after enrollment.

****** Participants entering on controller therapy will perform MaxBD at least one week after Visit 1 and at least one day prior to Visit 2.

A. Subjects

This study will require the participation of 300 children ages 6-14 years with mild-moderate persistent asthma defined by symptom criteria and positive methacholine challenge. Enrolling children must demonstrate specific pulmonary function criteria during the run-in phase, as defined by a $FEV_1 \geq 80\%$ predicted. The NIH requirement for distribution by ethnicity (33% minority) will be followed. Enrollment will be monitored so that a 40% female target is reached. The rapidity of recruitment will be facilitated by the involvement of 5 geographically dispersed study centers. Patients will be recruited from "standing" populations at the 5 participating CARE centers, by advertisement, and by referral from collaborating physicians. The CARE DCC will distribute monthly accrual reports for each clinical center, listing the enrolled subjects and any reasons for exclusion during the assessment/characterization run-in period. This routine monitoring will allow for early identification and resolution of potential problems during the recruitment phase.

B. Inclusion and Exclusion Criteria

Inclusion Criteria

1. Male and female subjects more than 6 and less than 14 years of age at enrollment.
2. Able to perform reproducible spirometry according to ATS criteria.
3. Mild-moderate persistent asthma –

    3a. Subjects naïve to controller therapy: as defined by the presence of self-reported symptoms or inhaled bronchodilator (not including pre-exercise) use an average of at least 3 times per week during the 4 weeks preceding visit 1.

    3b. Subjects controlled on an asthma controller: as defined by the presence of self-reported symptoms on average no more than 2 times per week and less than 2 nights per month of nocturnal awakenings during the 4 weeks preceding visit 1.

4. Mild-moderate persistent asthma, as defined by the presence of diary-reported symptoms or inhaled bronchodilator (not including pre-exercise) use or peak flows in the yellow zone an average of at least 3 times per week during the run-in period. Yellow zone to be determined by reproducible personal best peak flow during the run-in period.
5. PC_{20} methacholine $FEV_1 \leq 12.5$ mg/ml at Visit 2.
6. History of clinical varicella or varicella vaccine.
7. Nonsmoker within the past year. No use of smokeless tobacco products in the past year.
8. Ability of parent to provide informed consent, as evidenced by signing a copy of the consent form approved by the Institutional Review Board of the subjects' respective study institution.
9. Verbal assent for children less than 7 years of age and written assent for children between 7 and 14 years of age.

Exclusion Criteria

1. Corticosteroid treatment for any condition within the defined intervals prior to enrollment.
    a. Oral – Use within one-month period of the screening visit.
    b. Injectable – Use within one-month period of the screening visit.
    c. Nasal corticosteroids may be used at any time during this trial at the discretion of the

study investigator or primary care physician.

2. Other asthma controller medications:
   2a. Subjects naïve to controller therapy within the defined interval prior to enrollment:
      a. Oral Inhaled corticosteroids – 2 weeks
      b. Leukotriene modifiers (zileuton, zafirlukast, montelukast) – 2 weeks
      c. Cromolyn/nedocromil – 2 weeks
      d. Oral beta-adrenergic agents – 2 weeks
      e. Theophylline products – 2 weeks
      f. Long-acting beta-agonists (salmeterol, formoterol) – 2 weeks

   2b. Subjects controlled on an asthma controller for at least 4 weeks and not exceeding the following doses:
      a. Beclomethasone CFC > 336 mcg/day
      b. Beclomethasone HFA > 160 mcg/day
      c. budesonide > 400 mcg/day
      d. flunisolide > 750 mcg/day
      e. FP MDI > 220~~176~~ mcg/day
      f. FP DPI > 200 mcg/day
      g. Triamcinolone > 800 mcg/day
      h. Montelukast > 4-5 mg qd
      i. Zafirlukast > 10 mg bid
      j. Theophylline (any dose allowed)
      k. Nedocromil MDI > 8 puffs/day
      l. Cromolyn MDI > 8 puffs/day
      m. Salmeterol MDI > 2 puffs bid
      n. Salmeterol DPI > 1 blister bid
      o. Advair > 100 mcg/50 mcg bid*

      * A two stage step-down plan will be used for participants using Advair. If a participant is adequately controlled on Advair for 4 weeks, Advair will be stopped and a low-dose inhaled corticosteroid (e.g. fluticasone 88 mcg bid) will be prescribed for 2 weeks. After 2 weeks on the low-dose inhaled corticosteroid, if the participant is adequately controlled, the low dose inhaled corticosteroid will be stopped.

3. Asthma symptoms (night awakenings more than 2 days per week on average) and/or albuterol use (more than 8 puffs per day on average, not including pre-exercise puffs) consistent with severe persistent disease during the run-in period.
4. Current or prior use of medications known to significantly interact with corticosteroid disposition (within a one-month period of Visit 1), including but not limited to carbamazepine, erythromycin or other macrolide antibiotics, phenobarbital, phenytoin, rifampin, and ketoconazole.
5. FEV_1 < 80% predicted at Visit 1 or FEV_1 < 70% predicted at Visit 2.
6. Two or more hospitalizations for asthma in the past year.
7. Presence of chronic or active lung disease other than asthma.
8. Significant medical illness other than asthma, including thyroid disease, diabetes mellitus, Cushing's disease, Addison's disease, hepatic disease, or concurrent medical problems that could require oral corticosteroids during the study.
9. A history of cataracts, glaucoma, or any other medical disorder associated with an adverse

effect to corticosteroids.

10. History of respiratory tract infection within 4 weeks of the screening visit (may be re-screened after resolution of URI).
11. History of significant asthma exacerbation within 4 weeks of the screening visit or more than 3 courses of systemic corticosteroids in the past year.
12. History of a life-threatening asthma exacerbation requiring intubation, mechanical ventilation, or resulting in a hypoxic seizure.
13. History of adverse reactions to ICS, LTRA, or LABA preparations or any of their ingredients.
14. Receiving hyposensitization therapy other than an established maintenance regimen (continuous regimen for ≥3 months).
15. Inability to swallow study capsules.
16. Inability to coordinate use of the study drug delivery systems or to adhere with therapy (≥75% of doses) during the run-in period.
17. Pregnancy or lactation.
18. If of child bearing potential, failure to practice abstinence or use of an acceptable birth control method.
19. Inability to perform study procedures.

C. Study Visits

Week –(4-6), Screening Visit for participants entering the study on Advair

a. Informed consent (parent's consent and child's assent based on age)
b. Review of asthma history and inclusion/exclusion criteria
c. Spirometry
d. Inhaler technique reviewed and rescue medication (albuterol) dispensed
e. Electronic peak flow meter dispensed and appropriate technique assured
f. Personal best peak flow estimated, and action plan and medications provided for management/treatment of asthma exacerbations
g. Diary instructions provided and diary dispensed
h. Dispense low-dose inhaled corticosteroid

2-4 week assessment/characterization phase

1. Week –(2-4), Visit 1
    a. Informed consent (parent's consent and child's assent based on age)
    b. Review of inclusion and exclusion criteria
    c. Physical examination (including vitals, height, weight)
    d. Urine pregnancy test for female patients who have reached menarche
    e. Exhaled nitric oxide
    f. Maximal bronchodilator testing with spirometry - Forced oscillation after maximal bronchodilator response. Participants entering on controller therapy will perform Maximum bronchodilator testing at least one week after Visit 1 and at least one day prior to Visit 2.
    g. Dispense Home Environment Questionnaire (HEQ)
    h. Dispense Physical Activity Questionnaire (PAQ-C)
    i. Inhaler technique reviewed and rescue medication (albuterol) dispensed
    j. Electronic peak flow meter dispensed and appropriate technique assured
    k. Personal best peak flow estimated, and action plan and medications provided for management/treatment of asthma exacerbations

l. Diary instructions provided and diary dispensed
m. Instructions provided for study drugs; 2-4 week supply of placebo dispensed

2. Week 0, Visit 2 (Randomization)
    a. Subject returns 2-4 weeks after Visit 1
    b. Review inclusion and exclusion criteria
    c. Height measurement
    d. Urine pregnancy test for female patients who have reached menarche
    e. Exhaled nitric oxide
    f. Forced oscillation/spirometry
    g. Methacholine challenge procedure
    h. Urinary leukotriene measurement
    i. Aeroallergen skin tests
    j. Blood sample for complete blood count with hematocrit, total eosinophil count, IgE, ECP, and genetic analysis (optional at Visit 2 or Visit 7)
    k. Administer Healthcare Utilization Review (HUR) questionnaire
    l. Administer Asthma Control Questionnaire (ACQ), and modified Asthma Therapy Assessment Questionnaire (MATAQ)
    m. Collect Home Environment Questionnaire (HEQ)
    n. Collect Physical Activity Questionnaire (PAQ-C)
    o. Symptoms and peak flow meter readings on diary reviewed
    p. Reestablish personal best peak flow and reestablish action plan for asthma exacerbations
    q. Inhaler and electronic peak flow meter techniques reviewed
    r. Run-in study medications returned; adherence reviewed and calculated
    s. Review diary card instructions and dispense new diary cards
    t. Patient randomized to treatment phase and provided with instructions on medication administration
    u. 12-week supply of study medications dispensed

Treatment Phase

3. Week 6, Visit 3
    a. Subject returns 6 weeks after Visit 2
    b. Exhaled nitric oxide
    c. Height measurement
    d. Forced oscillation
    e. Maximal bronchodilator testing with spirometry - Forced oscillation after maximal bronchodilator response
    f. Administer Healthcare Utilization Review (HUR) questionnaire
    g. Administer ACQ and MATAQ
    h. Dispense Physical Activity Questionnaire (PAQ-C)
    i. Symptom and peak flow diary and electronic peak flow meter techniques reviewed
    j. Study medication returned, adherence reviewed
    k. Use of action plan for asthma exacerbations reviewed
    l. Diary card dispensed
4. Week 12, Visit 4
    a. Subject returns 6 weeks after Visit 3
    b. Exhaled nitric oxide
    c. Height measurement

    d. Forced oscillation/spirometry with reversibility
    e. Administer Healthcare Utilization Review (HUR) questionnaire
    f. Administer ACQ and MATAQ
    g. Dispense/Collect Physical Activity Questionnaire (PAQ-C)
    h. Symptom and peak flow diary and electronic peak flow meter techniques reviewed
    i. Study medications returned, adherence reviewed
    j. Use of action plan for asthma exacerbations reviewed
    k. Diary cards dispensed
    l. 12-week supply of study medications dispensed.
5. Week 18 Telephone call
    a. Review peak flow, symptoms, rescue treatment, adverse events, and adherence
    b. Administer Healthcare Utilization Review (HUR) questionnaire
6. Week 24, Visit 5
    a. Subject returns 12 weeks after Visit 4
    b. Exhaled nitric oxide
    c. Height measurement
    d. Forced oscillation/spirometry with reversibility
    e. Administer Healthcare Utilization Review (HUR) questionnaire
    f. Administer ACQ and MATAQ
    g. Dispense/Collect Physical Activity Questionnaire (PAQ-C)
    h. Symptom and peak flow diary and electronic peak flow meter techniques reviewed
    i. Study medications returned, adherence reviewed
    j. Use of action plan for asthma exacerbations reviewed
    k. Diary cards dispensed
    l. 12-week supply of study medications dispensed.
7. Week 30 Telephone call
    a. Review peak flow, symptoms, rescue treatment, adverse events, and adherence
    b. Administer Healthcare Utilization Review (HUR) questionnaire
8. Week 36, Visit 6
    a. Subject returns 12 weeks after Visit 5
    b. Exhaled nitric oxide
    c. Height measurement
    d. Forced oscillation
    e. Maximal bronchodilator testing with spirometry - Forced oscillation after maximal bronchodilator response
    f. Administer Healthcare Utilization Review (HUR) questionnaire
    g. Administer ACQ and MATAQ
    h. Dispense/Collect Physical Activity Questionnaire (PAQ-C)
    i. Symptom and peak flow diary and electronic peak flow meter techniques reviewed
    j. Study medications returned, adherence reviewed
    k. Use of action plan for asthma exacerbations reviewed
    l. Diary cards dispensed
    m. 12-week supply of study medications dispensed
9. Week 42, Telephone call
    a. Review peak flow, symptoms, rescue treatment, adverse events, and adherence
    b. Administer Healthcare Utilization Review (HUR) questionnaire
10. Week 48, Visit 7
    a. Subject returns 12 weeks after Visit 6

b. Physical examination (including vitals, height, weight)
c. Exhaled nitric oxide
d. Forced oscillation/spirometry
e. Methacholine challenge procedure
f. Urinary leukotriene measurement
g. Urine pregnancy test for female patients who have reached menarche
h. Blood sample for complete blood count with hematocrit, total eosinophil count, IgE, ECP, and genetic analysis (optional at Visit 2 or Visit 7)
i. Administer Home Environment Questionnaire (HEQ)
j. Administer Healthcare Utilization Review (HUR) questionnaire
k. Administer ACQ and MATAQ
l. Dispense/Collect Physical Activity Questionnaire (PAQ-C)
m. Study medications returned, adherence reviewed
n. Electronic peak flow meter returned
o. Participation concludes and recommendations given for further care, including prescription for open-label controller medications
p. Exit interview (critique of study experience; child and parent asked which medication they believed to have received during the trial)

D. Asthma Symptom Exclusion Criteria During Run-in (visits 1-2)

1. Asthma symptoms consistent with a mild-intermittent pattern
2. Asthma symptoms and/or albuterol use consistent with severe persistent disease
3. Need for rescue asthma medication other than albuterol

E. Criteria for Assigning Treatment Failure During Treatment Period

1. Hospitalization due to asthma
2. Hypoxic seizure due to asthma
3. Intubation due to asthma
4. Requirement for a third burst of prednisone for an asthma exacerbation
5. Significant adverse event related to the use of a study medication

F. Criteria for Assigning Dropout Status during Treatment Period

1. Parent withdraws consent or child withdraws assent
2. Patient becomes pregnant
3. Study Physician determines that continuation in study is not in the best interest of the participant

G. Management of Asthma Exacerbations

The approach to rescue medications will be based on the consensus report presented in the National Heart, Lung and Blood Institute Guidelines[2] and structured according to the protocols successfully implemented in the CAMP trial. Each patient will be given specific guidelines for decision-making and institution of rescue management (action plan). Two medications, albuterol and/or oral prednisone, will be employed when increasing symptoms and/or fall in peak flow require treatment. For a severe acute asthma exacerbation, patients will be medicated according to the best medical judgment of the treating physician.

Home care:

The onset of an asthma exacerbation will be recognized by symptoms such as coughing, dyspnea, chest tightness and/or wheezing, or by a decrease in the patient's PEF. Caretakers

and patients will be educated to recognize the signs and symptoms of an asthma exacerbation early and the significance of falls in their peak flow readings so that prompt rescue treatment may be instituted and morbidity decreased.

Patients who experience symptoms of cough, dyspnea, chest tightness, wheeze, and/or PEF less than 80% of their personal best will initiate use of albuterol (2 puffs) by MDI every 20 minutes for up to 1 hour and then every 4 hours if necessary. If the patient cannot achieve a PEF of at least 80% of their personal best, or if symptoms persist after 3 treatments, the study center should be contacted. If the patient's peak flow reaches 80% of their personal best or greater, but the patient requires albuterol every 4 hours for 24 hours in order to maintain a peak flow of at least 80% personal best or if symptoms persist, the study center should be contacted. At the time of study center contact, a clinic visit may be necessary. The initiation of oral prednisone therapy will be based on specific guidelines and on physician discretion.

If symptoms are severe, the child has retractions, evidence of cyanosis based on saturations on room air of < 90% based on pulse oximetry, has evidence of increased work of breathing, shortness of breath and/or "air hunger", and/or the PEF is less than 50% of personal best after 4 puffs of albuterol, the patient must seek immediate medical care and should contact the study center.

Physician's office or emergency room:

In the primary physician's office or emergency room, the patient with an acute asthma exacerbation will be treated with nebulized albuterol or high dose MDI albuterol (6-8 puffs every 20 minutes x three or more often if needed). The dose of albuterol for the doctor-supervised situation is 0.10 – 0.15 mg/kg up to 5 mg per treatment. Albuterol can be delivered by nebulizer driven with oxygen, and treatments will be given every 20 minutes for up to 3 treatments.[59-64] If after 3 treatments, the child is not stable as described below, the physician may use additional albuterol treatments or other medications as is in his/her best clinical judgment. The child will be assessed for general level of activity, color, pulse rate, use of accessory muscles and airflow obstruction determined by auscultation,[65,66] and FEV1 and/or PEF before and after each bronchodilator treatment. Measurement of oxygenation with a pulse oximeter may also be indicated for complete patient assessment during the acute exacerbation.

- If the patient has a favorable response to initial albuterol nebulizer treatment (FEV_1 and/or PEF at least 80% predicted or personal best), the patient will be observed for 1 hour prior to being discharged home with instructions to continue albuterol every 4 hours as needed and to report any decline in PEF and/or symptom fluctuation promptly.
- If the patient does not improve (FEV_1 or PEF less that 80% predicted or personal best) after the initial albuterol nebulizer treatment, nebulized albuterol therapy will be continued for at least 2 more trials (for a total of 3 times in 1 hour). If the patient's clinical symptoms are stabilized and FEV_1 or PEF is between 50-80% of predicted or personal best, the patient will be discharged home to continue use of albuterol (2 puffs every 4 hours) and to start a four-day course of oral prednisone.
- If the patient's FEV_1 is less than 50% of predicted or PEF is less than 50% of personal best after 3 treatments with nebulized albuterol in 1 hour, the physician may use his/her best medical judgment to treat the patient. Such clinical judgment may include the need for hospitalization and inpatient monitoring.

Prednisone courses:

Oral prednisone will be administered for the treatment of impending episodes of severe asthma

when bronchodilator therapy is inadequate.[67] The decision concerning the initiation or continuation of a course of oral prednisone will be at the physician's discretion. Prednisone should be prescribed if:

- The patient uses more than 12 puffs of albuterol in 24 hours (excluding preventive use before exercise) and has a diary card symptom code of 3 or PEF less than 70% of personal best before each albuterol use, or
- The patient has symptom code of 3 for 48 hours or longer, or
- PEF drops to less than 50% of personal best despite albuterol treatment.

The recommended prednisone dose for acute exacerbations is 2 mg/kg/day (maximum 60 mg) as a single morning dose for two days followed by 1 mg/kg/day (maximum 30 mg) as a single morning dose for two days. All administered doses should be rounded down to the nearest 5 mg.

IV. Outcome Variables

A. Outcome Measures of Asthma Control

The principal assessed study outcome is the percentage of days without asthma during the 12-month treatment period. A day without asthma is defined as no albuterol rescue use (pre-exercise treatment permitted), no use of oral steroids for asthma, no use of non-study asthma medications, no daytime asthma symptoms (wheezing, coughing, chest tightness or shortness of breath), no nighttime awakenings due to asthma, no unscheduled primary care provider visits for asthma, no emergency room visits or hospital admissions for asthma, and no missed school due to asthma. Days without asthma will be calculated from daily diary card entries.

Other secondary outcomes of asthma control collected from these diary cards include percentage of: rescue-free days, albuterol-free days and episode-free days. A rescue-free day is defined as no albuterol rescue use (pre-exercise treatment permitted), no use of oral steroids for asthma, no use of non-study asthma medications, no unscheduled primary care provider visits for asthma, and no emergency room visits or hospital admissions for asthma. An albuterol-free day is defined as no albuterol use for rescue or for pre-exercise treatment. An episode-free day is defined in the same way as a day without asthma with the additional requirement that morning and evening peak flow are greater than 80% of personal best. Another important outcome of asthma control will be the number of asthma exacerbations requiring prednisone therapy and the time to the first asthma exacerbation.

A number of indicators of airway obstruction will be serially collected during the course of the trial. These include: forced oscillation and spirometry at each study visit, morning and evening PEF and FEV_1 by electronic home monitors, and bronchodilator response over time. Simple reversibility (FEV_1 pre- and post 2 puffs of albuterol MDI) will be determined at 3 study visits and maximum reversibility will be performed at baseline and 6 and 36 weeks after treatment initiation.

Additional secondary measures of asthma control will be serially evaluated in this trial. These include methacholine PC_{20}, FEV_1, PEF variability, and exhaled nitric oxide (ENO).

Measurement of ENO will be obtained prior to each measurement of spirometry including those preceding bronchodilator or challenge procedures. Exhaled nitric oxide will be measured employing the technique described by Silkoff et al.[68] This technique utilizes a resistive device

which provides a constant low expiratory flow rate and ensures vellum closure. The combination of vellum closure and low flow rates, specifically 50 ml/s, assures accurate measurement of specific pulmonary derived ENO, while excluding potential contamination by nasal and paranasal sinuses NO (which can be a large source of ENO). Nitric oxide concentrations will be measured using a rapid-response chemiluminescent analyzer (NIOX™ System, Aerocrine, Sweden) with a response time of < 200 ms for 90% full scale. The measurement circuit will consist of a mouthpiece connected to a two-way valve, through which the patient inhales from a reservoir previously flushed and filled with compressed air. The subject will insert the mouthpiece, immediately inhale to total lung capacity (TLC) and then immediately exhale. During expiration, the subject will maintain a constant mouth pressure of 20 mm Hg (displayed on the computer screen). Subjects will place their hands around their cheeks and lips keeping their cheeks from inflating. The end-point of measurement will occur when a plateau of ENO for 5 seconds is seen. Exhalations are repeated until a performance of three ENO plateau values with less than 10% variation is achieved.

An Asthma Control Questionnaire, (ACQ)[69] and a Modified Asthma Therapy Assessment Questionnaire will be administered at each study visit during the protocol, as well as an asthma specific quality of life questionnaire.[70] A healthcare utilization review questionnaire will be administered at each study visit and also during the telephone calls to determine important pharmacoeconomic outcomes including: unscheduled office visits for asthma, emergency department/urgent care visits, hospitalizations, lost school days, and parent lost work days. Questionnaires used in the ACRN IMPACT trial will be adapted for this purpose. A home environment questionnaire will be administered at baseline and at the final study visit to identify significant household changes (e.g., pets, household smokers). A physical activity questionnaire will be dispensed every 12 weeks to identify changes in recreational activities throughout the study.

Adherence to the 3 treatment regimens will be calculated by a combination of measures, including diary entries, electronic monitors, and subject query. Coordinators will record any potential side effects associated with PACT treatment regimens that are spontaneously reported at study visits by the child and/or parent, as well as those observed by study personnel during brief physical exams during these visits e.g. oral candidiasis.

B. <u>Asthma Phenotype Characterization and Genotype.</u>

In a manner similar to the CLIC protocol, the subject's asthma phenotype and selective genotype markers will be determined. These efforts will compliment those in the CLIC protocol. Potentially, these evaluations will determine whether short-term responses to treatment can predict long-term responses e.g. asthma exacerbation rates over 12 months.

Asthma history including duration of asthma, age of onset, and family history will be obtained at entry. In addition, allergen skin testing, total eosinophil count, plasma ECP, total serum IgE, methacholine challenges and exhaled nitric oxide will be obtained prior to study entry for patient characterization. DNA samples will be collected from consenting families at the beginning of the study period and utilized to measure selected indicators of asthma, allergy, drug response, and drug metabolism gene expression.

Serum ECP Determinations: Blood will be obtained in serum separator tubes, incubated at room temperature for 60 min. prior to centrifugation at 2,000 rpm for 10 minutes. Following serum separation, aliquots of 0.5 ml will be frozen at -20º until assays are performed. ECP levels will be determined using the Pharmacia CAP System, a fluorescence enzyme

immunoassay (FEIA) (Pharmacia Diagnostics AB, Uppsala, Sweden). The detection limit of the assay is < 0.5 µg/l, and the intra- and inter-assay coefficients of variation are approximately 7% and 8% respectively. Samples will be analyzed at a single site.

Genetic Analysis: Blood will be obtained at each study site and processed at the laboratory of Dr. Fernando Martinez at the Tucson CARE Network site. Specific policies and procedures have been developed to maintain confidentiality of samples with special coding to remove all patient name identifiers. A certificate of confidentiality will be obtained. A PACT Study Genetics Committee will determine the priorities for genetic analysis and will focus on the pharmacogenetics of the beta-agonist response. Dr. Fernando Martinez will lead the Committee from the CARE Network Genetics Laboratory.

The three medications being evaluated in PACT include an inhaled glucocorticoid, a leukotriene receptor antagonist, and a long-acting beta-agonist. Response to each medication could be related to an abnormality at the drug cellular response level or an alteration in drug metabolism. Potential genetic features have been identified that are relevant for all three medications.

Insensitivity to glucocorticoid therapy has been described in patients with severe asthma. This has been associated with reduced glucocorticoid receptor binding, increased glucocorticoid receptor β, increased cellular gene expression for mRNA of IL-4 and IL-5, and reduced cellular gene expression for interferon γ, as well as increased transcription factors for AP-1 and NF-κB. Genetic markers for evaluating gene expression for GRα (active form) and GRβ (inactive form that binds to GRE but does not bind glucocorticoid) are available through laboratories at the National Jewish Medical and Research Center, Denver, Colorado.[71] In contrast, a good response to glucocorticoids for asthma management could be associated with increased glucocorticoid sensitivity. A polymorphism in codon 363 of the glucocorticoid receptor gene has been associated with increased sensitivity to exogenously administered glucocorticoids with respect to cortisol suppression and insulin response.[72] The same sensitivity could predispose the asthma patient to adverse effects of glucocorticoids. Identification of this specific genotype could prompt closer monitoring for adverse systemic effects or the utilization of low dose therapy.

A poor response to leukotriene receptor antagonists could be related to decreased leukotriene synthesis. To date, several pharmacogenetic associations have been identified for leukotriene synthesis. One is related to decreased leukotriene production (ALOX5 promoter genotype) and another is related to increased leukotriene synthesis (LTC-4 synthase). The latter is present in aspirin-sensitive asthmatics.[73] A predisposition to increased leukotriene synthesis could be associated with a good response to a leukotriene antagonist. The frequency of ALOX5 promoter genotypes has been described with associated response to an inhibitor of the 5-lipoxygenase pathway.[74,75] This study demonstrated a poor response to a 5-lipoxygenase inhibitor in a mutant ALOX5 genotype. A similar observation could occur with a leukotriene receptor antagonist where decreased production of leukotrienes would be associated with absence of effect in response to a leukotriene receptor antagonist.

Available reports indicate that both ICS and montelukast are metabolized through the cytochrome P450 3A4 family. In addition, montelukast is metabolized through the cytochrome P450 2C9 pathway. Considerable information is now available regarding the features of the cytochrome family. Detailed information on the metabolic pathways of both medications will be obtained and considered for evaluation of the cytochrome P450 genotype based on considerations of race, age, and functional differences in genetic polymorphisms.

A number of polymorphisms of the beta-adrenergic receptor (β_2–AR) have been identified.[76]

Studies have shown that some forms of the β_2-AR display distinct differences in signaling and/or regulation after chronic exposure to beta–agonists.[77-80] It could thus be possible that these polymorphisms might explain altered pharmacological responses to beta-agonist therapy. Some investigators have reported a relationship between these polymorphisms and the degree of responsiveness or desensitization to the bronchodilator effect of beta-agonists.[81-84] However, these studies have produced inconsistent results. Altered desensitization to beta-agonists has alternately been associated with either arginine or glycine polymorphisms at the 16 position of the β_2–AR and in other cases with polymorphisms at the 27 position. Many of these studies have been short-term, and several of these studies have compared asthmatics of differing severities in which etiologic heterogeneity may influence apparent associations. PACT, because of the uniform severity of the asthma population to be enrolled, has the potential to differentiate pharmacogenetic explanations for the response to acute beta-agonist administration versus chronic beta-agonist administration.

C. Duration

The duration of the study will be approximately 23.5 months with an anticipated start date of August 2002 and an anticipated end date of July 2004. Children will be enrolled over a 12-month period and each child will complete the study during approximately 12 calendar months (2-4 week run-in plus 48-week study period).

V. PROTOCOL

A. Recruitment

Each clinical center involved in the CARE Network was chosen, in part, based on documentation for subject availability in clinical trials with similar entry criteria. Each center will randomize 60 study patients. The specific plans for recruitment at each center are summarized below.

National Jewish Medical and Research Center/Denver: Research subject recruitment has been very successful for all types of asthma patients at the National Jewish Medical and Research Center. The total subjects, including a one-third-minority population, will come from the following areas:

1. National Jewish Asthma Research Pool: There are over 1,500 asthma patients (not followed in the National Jewish outpatient clinic) that have participated in research studies conducted at the Denver Center. Many of these subjects have been through various medication studies. Their FEV_1's range from 60-120% of predicted.
2. National Jewish Outpatient Clinic: The pediatric clinic saw 500 new asthmatic patients over the last year with 250 being from the Denver metropolitan area. Another 500 from the Denver area were seen in follow-up. The severity of asthma varies among these patients, but approximately 50% are in the mild to moderate category. National Jewish has changed markedly over the last decade. It has evolved from a primary inpatient facility with a small clinic to a very active outpatient service. Thus, the Denver Center has access to many more asthmatic patients of all degrees of severity. In addition, National Jewish staffs clinics at various sites in the Denver Metropolitan area.
    a. Denver Health Medical Center – Dr. Andrew Liu, a member of the National Jewish Department of Pediatrics, is supporting efforts of the Denver Center by helping to recruit from the asthmatic patient population at the Denver Health Medical Center. This is a

large county hospital whose patient population comprises mainly Hispanic and African-American people.

b. Children's Hospital – Dr. Dan Atkins, a member of the National Jewish Department of Pediatrics, is supporting efforts of the Denver Center by helping to recruit from the asthmatic patient population at The Children's Hospital of Denver. This is a large regional hospital whose patient population includes Hispanic and African-American people. In addition, Dr. Szefler is Co-Principal Investigator of the Denver site NICHHD Pediatric Pharmacology Research Unit (PPRU) Network. The Denver PPRU site is a collaborative effort between National Jewish and The Children's Hospital. If necessary, The Children's Hospital Clinical Trials Organization could be invited to assist in recruitment of potential study subjects.

c. Private practice settings: Drs. Dan Atkins, Mark Boguniewicz, and Nathan Rabinovitch have established clinics in several practitioner settings in the Denver Metropolitan area.

3. Referring physicians – Dr. Peter Cvietusa, Kaiser Permanente, and Dr. Jay Markson, Dr. Wallace White, Gayle Spears, P.A. and Dr. Jeffrey Barter, pediatricians in private practice in the Denver area, have been actively involved in supporting research at National Jewish in the past by referring patients to the CARE Network studies. Their allergy and asthma clinic could be invited to assist in providing study subjects for the CARE Network.

In all cases, referring physicians will make the first contact to invite their patients to participate in the study.

San Diego: Patients will be recruited primarily from the 100,000 children and adolescents with asthma, in the Kaiser Permanente Health Plan membership in San Diego of which 60% are above the age of 5 years. The ethnic mix of the membership is 67% Caucasian, 18% Hispanic, 9% African-American, 4% Asian, and 2% other. About 2.5% receive MediCal assistance. Patients will be recruited from the membership of the Kaiser Health Plan in San Diego by a variety of mechanisms including (1) a research database of children ages 6-14 years attending the Kaiser Permanente Allergy Department over the past year, (2) pharmacy data bases of children ages 6-14 years with at least 2 dispensings of a beta-agonist over the past year and no chronic controller medication, (3) computerized records of hospitalizations and emergency department visits, (4) a computer generated data base of diagnostic classifications, and (5) referrals from primary care and pediatricians in the medical group. Patients meeting the eligibility criteria will be also identified in the pediatric and primary care departments that have over 350,000 pediatric visits yearly.

Patterning recruitment after the success in recruiting for the NHLBI Childhood Asthma Management Program and Prevention of Early Asthma in Kids (PEAK) Trial for the CARE network and our primary allergy prevention study, the Principal Investigator and his co-investigators and coordinators will contact all potential eligible families to maximize recruitment potential. In addition, modeling after the success of other study recruitment efforts, regular dinner or afternoon meetings will be held at which time invited groups of interested and potentially eligible families will learn more about the study during a slide presentation. In addition, individual families not able to make these meetings or should these meetings not prove valuable, personal appointments will be scheduled with the P.I. or designee to review all aspects of the study. Should difficulties occur with recruitment from the Kaiser Permanente base in San Diego, additional efforts will be extended to recruit patients from the Kaiser Permanente membership in South Orange County and Temecula County. As a last resort, if needed, the UCSD patient base will be accessed. UCSD has 18,875 outpatient visits yearly in its pediatric clinic.

A study coordinator will ascertain the eligibility status of these potential patients by checking the integrated computer database for eligible diagnoses as well as by contacting these families. Past success in recruitment, for all the studies to which the site has committed should encourage confidence in future recruitment success given the large patient base that is at the site's disposal. Parent or guardian will give and sign informed consent, children 6 years and younger will give verbal assent, and children 7 years and older will give and sign assent.

St. Louis: Recruiting will be done in several clinical sites. Drs. Strunk and Bacharier care for approximately 400 children with asthma in clinics of the Division of Allergy and Pulmonary Medicine at St. Louis Children's Hospital. At each visit, the patient's asthma is categorized by the criteria of the National Asthma Education and Prevention Program Expert Panel 2 Guidelines for the Diagnosis and Management of Asthma. The asthma in these children is well characterized and medication requirements to control asthma are well documented. Dictations of these visits can be scanned to generate lists of children with mild to moderate persistent asthma. Either Dr. Strunk or Dr. Bacharier will contact the patients under their care who are likely to be eligible, based on the diagnosis at the time of the last clinic visit as well as a review of the chart.

Drs. Gordon R. Bloomberg and James M. Corry are pediatricians who practice allergy and asthma in the St. Louis area. These physicians have been collaborators in the Childhood Asthma Management Program. They were instrumental in successful recruitment for the St. Louis CAMP center. They both have large practices with partners. They have committed to keeping lists of patients likely to be eligible for the CARE Network protocols and make personal contact with the patient to recruit them to enter screening.

Drs. Bloomberg and Strunk will be responsible for recruiting 5 pediatric practices to participate in the Network. These practitioners have participated in the care of patients in CAMP and we have high expectations that they will be interested in finding patients within their practices for screening in the Network protocols.

Dr. Strunk has organized a Community Asthma Program for Children (CAP-C) involving 4 other pediatric practices. Two of these practices have large numbers of African American patients. Patients in these practices are enrolled in the Program upon visiting the office for asthma. At the time of the visit, the pediatricians fill out a form containing the severity (based on the NAEPP criteria) and indicate the type of medication to be used by the patient. These data are in a database, now with over 2000 patients included. With permission of the Human Subjects Committee and the individual pediatricians, we will be able to scan the databases for names of patients likely to be eligible for the Network protocols.

Minority patients will be recruited from the clinics at St. Louis Children's Hospital and from the CAP-C practices. There will be minority patients cared for in the Hospital clinics not eligible for a specific protocol. We will make these parents aware of the Network and the opportunity for patients to participate in the hope that they will be able to help us identify family friends who might be interested in participating.

University of Arizona Respiratory Sciences Center/Tucson: Subject recruitment will be patterned after very successful methods practiced by the recent Inner City Asthma Study. Primary efforts will be in conjunction with the El Rio Community Health Center, one of the most important healthcare service providers for southern and central Tucson. El Rio maintains a database of almost 12,000 children ages 6 to 18; they expect approximately 1,000 children to be eligible for recruitment. More than two-thirds of the families receiving services at El Rio are minorities, most of them Hispanic. They have nurtured a strong working relationship with key

people at El Rio, which allows for rapid queries of the database based upon age, ethnicity, and asthma diagnosis. Additionally, they plan to work with pediatricians at El Rio to establish referrals to the study from potentially eligible families. Dr. Arthur N. Martinez, the Medical Director of El Rio, strongly supports collaboration between these organizations to promote asthma research.

Recruiting will also be done through several clinics at the University of Arizona Health Sciences Center and the Tucson Medical Center, pending Human Subjects approval. These large hospitals provide health care for the preponderance of the Tucson population being seen for asthma. Each hospital utilizes an after care discharge nurse who instructs parents and children being discharged for asthma. They intend to establish a referral system through these nurses whereby parents will give consent for telephone contact by their recruiter to discuss the study and determine eligibility. This method was successfully used by their center to recruit approximately 15% of moderate asthmatics for the Inner City Asthma Study.

They will participate actively in a Tucson based organization called ACASA (Asthma Care Alliance of Southern Arizona). This group is composed of a wide variety of physicians and other health care professionals working together to share resources pertaining to asthma care in Tucson. They will present this study to these physicians to encourage referrals of potentially eligible subjects for PACT. By discussing the study with potential participants, they also hope to identify family or friends who might be interested in participating.

If additional participants are still needed, they will use newspaper or radio advertisement targeted towards meeting the gender and ethnic recruiting goals. The Human Subjects Committee will approve all advertising in advance.

University of Wisconsin/Madison: The Asthma/Allergy Clinical Research Program of the University of Wisconsin maintains an ongoing computer database of potential subjects with mild to moderate asthma who are interested in future research participation and have given permission for re-contact. These individuals have been screened, participated in previous asthma studies, and/or have expressed interest in participating in studies. This entire database has been updated with current information relevant for CARE-initiated protocols. The following information is maintained: birth date, gender, ethnic background, age of asthma at diagnosis, atopic status, asthma and non-asthma medications, pulmonary function test data, and methacholine data (if available). This database of subjects will be used as the primary source of recruitment.

Newsletters outlining the CARE protocols will be sent to families that have participated in the Childhood Origins of Asthma (COAST) project, another NIH funded research program exploring the origins of asthma in infants born to over 300 area families (principal investigator Robert F. Lemanske, Jr., M.D.). The newsletter will target the older siblings of COAST children, since these families are already involved and committed to asthma research. The Madison CARE center will also recruit from clinical and community physician networks that the COAST project has established. This includes pediatricians and other primary care physicians who have previously collaborated. Additional children with asthma will be identified from the large network of Pediatric and Family Care practices in the U. W. system. In all cases, referring physicians will make the first contact to invite their patients to participate in the study.

Children of minority ethnic backgrounds will be identified through ongoing relationships with the Head Start program in Dane County. On an annual basis, over 500 families with preschool aged children are screened for asthma and wheezing illnesses, at the time of Head Start enrollment. Trained U. W. Allergy Research staff and physicians conduct the screening;

essentially 100% of families provide informed consent for this program. A high prevalence of physician-diagnosed asthma/wheezing illness has been consistently documented since this initiative started in 1992. A variety of asthma interventions are offered to the families, with high enrollment rates. Most of these children are of minority background and about one-third of children have at least one sibling (usually older) with asthma.

Additional subjects will be recruited by U. W. Human Subjects committee-approved newspaper advertising, as needed. The Madison Asthma Clinical Research Network (ACRN) has utilized a marketing expert to help coordinate and oversee efforts in recruiting and retaining minorities for its asthma program. He is uniquely qualified for this task due to his combined professional and personal background (he is an ethnic minority, has a long history of asthma, has a son with asthma, and has participated in previous asthma studies at the institution). The CARE network also utilizes his talents as protocols are initiated. He has worked closely with the U.W. Hospital public relations staff to coordinate television and newspaper reports on behalf of asthma research efforts. These joint efforts have benefited both ACRN and CARE recruitment.

If subject accrual becomes problematic, this center will develop strategies to expand the recruitment net to the outlying areas outside of Madison. According to the state vitals office, the entire Dane County area had 5,125 births in 1998, while the total population census was 409,910. Milwaukee County, about 1 hour from the U. W. campus, has a population census of approximately one million. The Children's Hospital of Wisconsin is located in Milwaukee and their Allergy/Asthma program has expressed a keen interest in becoming involved in CARE Network-initiated trials.

B. Drug Supplies

Drug supplies for this study will consist of fluticasone 100 mcg bid (Flovent Diskus®, Glaxo), fluticasone/salmeterol combination 100 mcg/50 mcg qd (Advair Diskus®, Glaxo) plus salmeterol 50 mcg qd (Serevent Diskus®, Glaxo), montelukast 5 mg qd, and corresponding placebos. Since the selected inhaled steroid/ long-acting beta-agonist combination (fluticasone/salmeterol) is not FDA-approved for the 6-14 year-old age group or for once a day dosing, an IND was requested on behalf of the CARE Network. However, after review, the FDA determined that an IND was not required (date of review: 05/17/2002). Rescue albuterol MDIs (Ventolin, Glaxo) will be donated and prednisone tablets will be purchased.

The CARE Network will contract with ProClinical Pharmaceutical Services to provide montelukast study drug and matching placebo. ProClinical will purchase commercial Montelukast 5 mg chewable tablets, and undertake an overencapsulation process to make identical active drug and placebo capsules. In accordance with FDA and USP standards, dissolution profiles for active drug will be generated for both the commercial tablets and overencapsulated tablets to verify that the backfill agent does not negatively effect the dissolution characteristics. Analysis of the data will be in accordance with FDA guidelines for statistical assessment of dissolution profile equivalency. A report will be generated for CARE summarizing the findings of these development studies for both potency and dissolution. Release testing on a random sample of overencapsulated drug will then be performed to verify that the potency is uniform and complete. This process will be done according to USP specifications and CARE will receive a written certificate of approval of such. During the course of PACT, the overencapsulated montelukast will be subjected to standard stability testing using stability chambers maintained at ICH conditions (as per NDA and IND requirements). The capsules will be pulled at 1,3,6,9 and 12 months for stability testing of appearance, moisture,

potency and dissolution.

C. Adherence and Monitoring

The following mechanisms will be employed to determine adherence and measure outcomes:

1. The AM1® electronic peak flow meter will be used to measure peak expiratory flows (PEF) and FEV_1, and serve as a general adherence check (date and time are electronically recorded). Subjects will be asked to record these measurements on a daily diary card. Electronic measurements will be downloaded at each study visit and compared to diary loggings. CARE coordinators will provide positive feedback to subjects who demonstrate good adherence, and ongoing encouragement when warranted.
2. Medications: The CARE Network has explored various published methods of assessing adherence to asthma treatment, including pharmacy records, canister weights, self-report, and electronic devices attached to metered dose inhalers. No single adherence measure is currently deemed to provide complete accuracy. Self-report accuracy is enhanced if the child and parent are asked to report on medication use within the previous 24-hour period, rather than asked to provide a global characterization of adherence. Additional objective measurements of medication adherence will be tailored to individual treatments as follows:
   a. The Diskus devices (fluticasone, salmeterol, fluticasone/salmeterol combination and placebo). The Diskus dry powder inhaler devices have a built-in dose indicator that allows for calculation of used doses.
   b. Montelukast and placebo capsules. Adherence with capsule medication can be assessed by capsule count and by utilization of the Electronic Drug Exposure Monitor (child-proof version), which consists of a medication bottle equipped with an electronic, microchip-based cap which records each time the container is opened, with data storage up to 6 months. This device is selected because of its relatively low cost and reliable track record.

D. Inhalation Techniques

To minimize the variability in the dose of fluticasone, salmeterol and fluticasone/salmeterol combination delivered to the lungs, the patient's medication technique will be reviewed at each study visit. Objective feedback will be given to each subject to improve performance.

E. Special Study Techniques

1. Maximum reversibility – The maximum reversibility procedure is detailed in the CARE Network Manual of Operations.
2. Methacholine challenge – The methacholine challenge procedure is detailed in the CARE Network Manual of Operations for children 5 to18 years of age.
3. Oscillometry – The oscillometry procedure is detailed in the CARE Network Manual of Operations.
4. Aeroallergen skin tests – The aeroallergen skin test is detailed in the CARE Network Manual of Operations.
5. Genetics analysis – The genetics analysis procedure is modified from that applied to the Asthma Clinical Research Network protocols and is detailed in the CARE Network Manual of Operations. This will be limited to genetics analysis related to drug response, drug metabolism, allergy, asthma and inflammation. A separate protocol will be developed that will prioritize genetic analysis for this study.

F. Risks/Benefits

This study will evaluate the 12-month efficacy and safety in children ages 6-14 years of three FDA-approved medications for the treatment of persistent asthma. No subject will receive placebo therapy. Subjects will not be withdrawn from controller therapy for the purpose of study enrollment. The assessment/characterization period will prevent enrollment of children whose asthma is either too mild (intermittent pattern) or too severe in nature. Since these subjects will be placed on one of 3 active medications, their asthma control should improve. However, all children will have action plans and rescue medications available for the duration of the trial.

Only low dose fluticasone therapy will be studied, thus, no significant systemic effects are anticipated. Height will be measured on 6 occasions during the course of the 12-month study period. Montelukast is approved in the 6-14 year-old age group and has extensive, published safety records.[42,43]

Direct benefits to study participants will include provision of active controller and rescue medications for a 12-month period, as well as access to an asthma specialist during the study. The study results may change the paradigm of management for children with mild-moderate persistent asthma, much as the CAMP trial has accomplished.

G. Anticipated Results

It is anticipated that, using the doses of ICS, ICS/LABA, and LTRA to be administered in PACT, that all three treatment groups will be observed to have improvement in asthma control during the 12-month study period. Specifically, it is anticipated that all three treatments will increase the percentage of days without asthma, prevent asthma exacerbations, improve pulmonary function measures, improve asthma-specific quality of life, and reduce markers of inflammation. The relative magnitude of these improvements is open for conjecture, and the major question of interest in PACT. The extent of asthma control achieved by any one treatment arm, coupled with the safety profile, will determine which of the 3 treatments is the best first-line management of mild-moderate persistent asthma in 6-14 year olds.

The potential magnitude of asthma control improvements in PACT is difficult to estimate due to the lack of clinical trials in this mild-moderate subset of children with asthma. Only two comparator trials of the controllers of interest as first line treatment of persistent asthma are published.[34,85] Table 2 outlines the entry criteria, treatment regimens, baseline measurements, and endpoint measurements for these two trials. Neither trial included children 6-14 years of age and both were relatively short duration (12-24 weeks). Both trials enrolled individuals with moderate-severe persistent asthma, based on lung function parameters, who were being treated (under treated) with beta-agonists alone. The Busse trial[85] compared an LTRA versus low-dose fluticasone and the Calhoun trial[34] compared an LTRA to low-dose fluticasone in fixed combination with salmeterol. All three regimens improved measures of asthma control; the means, standard-deviations, and percent improvement outcomes will be used for PACT sample size calculations, in conjunction with the outcomes from the CAMP trial.[3] Based on the results of the Calhoun trial, one might predict a greater improvement with the ICS/LABA combination compared to monotherapy with an LTRA. However, as reviewed previously, the greater improvement demonstrable in adult patients with the ICS/LABA combination may not be as great in magnitude in children.[44] Therefore, it is possible that the LTRA will prove to be a more "comparable" controller in children with this level of disease severity versus how this class of compounds appears to perform in adult patients.

PACT has the potential to change the approach to management of mild-moderate persistent

childhood asthma, much as the CAMP trial accomplished. To our knowledge, no long-term evaluation of these three treatments is in progress by the NIH or the pharmaceutical industry. Table 3 outlines the construct of the three ongoing trials of controller therapies, two supported by Merck and one sponsored by the NHLBI. Whereas two of the trials (MIAMI and ACRN-IMPACT) have some comparable entry criteria to PACT, they are only evaluating adolescents and adults and are only two-armed treatment evaluations. Many of the outcomes selected for these three trials will also be evaluated in PACT, allowing for some interesting comparisons.

VI. ADVERSE EVENTS

A. Definitions

An adverse event shall be defined as any detrimental change in the patient's condition whether it is related to an exacerbation of asthma or to another unrelated illness. Adverse events related to asthma exacerbations will be assigned Treatment Failure status if the event results in hospitalization or the need for a third course of corticosteroid treatment. These adverse events will be managed according to rescue algorithms utilized in the CAMP trial.

B. Adverse Events Unrelated to Asthma

Adverse events due to concurrent illnesses other than asthma may be grounds for withdrawal: 1) if the illness is considered significant by the study investigator, 2) if the illness requires systemic corticosteroids, or 3) if the patient is no longer able to effectively participate in the study. Subjects experiencing minor intercurrent illnesses may continue in the study provided that the nature, severity, and duration of the illness are recorded and that any unscheduled medications required to treat the illness are also recorded. Examples of minor intercurrent illnesses include acute rhinitis, sinusitis, upper respiratory infections, urinary tract infections, and gastroenteritis. Medications are allowed for treatment of these conditions in accordance with the judgment of the responsible study physician.

Documentation of an adverse event unrelated to asthma will be recorded on an Adverse Event Report Form and will include the following information:

1. Description of the illness
2. Dates of illness
3. Treatment of illness and the dates of such treatment (medications, doses, and dose frequency)
4. Whether emergency treatment or hospitalization was required
5. Treatment outcome

C. Adverse Events Related to Asthma Exacerbations

For this protocol, an asthma exacerbation is defined as the development of an increase in symptoms of cough, chest tightness, and wheezing or by a decrease in the patient's PEF. Patients developing asthma exacerbations during the double-blind treatment period will be managed according to a patient specific guide for decision-making and rescue management (action plan). Home care, Physician's office or emergency room visit, and prednisone course algorithms are previously described in Section III.G of the protocol.

Patients developing asthma exacerbations during the characterization/assessment period will be removed from the study. Once the exacerbation has been resolved, the patient may be considered for re-enrollment, starting again with Visit 1.

D. Criteria for Discontinuing Patients Due to Asthma Exacerbations

Treatment failure will be assigned if a third course of prednisone is required for an asthma exacerbation or if a subject is hospitalized for treatment of their asthma. The subject will return to the CARE center following resolution of the exacerbation. Subjects will be treated with open-label controller therapy, according to the discretion of the study investigator or primary physician.

E. Dropout Status

Any participant who becomes pregnant, withdraws assent to participate, whose parent withdraws consent to participate, or for whom the Study Physician determines that continuation in the study would not be in the best interest of the participant will be assigned dropout status.

VII. SAFETY MONITORING

A Data Safety Monitoring Board (DSMB) has been established for this study to monitor data and oversee patient safety. The DSMB consists of four physicians skilled in pediatric asthma management, asthma pharmacology, endocrinology, and/or asthma clinical research as well as a pediatric pharmacologist, a pediatric nurse educator, a statistician, and a bioethicist experienced in clinical trials. The Study Chair, the Director and a senior staff member of the Data Coordinating Center, and representatives from the NHLBI participate as non-voting members. Specific DSMB procedures are identified in the CARE Network Manual of Operating Procedures.

The current study will request DSMB review of study data every 6 months. The DSMB will assess the following:

- Study performance, including assessment of clinical centers' adherence to protocol, adequate subject accrual, and quality control of data collection and management.
- Study outcomes data (described in the Interim Analysis section) to assure patient safety. These data will be presented to the DSMB in a fashion blinded to treatment group assignment. However, the DSMB will have the option of unblinding when and if this action is deemed to be appropriate. Reports of serious adverse events will also be summarized in the interim study outcomes data submitted to the DSMB for review.

Serious Adverse Events. A Serious adverse event is defined as any event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect or other medically important condition. A life-threatening event is one in which, in the study physician's opinion, the patient was at immediate risk of death from the reaction as it occurred. Although not unexpected as an outcome in asthma clinical trials, hospitalizations for asthma will be included in the listing of adverse events as identified in the CARE Network Manual of Operations. Summary reports of the DSMB's review of serious adverse events will be distributed to each CARE Network PI by the DCC within 30 days following each DSMB meeting. The Summary Reports will include the following: a statement that a DSMB review of the data and outcomes across all centers took place on a given date; a summary of the DSMB review of the cumulative serious adverse events without specific disclosure by treatment group unless safety considerations require such disclosure; and the DSMB's conclusion with respect to progress or need for potential protocol modification. The CARE Network PIs are required to

forward the Summary Reports to their local IRBs.

VIII. COST, LIABILITY, AND PAYMENT

All tests will be performed without cost to the participating subjects. Since this is a trial comparing established asthma treatments, liability for patient care costs incurred by patients during the course of the trial will, in most cases, be borne by the patient or their insurer. Details of the NIH policies concerning this issue can be found in NIH Documents #5305 and 6352-2, Research Patient Care Costs Supported Agreements, in the CARE Network Manual of Operations. Each subject will be paid an amount determined by his/her Clinical Center for study reimbursement. For subjects who drop out, reimbursement will be pro-rated for the length of time they stayed in the study.

IX. STATISTICAL DESIGN AND ANALYSIS

A. Data Recording and Data Management

Recording of all data including informed consent, history, physical examination, adverse events, confirmation of medication dispensation, lung function testing, and initial data entry will be done at each Clinical Center and forms will be forwarded to the data coordinating center (DCC) for confirmatory entry. Results from pulmonary function tests and compliance will be transmitted electronically to the DCC where all data will be stored and analyzed.
Each Clinical Center will have a computer configuration that includes a PC, a printer, and a modem. This will give each clinical center the capability of logging directly into the CARE Network web site with the modem as a back up if the connection is not possible. Though this set-up is installed primarily to allow for distributed data entry into a centralized and secure database at the CARE Network web site, menu options will also include sending electronic mail, downloading study documents such as forms and reports, and viewing a calendar of CARE Network events. A sophisticated security system will limit access to qualified personnel and prevent corruption of the study database.

The DCC will be responsible for generating data collection forms based on input from each of the clinical centers. Once the data collection forms have been filled out and reviewed, the Clinic Coordinator will log into the CARE Network web site and enter the data within 3 days of the patient visit. The advantage of this distributed data entry system is that the Clinic Coordinators will review the data a second time as they are entering it, which serves as another level of quality control. However, the Clinic Coordinators will not be able to query their own data. The data base management system will have range checks and validity checks programmed into it for a second level of quality control. Forms will then be forwarded to the DCC for the second data entry and filing, which will be performed within 3 days of receipt. The DCC will be responsible for identifying problem data and resolving inconsistencies. Once the quality control procedures are complete, new study data will be integrated into the primary study database. Results from lung function tests will be sent directly to the DCC via a computer modem attached to the spirometer.

B. Randomization

Children between the ages of 6 and 14 years who satisfy the eligibility criteria during the run-in period will be randomized to one of three treatment arms (fluticasone, fluticasone/salmeterol or

montelukast), stratified by Clinical Center. Within each center, a blocked randomization scheme will be invoked in order to ensure balance across treatment arms with respect to the following blocking factors: bronchodilator response (<12% or ≥12%), race (caucasian or non-caucasian), and methacholine PC_{20} (<2 or ≥2 mg/ml). The target sample size is 300 randomized participants (100 each in the fluticasone, fluticasone/salmeterol and montelukast groups); each of the five Clinical Centers will randomize 60 participants (20 each in the fluticasone, fluticasone/salmeterol and montelukast groups).

When a child at a particular Clinical Center is deemed eligible for the study, the Clinic Coordinator will log into the CARE Network server and indicate to the system that a patient requires randomization. After entering the pertinent information with respect to Clinical Center and eligibility criteria, the Clinic Coordinator will be asked to verify that all of the entered information is correct. If so, the Clinic Coordinator will be given a packet number, from which all medication for that child will be dispensed.

C. Masking

To minimize the potential for bias due to knowledge of treatment, the study will be double-blinded. Thus, the investigators and the participants, along with their caregivers, will be blinded to the assigned treatment regimens. This is possible because the active and placebo formulations of the fluticasone, salmeterol and fluticasone/salmeterol combination are indistinguishable from one another, and likewise for the active and placebo formulations of the montelukast. Thus, the participants randomized to fluticasone will receive active fluticasone + placebo salmeterol + placebo montelukast, the participants randomized to the fluticasone/salmeterol combination will receive active fluticasone (at 50% dose) + active salmeterol + placebo montelukast, and the children randomized to montelukast will receive placebo fluticasone + placebo salmeterol + active montelukast. Study participants and their caregivers can be unblinded to their assigned treatment regimen upon request.

In addition, the biostatisticians at the DCC will be blinded to treatment identity when performing interim statistical analyses. Until the time of manuscript preparation DCC personnel will identify the randomized groups as X, Y, and Z and only two persons within the DCC will know the identity of X, Y, and Z.

D. Statistical Analysis

The primary study outcome measure is the percentage of days without asthma during the 12-month treatment period. There are three primary comparisons of interest with respect to this outcome, namely, fluticasone versus fluticasone/salmeterol, fluticasone versus montelukast and fluticasone/salmeterol versus montelukast. Therefore, statistical analyses for these multiple comparisons will use a significance level of 0.017 (based on the Bonferroni correction factor).

Descriptive statistics including mean, standard deviation, median and quartiles will be calculated. Statistical tests, such as analysis of variance (ANOVA) with post-hoc pair wise comparisons and Mann-Whitney pair wise comparisons, will be applied to assess differences in the primary outcome between the three groups. In addition, the analysis of covariance (ANCOVA) approach will be used to compare the mean outcome of the groups in the presence of other covariates. These covariates will include indicator variables for treatment assignment, Clinical Center, treatment × Clinical Center interactions, and other relevant baseline prognostic variables. Secondary analyses will examine the change in percentage of days without asthma from baseline to various time points during treatment. Related secondary outcomes including

percentage of: rescue-free days, albuterol-free days and episode-free days will be analyzed in a similar manner.

Other secondary outcomes of interest are the rate of asthma exacerbations requiring courses of oral corticosteroid and rate of adverse drug reaction events occurring during the randomized treatment period. To account for early terminations (treatment failures due to SAE, pregnancy, or prednisone use for other medical conditions), the number of occurrences will be adjusted by the number of observed months during the randomized period. A Poisson regression analysis, analogous to the ANCOVA described above, will be applied to compare the exacerbation and adverse event rates of the three groups.

Another secondary outcome is the time until the first asthma exacerbation requiring oral corticosteroid. To account for early terminations, the number of oral corticosteroid courses will be adjusted by the number of observed months during the randomized period. Kaplan-Meier survival curves will be constructed for the three treatment groups. Statistical tests, including the log rank test and the generalized Wilcoxon test, will be applied to compare the survival curves. A proportional hazards regression analysis adjusting for the covariates listed above will also be applied to compare the survival curves of the three groups.

Other secondary outcomes that are continuous will by analyzed via ANCOVA. These include:

- Morning peak flow
- FEV_1
- Asthma symptom score
- Methacholine PC20
- ENO
- PEF variability
- Asthma-specific quality of life
- Direct and indirect asthma costs
- Medication adherence

Genotype for each participant will be determined with respect to selected markers. Subgroup analyses within each randomized group will be performed to investigate differences among genotypes with respect to primary and secondary response variables.

In order to assess the predictive value of short-term treatment response, the primary and secondary outcomes at end of study will be correlated with changes in FEV, ENO and PEF during the initial six weeks of therapy.

All statistical analyses will invoke the intent-to-treat paradigm, i.e., data will be analyzed according to randomized treatment assignment. Statistical analyses based on actual treatments received may be conducted if deemed important for further interpretation of study results.

All statistical analyses will be performed using SAS statistical software (version 8.2 or later).

E. Interim Analyses

Because one of the primary goals of this study is to assess the long-term effects of treatment in children with persistent asthma symptoms, formal statistical analyses to evaluate efficacy at interim time points will not be scheduled. However, an interim statistical analysis to evaluate the safety of each of the fluticasone, fluticasone/salmeterol and montelukast treatments will be scheduled at the trial's midpoint and then presented to the Data and Safety Monitoring Board

(DSMB). The DSMB will also receive any reports of serious adverse events as they occur throughout the course of the trial.

F. Sample Size Calculation

There are three primary comparisons of interest in this trial, namely, testing whether the percentage of days without asthma during the 12-month treatment period is significantly different for (1) the fluticasone group and the fluticasone/salmeterol group, (2) the fluticasone group and the montelukast group and (3) the fluticasone/salmeterol group and the montelukast group. As described above, the Type I error rate (significance level) will be set at α = 0.017 for each of the three primary comparisons. The Type II error rate will be set at β = 0.10 for each of the primary comparisons, yielding 90% statistical power. A sample size formula for comparing two groups with a two-sided test at significance level α and statistical power $(1 - \beta)100\%$ based on a t-test is:

$$N = \frac{\left(\sigma_1^2+\sigma_2^2\right)^2\left(Z_{1-\alpha/2}+Z_{1-\beta}\right)^2}{\Delta^2}$$

Where N represents the total number of subjects in each group, $z_{1-\beta}$ and $z_{1-\alpha/2}$ represent percentiles from the standard normal distribution, σ_1 and σ_2 are the group standard deviations and Δ is the difference between the group means (effect size). The values of α = 0.017 and β = 0.10 yield the percentiles $z_{0.90}$ = 1.28 and $z_{0.9917}$ = 2.39 in the sample-size formula.

In an earlier version of this protocol, the primary outcome variable was the change from baseline to end of study in percent symptom-free days as measured by two-week symptom diary. This outcome was chosen primarily because of the availability of previously published results (Busse[85], CAMP[3]) that could be used to estimate variance parameters needed for sample size calculations. Based on these studies, a value of 35 was chosen for both σ_1 and σ_2. A clinically relevant difference between treatments (effect size Δ) was determined to be 20%. This would translate into one less day of symptoms per 5-day school week. Using these values for σ and Δ, a sample size of 85 per group will yield 90% power for detecting a mean difference between any two treatment groups. The top panel of Figure 1 below shows the relationship between sample size and statistical power, the curve indicates that a sample size of 85 per group is reasonable in terms of the sample size versus power trade-off.

It was later determined that percentage of days without asthma during the entire treatment period is preferable to change in percent of symptom-free days because it incorporates all of the available symptom data and is more reflective of the long-term effects of the treatments. The percentage of days without asthma is expected to increase gradually during the course of the study for all treatment groups. The power of this study design depends on the difference in rate of increase between treatment groups. The bottom panel in Figure 1 below shows the power associated with this design under three potential scenarios. The y-axis denotes the difference (between any two treatment groups) in percentage of days without asthma at any point in the study. All three scenarios assume that the group difference will be zero at baseline and 20% at end of study; they differ with respect to rate of increase of group difference. In order to calculate the effect size under each scenario, the average group difference across the entire study period was calculated. If the rate of increase is higher, the overall difference in percentage of days without asthma will be larger, the effect size will be larger, and thus the power of the study will be larger. The bottom panel in Figure 1 indicates that this design will have adequate power for

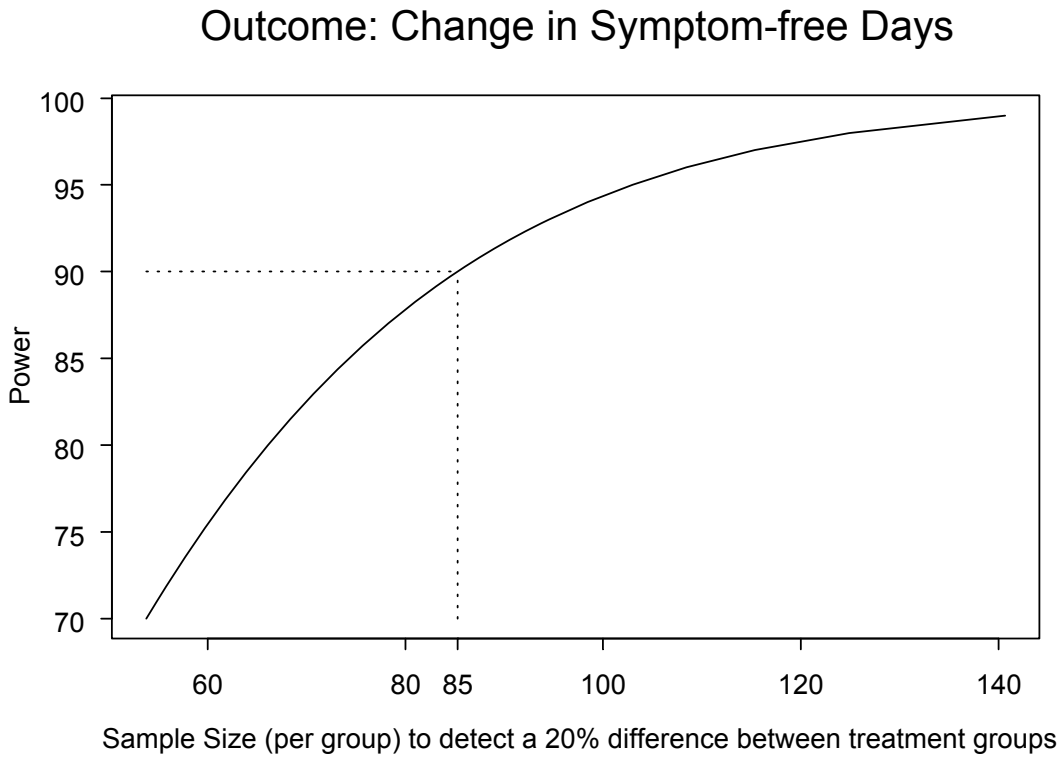
detecting group difference in percentage of days without asthma if the group difference reaches at least three-quarters of the final difference (20%) by the midpoint of the study period. The standard deviation of percentage of days without asthma days during the entire study period was assumed to be 26.25 for all three treatment groups. This value was calculated by using the previously described value of 35 for the standard deviation of one 2-week block of percentage of days without asthma, assuming a correlation of 0.9 between adjacent 2-week blocks that decays exponentially as the time between blocks increase.

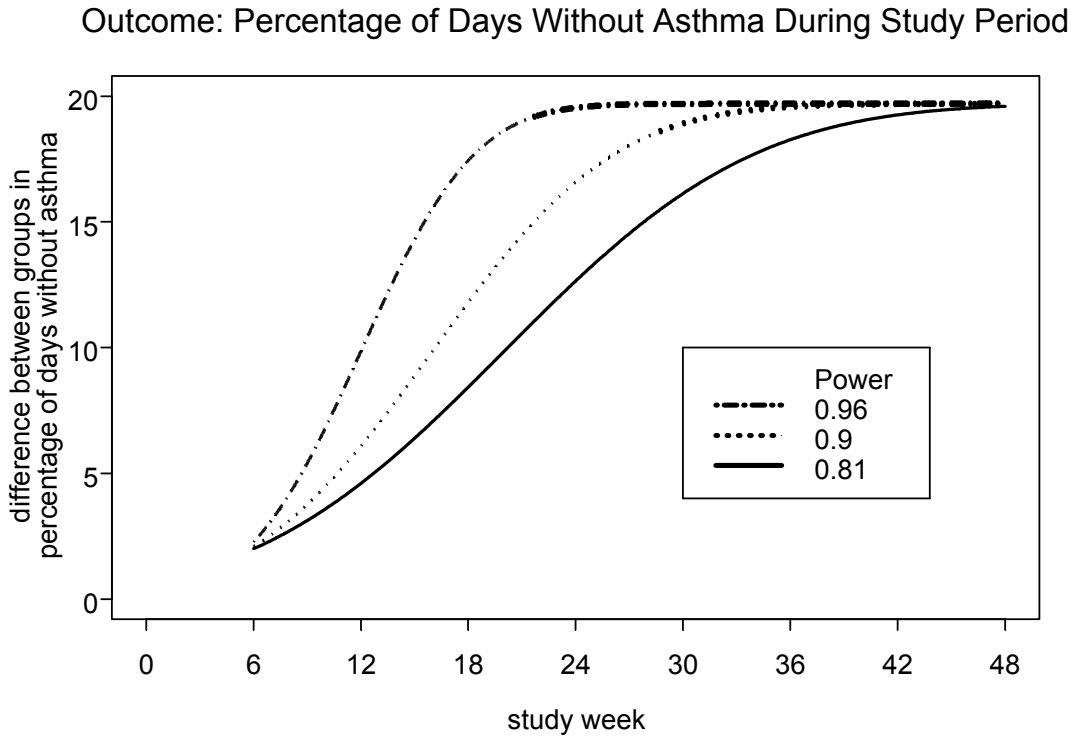
The four panels in Figure 2 below show the statistical power (with 85 subjects per group) for detecting differences in several of the secondary outcomes over a range of potential effect sizes. It appears that the proposed study design will have adequate power to detect a difference in change from baseline to end of study as small as

- 33 liters/minute for morning peak flow
- 5% for FEV percent predicted
- 0.18 for mean symptom score (CAMP definition)
- 0.6 for exacerbation rate per year

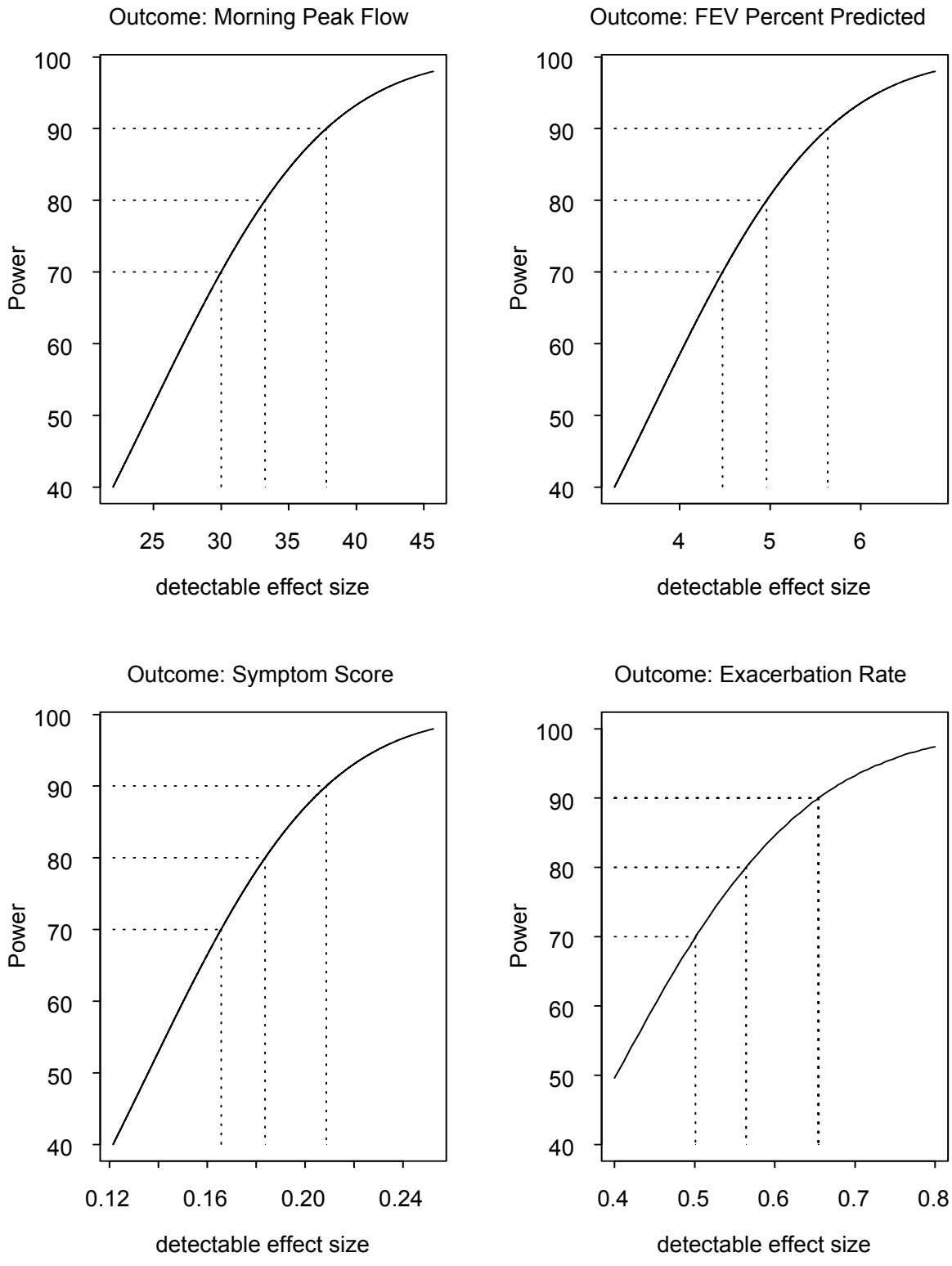
To account for as much as a 15% loss of randomized subjects due to withdrawal, a total of 100 randomized subjects are needed in each treatment arm. Thus, each of the five Clinical Centers will randomize 60 participants (20 each in the fluticasone, fluticasone/salmeterol and montelukast groups).

G. <u>Figure 1: Study power for primary outcome</u>





H. Figure 2: Study power for secondary outcomes



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XI. Appendix

A. Table 1: Summary of the Most Common Clinical Adverse Effects, Regardless of Causality, Among Pediatric Patients in Montelukast Trials

Knorr B et al. Montelukast, a Leukotriene Receptor Antagonist, for the Treatment of Persistent Asthma in Children Aged 2 to 5 years. Pediatrics 2001; 108 (3): 1-10.

ADVERSE EFFECT	PLACEBO (N= 228)	MONTELUKAST (n = 461)
Upper respiratory infection	63 (28%)	123 (27%)
Fever	61 (27%)	125 (27%)
Vomiting	45 (20%)	75 (16%)
Pharyngitis	35 (15%)	54 (12%)
Cough	26 (11%)	58 (13%
Abdominal Pain	21 (9%)	51 (11%)
Diarrhea	17 (8%)	45 (10%)
Lab adverse effects (≥ 1)	12 (5.4%)	16 (3.5%)

Williams B. et al. Clinical Safety and Tolerability of Montelukast, a Leukotriene Receptor Antagonist, in Controlled Clinical Trials in Patients ≥ 6 years (Phase III Studies 6-14 year olds). Clinical and Experimental Allergy 2001; 31:77-87.

ADVERSE EFFECT	PLACEBO (N=135)	MONTELUKAST (N=201)
Upper respiratory infection	40 (29.6%)	48 (23.9%)
Headache	29 (21.5%)	38 (18.9%)
Pharyngitis	17 (12.6%)	28 (13.9%)
Abdominal Pain	14 (10.4%)	10 (5.0%)
Influenza	6 (4.4%)	17 (8.5%)
Cough	10 (7.4%)	12 (6.0%)
Fever	5 (3.7%)	15 (7.5%)
Nausea	5 (3.7%)	8 (4.0%)
Vomiting	6 (4.4%)	3 (1.5%)

ADVERSE EFFECT	MONTELUKAST 5 MG (N=207)
Upper respiratory infection	117 (56.5%)
Headache	68 (32.9%)
Pharyngitis	54 (26.1%)
Sinusitis	42 (20.3%)
Cough	40 (19.3%)
Fever	31 (15.0%)
Abdominal pain	23 (11.1%)
Rash	22 (10.6%)
Nasal congestion	23 (11.1%)
Infectious gastroenteritis	21 (10.1%)
Dizziness	6 (2.9%)
Rhinorrhea	3 (1.4%)

B. Table 2: Published Comparator Trials of Controllers as First-Line Treatment of Persistent Asthma

Trial	Age Range	Entry Criteria	Treatments	Baseline	Endpoint
Busse et al JACI 2001 (24 weeks)	≥15 years μ =35 years n=533	FEV1 50-80% ≥15% BD revers. β-agonists prn only	Montelukast 10 mg qd vs. fluticasone 88 mcg bid MDI	μ FEV1 65% μ a.m. PEF (L/min) FP 349.6 (6.3) M 357.8 (6.1) % of Sx-free days FP 1.9 (0.5) M 2.3 (0.4) % rescue-free days FP 2.5 (0.4) M 2.5 (0.4)	Δ FEV1 FP 22.87 (1.41) M 14.47 (1.29) p<0.001 Δ a.m. PEF (L/min) FP 68.5 (5.2) M 34.1 (4.2) p< 0.001 Δ % of Sx-free days FP 32.0 (2.5) M 18.4 (2.1) p < 0.001 Δ % Rescue-free days FP 45.9 (2.5) M 31.2 (2.3) p < 0.001
Calhoun et al Am J Resp Crit Care Med 2001 (12 weeks)	≥15 years μ = 37 years n = 423	FEV1 50-80% ≥12% BD revers. β-agonists prn only	Montelukast 10 mg qd vs. Advair® 100/50 bid	μ FEV1 67% μ a.m. PEF (L/min) A 383.0 (8.0) M 365.6 (7.4) % Sx-free days A 3.9 (0.7) M 5.8 (1.0) % Rescue-free days A 5.9 (1.1) M 6.8 (1.2)	Δ FEV1 A 22.8 (1.3) M 11.4 (1.3) p≤0.001 Δ a.m. PEF (L/min) A 89.9 (6.7) M 34.2 (4.7) p≤0.001 Δ % of Sx-free days A 48.9 (2.9) M 21.7 (2.5) p≤ 0.001 Δ % Rescue-free days A 53.0 (2.8) M 26.2 (2.5) p≤ 0.001

C. Table 3: Ongoing Comparison Trials of Controller Therapies in Mild-Moderate Persistent Asthma

Trial	Age Range	Duration	Entry Criteria	Treatments	Outcomes
MIAMI (Merck)	15-85 years	12 weeks blinded then 36 weeks open-label	FEV_1 ≥ 80% ≥12% BD revers. or PC_{20} ≤12.5mg/ml or EIB (+) Sx and β-agonist use ≥ 2 days/week and ≤ 6 days/week (over 2 weeks) β-agonists prn only	Montelukast 10 mg qd vs. fluticasone 88 mcg bid MDI	Primary: % rescue –free days Secondary: Sx, QOL, FEV_1, nocturnal awakenings, asthma attacks, adverse drug reactions
Merck – IMPACT (Merck)	15-65 years	48 weeks	FEV_1 50-90% ≥12% BD revers. Inadequate control after 4 weeks of fluticasone 200 mcg/day	Addition of montelukast 10 mg qd vs. salmeterol 100 mcg qd	% of patients experiencing at least one asthma attack
ACRN – IMPACT (NHLBI)	18-65 years	18 months	FEV_1 ≥80% ≥12% BD revers. or PC_{20}≤ 8 mg/ml Mild persistent asthma as per NAEPP criteria β-agonists prn only	Budesonide 200 mcg bid vs. zafirlukast 20 mg bid vs. placebo (each arm with open-label ICS as per Sx-based action plan)	Primary: A.M. PEF averaged over 2 weeks Secondary: FEV_1, pharmacoeconomics, PC_{20}, ENO, asthma control, asthma exacerbations