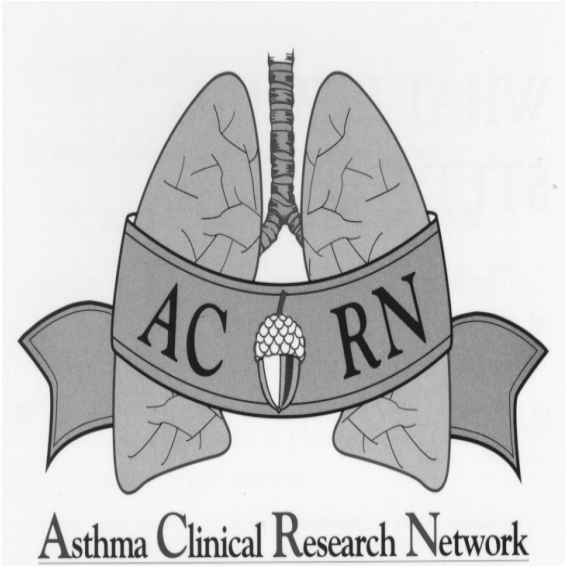

IMProving Asthma Control Trial

(IMPACT)

Study Protocol

A study of patients with mild, persistent asthma comparing the effects of 18 months of treatment with an inhaled corticosteroid taken only "as needed," with an inhaled corticosteroid taken regularly, and with an oral leukotriene receptor antagonist taken regularly.

Version 9.8

DECEMBER 1, 2000

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I. PRINCIPAL HYPOTHESIS TO BE TESTED

Proposed Null Hypothesis: In patients with **mild, persistent asthma*,** continuous, daily treatment for 12 months with: (1) inhaled and oral placebos, (2) an inhaled corticosteroid, or (3) an oral leukotriene antagonist do not differ in their effects on airflow obstruction, as reflected by the change in AM peak expiratory flow (PEF).

II. ADDITIONAL HYPOTHESES TO BE TESTED

Additional Null Hypotheses:

- The three treatments do not differ in their effects on the changes over 12 months in peak expiratory flow PEF measured after a **P**eriod of **I**ntense **C**ombined **T**herapy [PICT – PEF measured after 10-16 days of treatment with prednisone (0.5 mg/kg/d), an inhaled corticosteroid (budesonide 1600 μ/d), and a leukotriene receptor antagonist (zafirlukast 20 mg bid)] and after acute administration of repeated doses of albuterol].

- None of the three treatments results in a decline in PEF over a six month period from (6 to 12 months of treatment) while on therapy.

- The three treatments do not differ in their effects on the changes over 12 months in other indicators of airway obstruction; i.e., FEV_1, FEV_1 after repeated treatment with albuterol, and FEV_1 after a PICT.

- The number of exacerbations requiring open- label inhaled corticosteroids and the number of exacerbations requiring open-label oral corticosteroids do not differ among treatment groups.

- The sum of the **direct costs** of medications taken regularly, of medications taken "as needed", of unscheduled office, emergency department, urgent care center and hospital visits, and of the **indirect costs** for days lost from work or school do not differ among treatment groups.

- Asthma control, as measured by a weighted scoring of symptoms, β-agonist use, and FEV_1 , does not differ among the three treatment groups.

* Mild, persistent asthma, is associated with one or more of the following: symptoms occurring > 2 times a week with exacerbations that may affect activity, nighttime symptoms >2 times a month, or PEF variability $\geq$20% an FEV_1 or PEF $\geq$ 70% predicted (see Sect VI A).

- The changes in the indicators of airflow obstruction (AM PEF, PICT PEF, FEV_1, post-albuterol FEV_1 and PICT FEV_1) are unrelated to the degree of bronchial reactivity, the percentage of eosinophils in induced sputum samples, and the concentration of nitric oxide (NO) in exhaled air before therapy is started and are also unrelated to the changes in these indices of airway inflammation over three or eighteen months of treatment.

- In patients with mild, persistent asthma, changes in the values for the indicators of airflow obstruction, for "asthma control," and for "asthma related quality of life" over 12 months of randomized treatment are unrelated to variations in genetic loci thought to be related to asthma or its severity; e.g. in the promotor regions for IL-4 and 5-LO.

III. BACKGROUND AND RATIONALE

The National Institutes of Health "Guidelines for the Diagnosis and Management of Asthma" recommend daily treatment with an anti-inflammatory controller medication for mild persistent asthma.[1] This recommendation was prompted by studies reporting that improvements in indices of airway obstruction (PEF or FEV_1) and in bronchial reactivity were significantly lower in patients not treated with an "anti-inflammatory medication" – in these cases an inhaled corticosteroid. Further, these studies suggested that when inhaled corticosteroid (ICS) therapy was delayed, rather than started soon after the appearance of asthma symptoms, patients might not "catch up" in terms of final airway function.[2-6] Although conducted as prospective, double-blind studies, certain limitations of these studies restrict the group of asthmatics to which the study findings can be applied and raise questions concerning how the findings should be interpreted. Some of these limitations are as follows:

1. Some of the subjects examined in these studies had asthma more severe than "mild, persistent asthma" as defined by the NAEPP Guidelines.

2. The differences in FEV_1 and PC_{20} associated with active treatment were small on average and do not appear to have occurred in all subjects. Judging from the variances reported, the differences in mean FEV_1 and PC_{20} appear to have been driven by a sub- group of subjects.

3. Only small and often statistically insignificant differences in clinical outcomes were reported in the study groups in whom deteriorations in tests of airway caliber occurred.

4. It has not been examined whether the deteriorations in FEV_1 and PC_{20} persisted after intense treatment with corticosteroids and bronchodilators. ...It is, thus, not known whether these deteriorations were easily reversible or reflected "remodeling" of the airways.

The recommendation that patients with mild, persistent asthma be treated daily with an ICS was thus not strictly "evidenced based." It was instead derived from the best opinion of asthma experts working with a limited set of data. The essential concern of the experts was that the small differences reported to occur when inhaled corticosteroid treatment was delayed indicated an increased risk of developing symptomatic irreversible airflow obstruction, now known to be a consequence of chronic asthma in some patients.[6-9] Whether the small changes in airway function would occur in the group of mild-persistent patients as defined by the NAEPP (who have normal airway function at baseline), and to whom the recommendation of continuous treatment was extended, is unclear. The changes in health care utilization associated with such small changes in airway function is also unclear. Further, whether the small decrements in FEV_1 (noted in subjects in whom ICS therapy had been "delayed") were reversible with a short course of intense therapy was not determined. Whether such changes would occur to a greater or lesser extent with leukotriene modifiers, and whether a delay in initiation of treatment with those drugs is of importance, is also unknown.

We, therefore, propose in this study to examine patients who meet at least the NAEPP criteria for mild, persistent asthma and to analyze whether changes in airway function occur in this population. Additionally, we will examine the effect of these different treatments on the use of health care resources, symptoms adjusted according to validated symptom utility indices, symptom-free days, and standardized quality of life scores. Further, we intend not only to analyze changes in the "baseline" airway function; i.e., PEF and FEV_1 obtained without prior treatment with bronchodilators but also changes in airway function after a **P**eriod of **I**ntense **C**ombined **T**herapy (PICT) which we have defined as the value measured after 10-16 days of treatment with – prednisone 0.5 mg/kg/day (maximum dose = 50 mg/day), a high dose of an ICS (budesonide 1600 μg/day), an LT-receptor antagonist (zafirlukast 20 mg bid), and after acute administration of up to eight puffs of albuterol.

Population studies of elderly, non-smoking asthmatics show that some have developed chronic, apparently irreversible, airflow obstruction. The proportion of asthmatics who develop such changes is unknown, and it is also unknown whether those at risk can be identified by an easily measurable marker of disease activity. An aim of this study is to examine the relationship between the change in PEF over time (whether on or off continuous therapy) and bronchial reactivity and pathobiologic markers of bronchial inflammation. Tests of airway caliber at entry, e.g., FEV_1, bronchial reactivity (PC_{20}), markers of airway inflammation (sputum eosinophil percent;

exhaled NO), and markers of sensitization to environmental allergens (skin test reactions, serum lgE levels, blood eosinophils), as well as the changes in these markers observed during the first 3 months of treatment and/or after 12 months of treatment will be examined.

Further complicating an easy determination of the best treatment for mild, persistent asthma is the NAEPP guidelines' recommendation that regular treatment with a leukotriene antagonist can be used as an alternative to regular treatment with an ICS. Leukotriene antagonists have been shown to reduce the incidence of steroid-requiring exacerbations, and some studies have suggested that they can be used to reduce or substitute for ICS.[10-13] They are available in oral formulation. Oral leukotriene antagonists are now commonly prescribed for patients with asthma, possibly because patients have been shown to be more likely to comply with regular oral therapy than with regular inhaled therapy.[14] Studies of renewal patterns for ICS prescriptions indeed suggest that most patients do not take them regularly.[15]

Considering the limitations of the studies upon which the recommendations for treatment of mild, persistent asthma were based, several questions present themselves—

1. Do patients with mild, persistent asthma require continuous therapy, or is intermittent "as needed" anti-inflammatory therapy acceptable?

2. If there are advantages to continuous therapy, does an LT-receptor antagonist produce effects that differ from those of an inhaled corticosteroid?

3. Does a temporal delay in the initiation of these treatment regimens in patients with mild, persistent asthma result in chronic, persistent airway obstruction that cannot be fully reversed with a period of intense combined treatment?

4. Does any distinguishing characteristic identify patients with mild, persistent asthma who develop large changes in PEF or FEV_1 over one year, before or after PICT?

The question as to whether mild persistent asthma requires daily "controller" therapy is important. The direct costs of the increased use of medication can be calculated by making a few assumptions. The first is that roughly 30% of the 15 million Americans with asthma have "mild, persistent asthma." Additional assumptions are as follows: 1) about two canisters of an ICS are needed per year when they are taken on an "as needed" basis; i.e., for 1-2 weeks when symptoms interfere with function, stopping the treatment after symptoms subside; 2) 12 canisters will be needed each year when they are taken regularly; and 3) the average cost of an ICS canister is $45. With these assumptions, the cost of compliance with the recommendation that an ICS

be used daily would increase expenditures by over $2 billion per year. It is not known whether the benefits of long-term ICS treatment of mild, persistent asthma justify this expense. It is the purpose of this protocol to answer these questions, and those outlined above, to provide an objective basis for making treatment recommendations for mild, persistent asthma.

IV. SPECIFIC AIMS

Principal Aims:

(1) To determine whether subjects with mild, persistent asthma differ in their change in AM PEF after 12 months of treatment with oral and inhaled placebos (**continuous placebo**), with a standard, low dose of an ICS and an oral placebo (**continuous inhaled corticosteroid**), or with a standard, daily dose of an LT-receptor antagonist and an inhaled placebo (**continuous oral leukotriene antagonist**), when all subjects are allowed to use inhaled albuterol on an "as needed" basis for relief of symptoms and short courses of inhaled or oral corticosteroids for exacerbations.

(2) To determine whether the three treatment regimens differ in their effect on the change in PEF after a10-16 day period of intense combined treatment (PICT) with prednisone, budesonide, zafirlukast and acute repeated treatment with albuterol.

(3) To determine whether subjects with mild asthma have a decline in PEF over a six month period while on therapy (6 to 12 months of treatment).

(4) To determine whether the three treatment regimens differ in their effect on the change in other indicators of airway obstruction; i.e. FEV_1, FEV_1, after repeated treatment with albuterol, and FEV_1 after a 10-16 day period of intense combined treatment (PICT) with prednisone, budesonide, zafirlukast and acute repeated treatment with albuterol.

(5) To determine whether the three treatment regimens differ in their effect on the number of exacerbations requiring open-label inhaled corticosteroids and the number of exacerbations requiring open-label oral corticosteroids.

(6) To determine whether the three treatment regimens differ in their effect on the estimated annual cost of care for asthma. These costs will include direct costs for medications, unscheduled office visits, emergency department/urgent care visits, and hospitalizations, and also the indirect costs for days lost from work or school.

(7) To determine whether the three treatment regimens differ in their effect on

asthma control. Asthma control will be assessed by validated asthma control questionnaires.[16]

Secondary Aims:

To determine the relationship between various markers of airway inflammation and the changes in the indicators of airflow obstruction of the 12 months of randomized treatment. These markers will include:

(1) The degree of bronchial reactivity (as measured by PC_{20}) at baseline
(2) The degree of bronchial reactivity after 3 and 12 months of randomized treatment
(3) The degree of sputum eosinophilia (sputum eosinophil %) at baseline
(4) The degree of sputum eosinophilia (sputum eosinophil %) after 12 months of randomized treatment
(5) The change in FEV_1 over the first 3 months of randomized treatment
(6) The concentration of NO in exhaled air at baseline, and after 3 and 12 months of treatment

Other Aims:

We also propose to examine the relationships between the changes in the indicators of airflow obstruction after the 12 months of randomized treatment and markers of allergic sensitization at baseline. These markers will include eosinophil numbers in blood, serum levels of IgE, and the number of positive skin tests. Our interest in these relationships derives from the widespread assumption that "irreversible airflow obstruction" or "airway wall remodeling" result from chronic or recurrent eosinophilic inflammation of the airways.

Finally, we will examine the relationships between the changes in the indicators of airflow obstruction to genetic markers of predisposition to asthma or to greater asthma severity. To enable this examination, genomic DNA will be isolated from each subject and will be examined for mutations in the known promoter regions for the IL4 and 5-LO genes and other allelic variations that appear to contribute to asthma pathobiology as they are proposed over the course of the study.

V. PROTOCOL OVERVIEW

A 15-month study with 12 scheduled visits is proposed. After an eight week run-in period, subjects who meet at least the NAEPP criteria for mild, persistent asthma (see below, section VI A) will be assigned to one of three treatment arms for 12 months: daily oral placebo and twice daily inhalation of placebo from a turbuhaler (placebo treatment); daily oral placebo and twice daily inhalation of 200 μg budesonide (regular inhaled corticosteroid treatment), and zafirlukast 20 mg bid and twice daily inhalation of placebo (regular oral leukotriene antagonist treatment). Subjects in all treatment arms will be instructed to take short courses of an inhaled corticosteroid or prednisone on an "as needed" basis as guided by a symptom based action plan (see subsection A, "Treatments" in section VII). Treatment assignment will be made by a double blind randomized parallel group design, stratified by center. Within each center, an adaptive randomization scheme will be invoked in order to ensure balance across treatment arms with respect to PC_{20}, age and race. This will provide equal representation of subjects with mild ($PC_{20} \geq 1$ mg/ml) and more severe ($PC_{20} < 1$ mg/ml) bronchial reactivity, with ages less than and greater than 25 years, and with racial categorization as African-American (reported to have a higher prevalence of polymorphism at the 5-LO promoter locus) and non African-American in each treatment group.

The protocol can be viewed as consisting of two phases: a run-in period of eight weeks ending with a short Period of Intense Combined Therapy (PICT, an open oral prednisone + ICS + oral LT-receptor antagonist treatment phase of approximately 10-16 days duration + acute administration of up to eight puffs of albuterol), and a blinded treatment phase of 12 months once again terminating with a PICT.

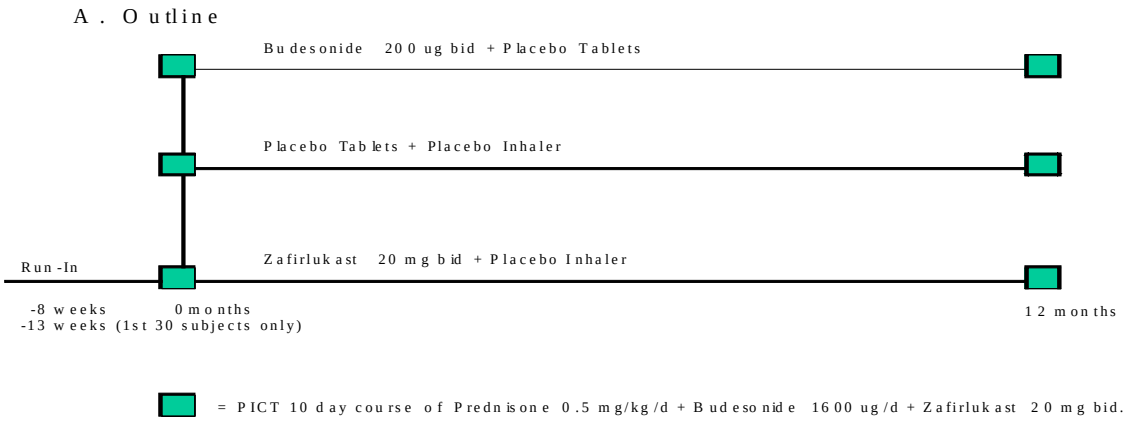
In the run-in phase, subjects will make five visits to the clinic. The purposes of these visits are first to determine that the subjects have mild, persistent asthma and qualify for inclusion in the study, and second to obtain baseline data on the outcomes to be followed. At the end of the run-in, all subjects will receive a PICT. This treatment will consist of prednisone, 0.5 mg/kg/day, a high dose of an ICS (budesonide 1600 μg/d), and a standard daily dose of zafirlukast 20 mg bid, for at least 10 days followed by acute administration of up to 8 puffs of albuterol until the maximal value for FEV_1 is measured.

In the active treatment phase, subjects will be randomized to one of the three treatment arms and will be seen at least every three months and will be called midway between visits. At the end of 12 months of treatment, a period of intense combination therapy will again be given to determine airway function after the PICT.

In addition, the first 30 patients to be enrolled will undergo an extended run-in phase of 13 weeks duration (an additional 5 weeks of run-in) to assess our symptom-based action plan. Since this plan determines the frequency of inhaled corticosteroid therapy for exacerbations, we wish to assure ourselves that it does not result in a

frequency of ICS use in the placebo group that would make it difficult to distinguish the placebo group from the intervention groups due to an overuse of ICS for “symptom based exacerbations.”

Details on the run-in and treatment phases are described below, after presentation of the overall study schematic.



B. Study Protocol Detail

1. Run-In Phase

				DR AWR eDEM-C Tur-C SBAP-R AQLQ(S) ACQ	
PT Med Hx SE Blood-G S Mch SBAP-E eDEM-I DD+MW-I	 DR MW-R eDEM-C SBAP-R S	DR MW-R eDEM-C Tur-C SBAP-R AWD Max Rev LE Skin Test	** DR AWR eDEM-C SBAP-R S	SFDQ ASUI HUR UG/BP PT BLOOD-E S/NO Mch SI	DR, CD AWR/CAW eDEM-C Tur-C SBAP-R PAEQ UG/BP S Max Rev
Inhaled Placebo and Oral Placebo				Prednisone + high dose Budesonide + Zafirlukast	

V	1	2	3	4**	5	6
W	8	6	-4		-1.5	0

Standard Run-In

Extended Run-In: -13 -11 -9 -6 1.5 0

** 1st 30 Subjects only

ACQ = Asthma Control Questionnaire; **AQLQ(S)** = Asthma Quality of Life Questionnaire; **ASUI** = Asthma Symptom Utility Index; **AWD** = AirWatch™ Dispensed; **AWR** = AirWatch™ Review; **Blood** = Blood Test for Serum IgE and Blood Eosinophil% and Genetic Analysis;**Blood-G**=Blood for Genetic Analysis: **CAW** = Collect AirWatch™ Device; **CD** = Collect Symptom Diary; **DD+ MW** = Dispense Symptom Diary; **DR**=Symptom Diary Review; **eDEM-C**=eDEM Monitor-Check Compliance; **eDEM-I**=eDEM Monitor Instruction; **HUR**-Healthcare Utilization

Review; **LE**=Long Exam; **MAX REV**=Maximum Reversibility; **Mch**=Methacholine Challenge; **Med Hx**=Medical History; **MW-I**=MiniWright™ Instruction; **MW-R**=MiniWright™; Review; **PAEQ** = PICT Adverse Event Questionnaire; **PT**=Pregnancy Test; **S**=Spirometry; **SBAP-E**=Symptom Based Action Plan Explained; **SBAP-R**=Symptom Based Action Plan Reviewed; **SE**=Short Exam; **SFDQ**=Symptom Free Day Questionnaire; **SI**=Sputum Induction; **Skin test**=Allergen Prick Skin Testing; **S/NO**=Spirometry and Exhaled Nitric Oxide Measurement; **Tur- C**=Turbuhaler/ Check Compliance; **UG/BP**=Urine Test for Glucose and Blood Pressure; **V**=Visit; **W**=Week.

Study Visits

1. Week (-8 weeks standard run-in; -13 weeks extended run-in)
   a. Informed consent.
   b. Pregnancy Test.
   c. Medical History – Short Exam.
   d. Blood for genetic analysis.
   e. Spirometry.
   f. Methacholine challenge (to confirm diagnosis of asthma; done only if subjects not known to have reversible airflow obstruction or bronchial hyperreactivity).
   g. Symptom-based action plan explained. Open label Pulmicort + prednisone dispensed.
   h. Inhaler technique reviewed and rescue medication (albuterol) refills dispensed as needed throughout remainder of trial.
   i. eDEM Monitor Instruction.
   j. Placebo medications (inhaler and tablets) dispensed.
   k. Asthma symptom diary dispensed.
   l. MiniWright™ peak flow meter dispensed and appropriate technique taught.

2. Week (-6 weeks standard run-in; -11 weeks extended run-in)
   a. Review of symptoms and peak flow on diary.
   b. Review of medication use.
   c. Review MiniWright™ peak flow data for compliance.
   d. eDEM Monitor – Check Compliance.
   e. Symptom based action plan review.
   f. Spirometry.

3. Week (-4 weeks standard run-in; -9 weeks extended run-in)
   a. Review of symptoms and peak flow on diary.

b. Review of medication use.
c. Review MiniWright™ peak flow data for compliance.
d. eDEM Monitor – Check Compliance.
e. Turbuhaler – Check Compliance.
f. Symptom based action plan-review.
g. AirWatch™ dispensed and appropriate technique taught.
h. Spirometry.
i. Diagnosis of asthma severity based on spirometry, peak flow, and symptoms. Subsequent procedures and visits only done if subject has mild, persistent asthma and has demonstrated compliance with study procedures. Clinic coordinator discretion to continue with run-in (no PICT) to determine eligibility.
j. Spirometry after bronchodilator. (Max Rev)
k. Long Exam
l. Allergen skin tests.

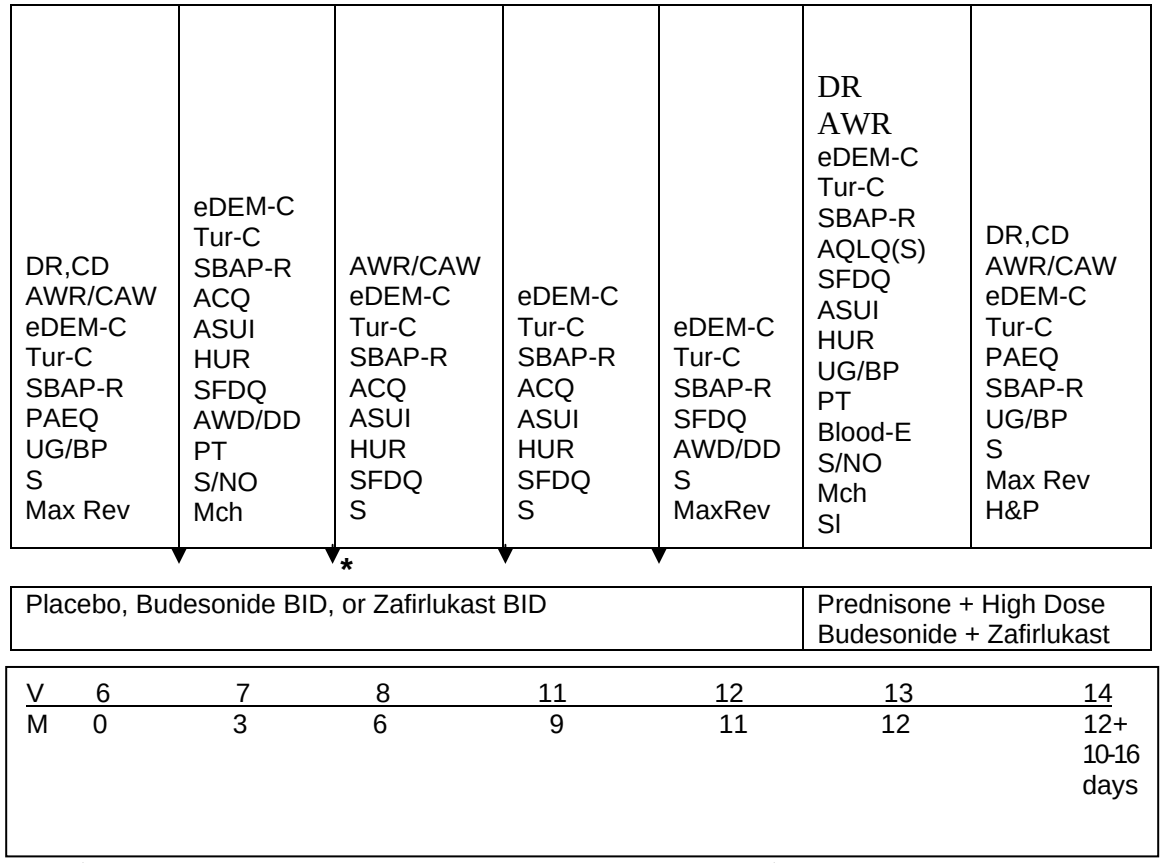
4.** Extended run-in only 1st 30 subjects
a. Review of symptoms and peak flow on diary.
b. Review of medication use.
c. Review AirWatch™ peak flow data for compliance.
d. eDEM Monitor – Check Compliance.
e. Symptom based action plan review.
f. Spirometry.

5. (-10 days)
a. Review of symptoms and peak flow on diary.
b. Review AirWatch™ peak flow data for compliance.
c. eDEM Monitor – Check Compliance.
d. Turbuhaler – Check Compliance.
e. Symptom based action plan – review.
f. Asthma Quality of Life Questionnaire.
g. Asthma Control Questionnaire.
h. Symptom Free Day Questionnaire.
i. Asthma Symptom Utility Index Review.
j. Healthcare Utilization Review.
k. Urine test for glucose/Blood pressure.
l. Pregnancy Test.
m. Blood test for lgE level and eosinophil %.
n. Spirometry
o. Exhaled nitric oxide.
p. Methacholine challenge.
q. Sputum induction.

r. Stop placebo medications.
s Start prednisone, high dose budesonide and zafirlukast 20 mg bid for 10 -16 days. (PICT)

6. Week 0/Month 0.
   a. Review of symptoms and peak flow on diary. Collect diary.
   b. Review AirWatch™ peak flow data for compliance. Collect AirWatch™ device.
   c. eDEM Monitor – Check Compliance.
   d. Turbuhaler – Check Compliance.
   e. Review of medication use.
   f. Stop high dose combination treatment.
   g. Symptom based action plan – review.
   h. PICT Adverse Event Questionnaire.
   i. Urine test of glucose/Blood pressure.
   j. Spirometry.
   k. Spirometry after Bronchodilator. (Max Rev)
   l. Remind subject of the right to withdraw from study.
   m. Randomize eligible subjects.
   n. Dispense trial medications.

2. Randomization Phase



↓ interim phone call (six weeks after prior visit); ↓*remind to monitor peak flow; **ACQ**=Asthma Control Questionnaire; **AQLQ(S)**=Asthma Quality of Life Questionnaire; **ASUI**=Asthma Symptom Utility Index; **AWD**=AirWatch™ Dispense; **AWR/CAW**=AirWatch™ Review and Collect AirWatch™ Device; **Blood – E**=Blood for Eosinophil%;**CD**=Collect Diary; **DD**=Dispense Symptom Diary; **DR**=Symptom Diary Review; **eDEM-C**=eDEM Monitor Check Compliance; **H&P**=History and Physical; **HUR**=Healthcare Utilization Review; **Mch**=Methacholine Challenge; **M**=Month; **Max Rev**=Maximum Reversibility; **PAEQ**= PICT Adverse Event Questionnaire; **PT**=Pregnancy Test; **S**=Spirometry; **SBAP-R**=Symptom Based Action Plan Review; **SFDQ**=Symptom Free Day Questionnaire; **SI**=Sputum Induction; **S/NO**=Spirometry and Exhaled Nitric Oxide Measurement; **Tur-C**=Turbuhaler-Check Compliance; **UG/BP**=Urine Test for Glucose and Blood Pressure; **V**=Visit.

Study Visits

7. Month 3
   a. Review of medication use/dispense medications.
   b. eDEM Monitor – Check Compliance.
   c. Turbuhaler – Check compliance.
   d. Symptom based action plan review.
   e. Asthma Control Questionnaire.
   f. Asthma Symptom Utility Index.
   g. Healthcare Utilization Review.
   h. Symptom Free Day Questionnaire.
   i. AirWatch™ dispensed/symptom diary dispense (six weeks after visit)
   j. Pregnancy Test.
   k. Spirometry/Exhaled Nitric Oxide.
   l. Methacholine Challenge.

8. Month 6
   a. AirWatch™ Review – Collect Airwatch™.
   b. Review of medication use/dispense medications.
   c. eDEM Monitor – Check Compliance.
   d. Turbuhaler – Check Compliance.
   e. Symptom based action plan review.
   f. Asthma Control Questionnaire.
   g. Asthma Symptom Utility Index.
   h. Healthcare Utilization Review.
   i. Symptom Free Day Questionnaire.
   j. Spirometry.

11. Month 9
   a. Review of medication use/dispense medications.
   b. eDEM Monitor – Check Compliance.
   c. Turbuhaler – Check Compliance.
   d. Symptom based action plan review.
   e. Asthma Control Questionnaire.
   f. Asthma Symptom Utility Index.
   g. Healthcare Utilization Review.

h. Symptom Free Day Questionnaire.
i. Spirometry.

12. Month 11
    a. Review of medication use/dispense medications.
    b. eDEM Monitor – Check Compliance.
    c. Turbuhaler – Check Compliance.
    d. Symptom based action plan review.
    e. Symptom Free Day Questionnaire.
    f. Distribute AirWatch™ device –Dispense Diary.
    g. Spirometry.
    h. Spirometry after Bronchodilator. (Max Rev)

13. Month 12
    a. Review of symptoms and peak flow on diary.
    b. Review AirWatch™ peak flow data for compliance.
    c. Review of medication use/dispense medications.
    d. Diary Review.
    e. eDEM Monitor – Check Compliance.
    f. Turbuhaler – Check Compliance.
    g. Symptom based action plan – review.
    h. Asthma Quality of Life Questionnaire.
    i. Asthma Control Questionnaire.
    j. Symptom Free Day Questionnaire.
    k. Asthma Symptom Utility Index.
    l. Healthcare Utilization Review.
    m. Urine for Glucose/Blood pressure.
    n. Pregnancy Test.
    o. Blood Test for IgE Level and Eosinophil%.
    p. Spirometry/Exhaled Nitric Oxide.
    q. Methacholine Challenge.
    r. Sputum Induction.
    s. Start prednisone, high dose budesonide and zafirlukast 20 mg bid for 10 –16 days. (PICT)

14. Month 12 + 10 – 16 Days.
    a. Review of Medication Use.
    b. AirWatch™ Review/Collect AirWatch™.
    c. Diary Review – Collect Diary.

d. eDEM Monitor – Check Compliance
e. Turbuhaler – Check Compliance.
f. PICA Adverse Event Questionnaire.
g. Symptom Based Action Plan Review.
h. Urine for Glucose/Blood Pressure.
i. Spirometry.
j. Spirometry after Bronchodilator. (Max Rev)
k. History and Physical.
l. Discharge from study.

VI. SUBJECTS

This study will require a total of 234 adults with mild, persistent asthma. In order to permit generalizability of the findings to the United States population of people with asthma, these patients will be appropriately distributed by gender (50% female) and by ethnicity (33% ethnic minority). Both heterogeneity of the study group and rapidity of recruitment are greatly facilitated by the involvement of several geographically dispersed study sites in a multicenter collaboration. Subjects will be recruited from the "standing" populations of the participation centers, by advertisement, and by referral from participating physicians. The ACRN Data Coordinating Center (DCC) will distribute monthly accrual reports for each clinical center, listing patients entered by age, gender, and ethnicity. This routine monitoring will allow early identification and resolution of potential problems in achieving demographic goals.

Potential subjects who appear on initial screening to qualify for the study will be evaluated by spirometry at the first visit. A methacholine challenge will be done only if the subject is not known to have $\geq$12% and $\geq$200 ml improvement in FEV_1 after bronchodilator administration or a $PC_{20} < 16$ mg/ml from testing within the previous two months. At this visit, they will also be instructed in the use of a portable peak flow device (MiniWright/AirWatch™), in the use of an albuterol metered dose inhaler for relief of symptoms on an as needed basis, and in the completion of a diary of asthma symptoms, nocturnal wakenings, albuterol use, and AM and PM peak flow. Subjects will also be given a placebo-dispensing inhaler that resembles the ICS inhaler and an oral placebo that resembles the LT-receptor antagonist and will be instructed to take one puff of the inhaler each morning and evening and a regular dose each morning and evening of the tablets. All subjects will be seen again two weeks later for spirometry, review of their understanding and performance of measuring peak flow and recording information in the asthma diary, and their compliance with taking oral and inhaled placebo medications. Subjects will be seen again two weeks later (four weeks after enrollment) and will be continued in the study only if the severity of symptoms, number of nocturnal wakenings, frequency of albuterol use, variability of peak flow values, and FEV_1 indicate they have mild, persistent asthma. Subjects will also be continued only if

their diary records of inhaler (budesonide placebo) use, their MiniWright/AirWatch™ peak flow records, determination of Turbuhaler use by handclicks and their eDEM monitor records of taking oral medication (zafirlukast placebo) indicate an adherence rate of ≥ 70% for each activity over the previous two weeks. If a subject fails to meet this standard, the coordinator may decide to re-instruct the subject and have him/her return for an additional (un-numbered) visit two weeks later or simply return at scheduled visit 5. The subject should then be continued in the study only if their records indicate an adherence rate of ≥ 70% for all three activities.

A. Inclusion and Exclusion Criteria

Subjects who appear by their history of symptom frequency and severity, β-agonist use, and baseline spirometry to have mild persistent asthma will be evaluated in an eight-week run-in period. Only subjects whose symptoms, PEF measurements, "as needed" β-agonist use and spirometry indicate that they have mild, persistent asthma over the first four weeks will be continued in the study.

1. Inclusion Criteria

a. Male and female subjects 18 to 65 years of age. A goal of 50% female and 33% minority subjects will be incorporated in recruitment.
b. History of asthma.
c. Heightened airway reactivity, shown by reversible airflow obstruction ≥ 12% or by methacholine PC_{20} < 16 mg/ml.
d. Baseline FEV_1 ≥ 70% of predicted, after withholding bronchodilator and restricted medications per Manual of Operations.
e. Diary data over four weeks of observation in the run-in period indicating mild, persistent asthma, defined as any of the following: asthma symptoms > 2 times per week; nocturnal wakenings from asthma > 2 per month or PEF variability ≥ 20%.
f. Nonsmoker (< 10 pack-years and no smoking within the previous year).
g. For heterosexually active women of child-bearing age, agreement to use reliable form of contraception (tubal ligation, oral contraceptive, single barrier method, stable partner with vasectomy) for the duration of the study.
h. Willingness to provide informed consent, as evidenced by signing a copy of the consent form approved by the Institutional Review Board of the subject's respective study institution.
i. Compliance described above.

2. Exclusion Criteria

a. Asthma more or less severe than “mild, persistent” asthma, as defined above.
b. Presence of lung disease other than asthma.
c. Significant medical illness other than asthma in particular, Cushings, Addison’s and hepatic disease or concurrent medical problems that could require oral prednisone during the study.
d. History of respiratory tract infection within the six weeks prior to screening visit.
e. History of a life-threatening asthma exacerbation requiring intubation and/or mechanical ventilation within 10 years.
f. Receiving hyposensitization therapy other than an established maintenance (continuous for three months duration or longer) regimen.
g. Pregnancy or lactation.
h. Inability, in the opinion of the study investigator, to coordinate use of powder or MDI inhalers or to comply with medication regimens or with the procedures of the study.
i. Use of inhaled or oral corticosteroids within the previous six weeks.
j. Two or more emergency department visits for asthma in the past year.
k. Hospitalization for asthma in the past year.

VII. RANDOMIZATION TO THREE GROUPS

1. Inhaled corticosteroid by inhaler twice daily (budesonide 200 µg bid), plus an oral placebo daily (continuous inhaled corticosteroid).
2. Oral LT-antagonist daily (zafirlukast 20 mg bid) plus placebo by inhaler twice daily (continuous oral leukotriene antagonist).
3. Placebo by inhaler twice daily plus oral placebo twice daily (continuous placebo).

The randomization scheme will be stratified according to center because differences among clinical centers typically yield a large amount of variability. Within each clinical center, an adaptive randomization scheme will be invoked in order to ensure balance across treatment arms with respect to the following strata: $PC_{20} \geq$ or $<$ 1.0 mg/ml, age $\geq$ or $<$ 25 years, and ethnicity (African American or non African American). The stratification according to PC_{20} is prompted by our findings in the CIMA (colchicine for moderate asthma) study, in which we found that the degree of bronchial reactivity was a strong predictor of early exacerbation of asthma after inhaled corticosteroids were withdrawn. We expect a PC_{20} of 1.0 mg/ml to be close to the median PC_{20} value in the enrolled population because the median PC_{20} in the BAGS study was 0.7 mg/ml. By using adaptive randomization, we also hope to ensure balance across the treatment arms of other characteristics we believe may be important: age and ethnicity. The rationale for considering age to be important is that there is continued modest increase in lung volume (and hence in FEV_1) in males up to age 25; the rationale for believing ethnicity to be important is that the prevalence of

polymorphism at the 5-LO locus has been reported to be 20% in subjects of African-American ethnicity and 1% in subjects of white, predominantly European-American ethnicity.[17]

A. Treatments

The selection of the inhaled corticosteroid is based on its availability for use in the United States in a non-CFC containing formulation, and its continued availability over the period of performance of this study. Astra-Zeneca will provide budesonide turbuhalers and zafirlukast tablets as well as matched placebos.

We will use budesonide as the corticosteroid for "as needed" treatment in a higher dosage; e.g. four puffs BID, according to the symptom-based action plan. (See below.) This approach is based on reports that inhalation of a high dose of an inhaled corticosteroid is effective for treating moderately severe exacerbations of asthma.[18,19]

Throughout this study, all subjects will be instructed in a modified symptom-based action plan.[20] This plan instructs subjects to adjust their medications according to the severity of respiratory symptoms using the following guidelines:

Step 1 (Green Zone):
Symptoms and albuterol use stable.

Action: Continue "as needed" treatment with albuterol

Step 2 (Yellow Zone):
Awakening from asthma $\geq$ three times in a two-week period or on two consecutive nights, or using albuterol for relief of symptoms $\geq$ four times/day for $\geq$ two consecutive days, or

albuterol has been relieving symptoms for < four hours each treatment over a 12-hour period, or

using albuterol for relief of symptoms daily for seven days, and this use exceeds two times the weekly use of albuterol in the baseline period, or

exercise induces unusual breathlessness.

Action: Start an ICS at 4 puffs (budesonide = 800 μg) BID for 10

days and notify study coordinator. If symptoms worsen or do not improve after seven days, contact study coordinator or research center physician.

Step 3 (Red Zone):

For the previous 24 hours, daily life activities cause shortness of breath, or

breathlessness is present at rest, or

albuterol has been relieving symptoms for < two hours after each treatment over an eight hour period.

Action: Notify study coordinator or research center physician and start prednisone, 0.5 mg/kg per day for five days. If symptoms do not improve over two days, recontact study coordinator or research center physician.

Step 4 (Extra Red):

Severe shortness of breath at rest, or

difficulty talking because of shortness of breath, or

albuterol has been relieving symptoms for < one hour after each treatment over a four hour period, or does not relieve symptoms after two treatments repeated within a single hour.

Action: Use albuterol up to 4 puffs every 20 minutes if necessary and take 0.5 mg/kg of prednisone, go directly to an emergency clinic or call 911, and notify research center physician or study coordinator.

VIII. OUTCOME VARIABLES

The principal outcome to be assessed in this study is the AM PEF averaged over two weeks of daily diary entries. AM PEF will be measured daily for at least two and a half weeks prior to randomization and four weeks prior to the study end. Additionally, it will be measured for the four weeks prior to the six-month visit after randomization. The subjects will measure the AM Peak Flow using the AirWatch device, and they will record the values in a diary.

Other important secondary outcomes are the indicators of airway obstruction; i.e., PEF and FEV_1 (both recorded on a spirometer at the visit) at the end of a PICT, FEV_1, and FEV_1 after repeated treatment with albuterol,

The symptom-free day will be used as an outcome measure for the pharmacoeconomic analysis of IMPACT, as recommended by the NAEPP Task Force Report on the Cost Effectiveness, Quality of Care, and Financing of Asthma Care.[21] Since daily diary collection of symptoms is not part of this protocol, necessary estimates will be obtained by administration of a five-item Symptom-Free Day Questionnaire at six week intervals throughout the study. These five questions have been validated in other longitudinal studies for a 14-day subject recall of symptoms. As a complementary pharmacoeconomic outcome, the validated Multiattribute Asthma Symptom Utility Index[22] will also be administered at six-week intervals. This instrument has 14-day reproducibility and allows for calculation of an Asthma Symptom Utility Index score which represents patient preferences for combinations of asthma-related symptoms and side effects on a scale from worst possible state to best possible state.

Additional pharmacoeconomic endpoints to be compared among the three treatment arms of IMPACT will be the estimated cost of care, derived from the calculations of the costs for daily medications (an ICS and LTRA), for asthma exacerbations (costs of all rescue therapies, unscheduled office visits, urgent care/ER visits, days of hospitalization), and costs associated with school/work absenteeism. Information about these events will be captured by standardized questionnaires and structured interviews at each research center visit (every three months) and by telephone (in between visits at six week intervals).

Potential side effects associated with the IMPACT treatments (an ICS and LTRA) such as hoarseness, sore throat, oropharyngeal candidiasis, skin rash, gastrointestinal symptoms, arthralgias, and headache, elicited through the six-week structured interview, will be collected. Treatments for study drug-related adverse events will be assigned a cost value and included in the pharmacoeconomic analysis.

Differences among the treatment arms in overall “asthma control” will be assessed using an “asthma control score” that incorporates information about symptom frequency and severity, rescue medication use, and pulmonary function test results, and an “asthma specific quality of life” questionnaire. Both are validated instruments.[16,23]

IX. STATISTICAL ANALYSIS

A. Study Analysis:

The main outcome, AM PEF, is measured daily during the last two and a half weeks of the run-in period and daily during the last four weeks of the trial. The main research question is whether the change in AM PEF during the randomized phase differs among treatment arms.

The main secondary question is whether the change in PICT PEF differs among treatment arms.

Testing for changes across the randomized phase in PEF within each treatment arm is also a secondary question of interest. In particular we will examine the change over six months after the subjects have been in the randomized treatment for 6 months (i.e., change from 6 months to 12 months).

Other secondary questions include whether the following differ among treatment arms; (1) other indicators of airway obstruction (e.g., FEV_1, FEV_1 after repeated treatment with albuterol, and PICT FEV_1); (2) the number of exacerbations requiring open-label inhaled and /or oral corticosteroids; (3) the annual cost of care for asthma; (4) symptom-free days and (5) asthma control based on a weighted scoring system.

Changes over the randomized phase in other secondary outcomes; e.g., PC_{20} , sputum eosinophil, and exhaled NO, will also be compared among treatment arms.

The main outcome, AM PEF, will be summarized as an average over the two weeks prior to randomization, and an average over the two weeks prior to study end for each subject. An analysis of variance (ANOVA) will be used to compare the average change from randomization to study end among treatment groups. Each pairwise comparison between groups will also be tested.

More specifically, the appropriate statistical model is:

$E(Y_{ij}) = \alpha_i$

Where

i = 1,2,3, denotes treatment arm i

j = 1, . . ., n_i denotes subject within treatment arm i

Y_{ij} = change over the randomized treatment phase for subject j and treatment arm i

α_i = average change across the randomized treatment phase within treatment arm I

The main hypotheses are:

Ho: $\alpha_I = \alpha_2$

Ho: $\alpha_I = \alpha_3$

Ho: $\alpha_2 = \alpha_3$

Other effects can be included in the model, such as center, center by treatment interaction, age, baseline PC_{20}, baseline FEV_1 , duration of asthma, etc. It will be

important to include such effects and determine their impact on the treatment arm comparisons. However, for the sake of illustrating the statistical approach for this trial, these are not discussed any further.

Several of the secondary outcomes e.g., PICT PEF, PICT $FEV_{1,}$ sputum eosinophil % and blood eosinophil number and IgE level, are measured only at the time of randomization and at the end of the trial. These will also be compared using the ANOVA model.

Other secondary outcomes are measured several times during the randomized treatment phase, e.g. FEV_1, PC_{20}, blood eosinophil, asthma control, and symptom free days. These will be modeled as a mixed effects model. Longitudinal data analysis will provide the most statistical power to address the hypothesis of whether the change over the treatment period differs among treatment arms.

We will assess whether a linear parameter across time for each group is appropriate or whether a separate parameter for each group and each time point is necessary. The hypothesis of whether the change during the randomized treatment phase differs among treatment groups will be tested using the appropriate contrast of the parameter estimates. In particular, comparisons will be made between continuous ICS versus placebo, continuous ICS versus continuous zafirlukast and continuous zafirlukast versus placebo.

The appropriate statistical model (assuming a linear relationship) is

$E(Y_{ijk}) = \alpha_i + \beta_i x_{ijk}$

where

i = 1,2,3, denotes treatment arm i
j = 1, . . ., n_i denotes subject within treatment arm i
k = 1, . . .,p_{ij} denotes visit for subject j within treatment arm i
Y_{ijk} = response at visit k for subject j within treatment arm i
α_i = intercept for treatment arm i
β_i = slope for treatment arm i during the randomized treatment period
x_{ijk} = the number of weeks between visit k and visit 1 for subject j within treatment arm i

The main hypotheses to be tested for each secondary outcome are:

Ho: $\beta_l = \beta_2$
Ho: $\beta_l = \beta_3$
Ho: $\beta_2 = \beta_3$

Details for performing restricted maximum likelihood (REML) estimation and empirical generalized least squares (EGLS) estimation of the intercepts and variance

components are provided elsewhere.[24,25] Both REML and EGLS estimation are available in PROC MIXED of SAS.[26]

The number of exacerbations will be compared among treatment arms using a Fisher's exact test. The time to exacerbation will be compared using the Kaplan-Meier method.

The estimated total costs of care will be calculated for each treatment arm. The average total cost will be compared among treatment arms using an analysis of variance (ANOVA). Each pairwise comparison between arms will be made using a t-test.

B. Interim Analysis and Subject Safety

An interim analysis assessing whether the main outcome differs among treatment arms is planned at the time that half of the subjects have completed the trial. O'Brien-Fleming's adjustments of the significance level will be applied. The interim analysis will be done at the significance level of 0.005 and the final analysis of 0.048. These ensure an overall significance level of 5%.

Reports on subject accrual and safety are sent monthly to the Data Safety and Monitoring Board (DSMB). These reports include safety summaries such as frequency of withdrawals, treatment failures and significant exacerbations. In addition, DSMB members are notified immediately of all serious adverse events.

X. SAMPLE SIZE

The main hypothesis is whether the change in AM PEF from the time of randomization to the end of the trial differs among the treatment arms. There are three comparisons of interest, continuous ICS versus placebo, continuous zafirlukast versus placebo, and continuous ICS versus continuous zafirlukast. The clinically important difference in the change in AM PEF between any two treatment arms is specified to be 25 Liters/Minute. The estimate of the standard deviation of the change in AM PEF is 36.608 and was obtained from the BAGS data for subjects with $FEV_1 \geq 80\%$ and the "as needed" treatment group[27].

A total sample size of 216 is necessary to have 90% power to detect a difference of 25 Liters/Minute between any two of the three treatment arms in the change in AM PEF during the randomized treatment period at a significance level of 4.8% (two-sided test and adjusted for three comparisons with Bonferroni correction). As a conservative approach, this sample size allows for 15% of the subjects to drop out during the trial. The clinics will be instructed and encouraged to aim for a drop out rate less than 10%.

The sample size is rounded up to allow for an even number of subjects in each arm at each center.

Given the importance of the secondary outcome, PICT PEF, we calculated the sample size necessary for this outcome. There are no data on the variance of a Period of Intense Combined Therapy. However, the run-in data from the SOCS trial may provide a reasonable estimate of change in subjects on therapy. The clinically important difference in the change in PICT PEF between any two treatment arms was specified to be 21 Liters/Minute. The estimate of the standard deviation is 36.9 based on the SOCS run-in data for those with an FEV_1 > 80% predicted at Visit 1 and using PEF measures from the spirometry session done during a clinic visit. A total sample size of 234 is necessary to have 80% power to detect a difference of 21 Liters/Minute between any two of the three treatment arms in the change in Period of Intense Combined Therapy PEF at a significance level of 4.8% (two-sided test and adjusting for three comparisons). This sample conservatively allows for 15% of the subjects to drop out during the trial.

Based on all of the above calculations, it was determined that we will randomize a total of 234 subjects to ensure we have a large enough sample for the main hypothesis and the important secondary outcome. Each center will be required to randomize 39 subjects (13 in each treatment arm), resulting in a total of 234 subjects (78 in each treatment arm).

Given a sample size of 234, we calculated the effect size that could be determined in the change within each treatment arm over a period of one year of treatment after subjects had been stable on the treatment for a period of time (six months). The standard deviation estimate is 37.4 based on the SOCS run-in data (for subjects with $FEV_1 \geq 80\%$ predicted at visit 1) using weekly averages of AM PEF taken from subject daily diaries. With 80% power, 5% significance level (adjusting for two sided tests), and allowing for 15% of the subjects to drop-out, we can detect a change within each treatment arm of 13 Liters/Minute.

XI. DATA COLLECTION AND DATA MANAGEMENT

Each center has a computer configuration that includes an X-terminal, a post-script printer, and a modem. This will give each center the capability of logging directly into the DCC computing system over the Internet 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 database on the ACRN project server at the DCC, menu options will also include sending electronic mail, downloading study documents such as forms and reports, and viewing a calendar of ACRN 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 the data collection forms based on input from the clinical centers. Once the data collection forms have been filled out and reviewed, the Clinic Coordinator will log into the DCC computer system and enter the data within three 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 three 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 modem in the computer attached to the spirometer.

A. Drug Supplies

Drug supplies for this study will consist of budesonide turbuhaler and zafirlukast tablets and their matching placebos, albuterol metered dose inhalers, and prednisone tablets. Astra-Zeneca has agreed to provide a full supply of budesonide, zafirlukast and placebos for the study.

B. Compliance and Monitoring

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

1. Compliance with regular use of budesonide will be assessed, by counting the number of doses remaining in the inhaler. Each inhaler contains 220 doses. Counting the remaining doses is done by twisting the brown grip fully to the right as far as it will go and then twisting it back again fully to the left. Each twisting sequence will be counted as one dose. The twisting sequences will be repeated until the indicator tape in the device is advanced to its final position. The number of remaining doses counted in this manner will be recorded.

2. Compliance with regular use of zafirlukast will be assessed using the eDEM electronic Drug Exposure Monitor. The eDEM monitor records the date and time the patient opens the medication bottle in which zafirlukast will be stored.

3. Diary data will be collected for four weeks during the run-in period as well as at four weeks prior to the six month and twelve month visits to monitor AM PEF as well as to determine adherence to study drug regimens.

4. All subjects will be given a wallet-sized card outlining the elements of their symptom-based "action plan" and will be asked to call their research center whenever they initiate a course of ICS therapy or prednisone, make an unscheduled office or clinic visit, make an emergency department visit (at three month intervals) and by telephone calls made between visits. At these times, subjects will also be asked about days lost from work or school.

C. Special Study Techniques

Few techniques new to the ACRN are proposed for this study. Standard methods have been developed and described in the Manual of Procedures for spirometry, methacholine challenge, measurement of exhaled NO, sputum induction and analysis, asthma diary instruction, skin testing, and quality of life assessment. Local laboratory methods will be accepted for measurement of total IgE and eosinophil numbers in blood samples. The ACRN also has experience in analysis of DNA extracted from blood samples for genetic variants thought to be of possible relevance to asthma severity. This analysis has been performed for the ACRN by Dr. Drazen's laboratory (Harvard site). The ACRN also has experience with methods intended to monitor and assure compliance, and peak flow monitoring with the AirWatch™ device. We will additionally incorporate the use of the eDEM monitor, which records the time and date of each opening of the study pill container.

We have developed a "healthcare utilization review questionnaire" which will be administered in person every three months at study visits and by telephone mid-way between study visits; i.e. six weeks after a study visit. These questionnaires will inquire about use of supplemental non-study medications; e.g. ICS, prednisone, unscheduled office visits, ER visits, hospitalizations, and about days lost from work or school since the questionnaire was last completed (usually six weeks). This questionnaire will also inquire about symptoms of hoarseness, sore throat, and bruising since the last visit, and will ask an open question about any new symptoms the subject believes may be related to the study medications.

D. Randomization

When a patient at a particular center is deemed eligible for the study, the Clinic Coordinator will log into the ACRN network server and indicate to the system that a patient requires randomization. After entering the pertinent information with respect to the clinical center and eligibility criteria, the Clinic Coordinator will be asked to verify that all the entered information is correct. If so, the Clinic Coordinator will be given a packet

number, from which all medication for that patient will be dispensed. In order to maintain security of the randomization schedules, the data manager of the DCC will receive automatically a notice from the ACRN network server that a patient has been randomized. If no follow-up information is forthcoming on such a patient, the data manager will contact the Clinic Coordinators concerning the status of the patient. Within each center, an adaptive randomization scheme will be used to balance across treatment arms with respect to PC_{20} (< and $\geq$ 1 mg/ml), age (< and $\geq$ 25 years), and ethnicity (African-American or other).

E. Data Recording

Recording of all data including informed consent, history, physical examination, results of pregnancy tests, adverse events, confirmation of medication dispensation, methacholine challenge testing, and initial data entry will be done at each Clinical Center and forms will be forwarded to the 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.

XII. RECRUITMENT, RETENTION, AND COMPLIANCE

The selection of the clinical centers involved in the ACRN was based in part on documentation of subject availability, and, to date, recruitment goals for all ACRN studies have been met on schedule. The number of subjects required for this trial is comparable to the number required for previous studies done by the ACRN, but the study is longer than any we have previously undertaken. Fortunately, some ACRN investigators have experience with conducting long clinical trials. Stan Szefler, M.D. has more than five years experience with subject recruitment and retention for the CAMP study, and Vernon M. Chinchilli, Ph.D. has seven years experience in a study of the effects of dietary calcium supplementation on bone metabolism in adolescent girls. [28]

Joanne Fagan, Ph.D., who chaired the Recruitment, Retention and Compliance (RRC) Committee for the development of IMPACT, has experience with subject recruitment and retention from the Pediatric Asthma Care PORT-II study. The RRC Committee enlisted the assistance of two consultants with extensive experience in the recruitment and retention of patients in long, clinical trials. Dr. Bruce Bender, a neuropsychologist/ behaviorist who has been responsible for developing the Patient Education Center for the CAMP Study acted as a consultant as did Dr. Cynthia Rand. If problems arise in recruitment or retention, as monitored on a monthly basis by the DCC and the principal investigators, the participants in the RRC Committee will provide

additional ad hoc advice for the study.

Recruitment: The major challenge in recruitment will be identifying subjects with mild asthma who are willing to participate over a 15-month period. In addition to the recruitment strategies already used by each center (see below.), we will target student health services at colleges and universities in the areas of each ACRN center. We will also seek collaboration from large primary care practices and managed care organizations to send mailing inviting participation of patients identified from data base screens as having a diagnosis of asthma or a prescription for β-agonists but no long-term controller medication. We recognize the need to discuss the length of the study with potential subjects at the outset, and hope that the provision of expert care, medications, and education about asthma and payment of a volunteer's fee will prove sufficiently attractive to enroll subjects. Special study materials are being produced to assist with recruitment including a study brochure, and a detailed Q & A handout.

Retention: Retention of subjects in a 15-month clinical trial presents a new challenge to the ACRN. We have analyzed the determinants of subject retention in a previous, shorter (24 week) ACRN study of the effects of regular versus as needed use of inhaled albuterol.[29] Because the subjects enrolled in this study are likely to be young adults who are more mobile than other study populations; e.g. CAMP subjects, we recognized the need to power the study sufficiently for a 15% dropout rate. We will, nonetheless, target a lower dropout rate of $\leq$ 10% for our recruitment/retention programs. Techniques that favor retention are numerous and include: education of the subjects about the purposes of the study and about asthma itself, a spirit of friendly acceptance and enthusiasm on the part of the research personnel, health promotion by the research personnel, frequent telephone contact and written reminders of study visits, frequent payment of subject honoraria as small landmarks are reached, the sending of tokens of personal importance (birthday cards, movie tickets, and coupons for meals at fast food outlets, T-shirts) and the development of a sense of collective ownership of the study by the study participants through group meetings for discussion of the study's purposes and conduct, and the subjects' needs. Special attention will be given to the staff well being and recognition of their hard work.

Compliance: Compliance with study medications and with the treatment algorithm outlined in the symptom-based action plan will be critical for the success of this study. In our first multi-center trial, the BAGS study, our analysis of data from diary cards and chronolog devices suggested that 60% took more than 70% of the treatments scheduled. By emphasizing the importance of compliance at all centers with the subjects and by reviewing with them compliance data from the number of twisting sequences on the inhaled corticosteroid and the eDEM monitor, we hope to improve on this record. As mentioned above, the selection of the clinical center of the ACRN was based in part on documentation of the capacity to enroll volunteers with asthma in clinical studies. The specific plans of each center are described below.

Harvard Clinical Center/Boston

Recruitment

The Asthma Clinical Research Center at the Brigham & Women's Hospital utilizes three primary resources for identifying and recruiting potential subjects as described below.

1. Research Patient Database: The Asthma Clinical Research Center at the Brigham and Women's Hospital has a database of over 1,500 asthmatics who have expressed interest in participating in research. All of these patients have completed questionnaires regarding their asthma and medication use. In addition, many have undergone physiological screening. The database is screened based on entry criteria, and subjects are contacted in a manner approved by the IRB to ascertain their interest in participation.

2. Asthma Patient Lists: Following IRB guidelines, the center has permission to contact patients with a diagnosis of asthma to ascertain these patients' possible interest in participating in asthma studies. Lists generated at the Brigham & Women's Hospital contain over 5,000 such patients. In the past, we have also used patient lists from the Harvard Pilgrim Health Care HMO. The latter list can be screened by medication use to preliminarily identify patients with specific patterns of medication use.

3. Advertisements: We utilize IRB-approved radio and newspaper advertisements to inform potential subjects of our studies and solicit participation. In addition, we use posters in selected locations.

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 number of subjects, with one-half being female and one-third minority population, will come from the following areas.

1. National Jewish Outpatient Clinic

The adult clinic saw 1,079 new asthmatic patients over the last year with 503 being from the Denver metropolitan area. Another 335 from the Denver area were seen in follow-up. The severity of asthma varies among these patients, but at least 15% are in the mild category. The pediatric clinic saw 490 new asthmatic children with 352 being from the Denver metropolitan area. Again these patients were of varying severity, but about 10-15% are in the mild category. Ninety-seven additional children were seen in follow-up. National Jewish Center changed markedly over the last decade. We have evolved from a primary

inpatient facility with a small clinic to a very active outpatient service. Thus, we are seeing many more asthmatic patients of all degrees of severity.

2. National Jewish Asthma Research Pool

There are over 600 asthma patients (not followed in the NJC outpatient clinic) who have participated in our research studies. Many of these subjects have been through various medication studies and bronchoscopies with lavage/biopsies. Their FEV_1 range from 30-110% of predicted.

a. Denver Health Medical Center

Dr. James Fisher, Head of Pulmonary Medicine, is supporting our efforts by helping us to recruit from the asthmatic patient population at Denver General. This is a large county hospital whose patient population comprises mainly Hispanic and African-American people.

b. Denver Veterans Administration Hospital

Dr. Clifford W. Zwillich, Head of Medicine, will support this grant. The V.A. hospital has a large outpatient clinic of patients with asthma, and without chronic obstructive pulmonary disease.

c. Denver Kaiser Permanente HMO

Dr. Timothy Collins is the Director of Pulmonary Medicine and Dr. John Williams is the Director of Allergy at Kaiser. Drs. Collins and Williams have been actively involved in supporting research at NJ in the past by referring us patients. Their groups will continue to play an active role.

University of Wisconsin/Madison

The Asthma/Allergy Clinical Research Program of the University of Wisconsin maintains an ongoing computer database of potential subjects with asthma and allergic diseases who are interested in future research participation. These individuals have been screened and/or participated in previous clinical studies with our unit. Their names have been generated in response to extensive newspaper advertisements, physician referrals, radio advertisement campaigns, community health screening events, and by email communications to the entire student enrollment of the University of Wisconsin (approximately 40,000 students); all advertisement modalities have been approved by the Human Subjects Committee. Approximately 85% of the subjects in this database have “mild to moderate persistent asthma” and are, therefore, eligible for ACRN protocols. The following patient data is maintained: birth date, gender, ethnic background, duration of asthma, childbearing and contraceptive use status, smoking history, atopic status (including allergy skin testing results if previously performed), pulmonary function tests, concurrent medical history, asthma and non-asthma medication use, methacholine test results, and exercise challenge test results (if previously performed). When additional subjects are needed, referrals from physicians in the University of Wisconsin Clinics and Physicians Plus network are solicited.

Even though this database serves as the foundation of our recruitment efforts, the Madison ACRN site has utilized some additional approaches to target minority recruitment. We have utilized a marketing expert to coordinate and oversee our overall efforts in recruiting and retaining minorities. 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, and has participated in previous asthma studies with our unit). As a result of his efforts, we have advertised widely in newspapers and other publications that target ethnic minorities, established contacts with various ethnic community, university, church, and business groups, and conducted community-based asthma programs. For the upcoming ACRN protocols which will require long-term study participation, extra efforts will be made through these contacts. For example, student groups such as AHANA (a pre-health careers organization focusing on minority concerns) will be contacted. We will continue our annual asthma screening services for all of the incoming University of Wisconsin freshmen athletic teams, which has been highly successful. Historically, retention of students in our asthma studies has been excellent, especially if contacted early upon arrival to the campus. These individuals discover that study participation serves as an ongoing source of quality medical management for their asthma. In addition, we will utilize published examples of successful retention strategies such as frequent payment of subject honoraria as study landmarks are achieved and study participant group social events. Study visits will be carefully planned and scheduled to avoid exam-time and university calendar breaks.

Harlem Hospital Center, Columbia University, New York City

The ACRN clinical center at Harlem Hospital Center draws study participants from four sources, including the Chest Clinic, the Emergency Department, the general community, and through advertising and outreach efforts. We advertise through local radio stations, newspapers, and newsletters of local churches and other community based organizations. In addition, we disseminate information about inclusion criteria for specific studies through ongoing outreach activities with volunteers in the *AHA!* (Asthmatics Helping Asthmatics) support and advocacy group, and through educational efforts in the community, including a series of asthma educational workshops.

The Chest Clinic, an outpatient pulmonary clinic in Harlem Hospital Center, sees a diverse group of patients with asthma. Patients learn about research at the Lung Center and about opportunities for participation in clinical trials, during their clinic visits.

The Harlem Hospital Center Emergency Department (ED) sees an average of eight adult patients per day for asthma. Through the REACH (Reducing Emergency Asthma Care in Harlem) project, we have been recruiting study participants at the ED. We have successfully recruited and interviewed 380 patients from the ED for that project, and most are currently being followed. One-third to one-half of REACH participants may be classified with mild intermittent or mild persistent asthma (self-reported symptoms, by NAEPP

guidelines criteria).

Responses to inquiries about participation in research studies are answered by a dedicated phone line that is manned during business hours and answered by voicemail at all other times. A research assistant responds to each inquiry immediately, using a screening instrument that inquires about potential respondents' contact information, demographics, smoking history, and medical history. Our database includes 1,600 individuals with physician-diagnosed asthma.

Retention Strategy: In order to maximize long-term retention in the IMPACT study, the clinical coordinator will routinely ask participants for the names, addresses, and phone numbers of three people who will always know how to reach them. We will also send a newsletter about asthma and send birthday- and holiday-greeting cards to each participant. An important component of our retention strategy will be the retention of clinic personnel. In addition, patients who move will be strongly encouraged to follow-up at their nearest ACRN clinical center.

Thomas Jefferson Medical College/Philadelphia

Patients are recruited for clinical trials at the Jefferson Center through two primary mechanisms: (1) local advertising and (2) identification in the asthma patient registry (database). Local advertising takes advantage of the printed as well as the audio-visual media. Printed media include posters placed in public information centers of local colleges and universities as well as brochures sent to selected physicians in the Philadelphia area. Printed advertising is placed in local neighborhood newspapers and occasionally in the *Philadelphia Inquirer*. Audio-visual media advertisements are also placed in public service announcements on television and radio. All advertising in the printed and audio-visual media has prior approval of the Institutional Review Board.

The Jefferson patient registry (database) has been maintained since 1992 and currently contains 3,100 patients. The patient registry infrastructure includes a computer network linking those divisions of the institution that serve significant numbers of asthmatic patients (pulmonary medicine, family medicine, pediatric and adult allergy, and general internal medicine). Personal computers in each outpatient clinic site are linked to a dedicated file server located in the clinical research offices of the Pulmonary Division. The network operates on Novell Netware 3.22, and the database application is a customized version of Approach for Windows. The database provides a graphic interface for data entry. Fields for demographic information, smoking history, allergic history, medication used, pulmonary function tests, other laboratory tests, and other diagnoses are provided. Designated personnel are able to access the database and perform searches based on any field or combination of fields to define subsets of patients who qualify for particular research studies. The data coordinator is responsible for maintaining the database, assuring its accuracy, and keeping it current. It is

estimated that 300-400 new asthmatic patients are seen each year, while a smaller number become inactive due to relocation, change of health care provider, etc. Once identified in the database, patients potentially eligible for a specific study are contacted by the nurse coordinator who explains the study and ascertains the patient's interest. If interested, the patient is seen in the clinical research laboratories where more detailed evaluations are made.

University of California/San Francisco

The approach to recruiting subjects with mild asthma for research studies at the San Francisco Center relies heavily on community advertising and on maintaining a database of subjects who have participated in previous studies, who have come for a "characterization" visit, or who have expressed interest in participating. Advertisements are placed in editions of the *San Francisco Chronicle*, the *San Francisco Examiner*, the *Bay Guardian*, and in small neighborhood and college campus newspapers. We post numerous fliers on bulletin boards on the UCSF campus, in community health centers, at campuses of local colleges and universities in the Bay Area, and we broadcast advertisements on local radio stations. We make frequent presentations to different physician groups on and off campus describing our research studies and the enrollment criteria for future studies. Responses to these advertisements are made to a dedicated telephone number equipped with voice mail. A dedicated recruiter, Lila Glogowsky, either responds herself or directs other staff (technicians and clinical coordinators) to respond to each inquiry to obtain basic information about the subject's demographics and about the severity, duration, required treatment, and frequency of symptoms of asthma. Subjects who appear to meet entry criteria for a study are then referred to a study coordinator, who then contacts the subject to schedule a "characterization visit" in which details of the medical history and medication use are obtained, and spirometry (before and after albuterol administration), and skin testing is performed. To date, over 3,000 subjects have been screened for the database. We have met the goals for recruitment of women and of members of ethnic minorities in all studies so far.

For the IMPACT study, we will use these established recruitment techniques, and we will also contact directors of the Student Health Services at San Francisco State University, San Francisco City College, the University of San Francisco, and the University of California at Berkeley to present the purposes, design and risks and benefits of participating in the study to seek permission to send letters directly to students with asthma. We have used this approach successfully in recruiting a small number of subjects with more severe asthma from the student health service at San Francisco State University. We will also explore similar interactions with Kaiser-Permanente, Brown and Toland Medical Group, La Clinica de la Raza, and other large HMO's and primary care organizations in the area.

XIII. RISKS/BENEFITS

This study compares the efficacy of three different approaches to the treatment of mild persistent asthma. Two of the approaches are recommended for asthma of this severity by the NAEPP's Guidelines. While the third arm (intermittent corticosteroid treatment for symptomatic flares of asthma) is not recommended, it resembles or exceeds most current treatment of asthma in the United States, where most patients prescribed an inhaled corticosteroid for asthma renew the prescription once or not at all over the next 12 months.[15] All subjects will be taught to treat themselves with inhaled corticosteroid therapy for worsening of asthma symptoms, based on standardized symptom-based action plan, so we expect even the subjects in the placebo arm to receive treatment for mild, persistent asthma more intense than that prescribed for "mild asthma" in the 1991 version of the NAEPP Guidelines. Treatment above the upper limit of recommended therapy is the 10-16 days of a high dose ICS (budesonide=1600 µg/day) plus 0.5 mg/kg/day of prednisone, plus zafirlukast 20 mg bid taken daily at the end of the run-in period and after 12 months of active or placebo therapy. This short course of intense therapy is necessary to determine important outcomes of the study, the peak flow and FEV_1 after a "Period of Intense Combined Therapy" but carries some risk of alteration of mood, fluid retention, hyperglycemia, hypertension, oropharyngeal candidiasis, and hoarseness, and possibly a very remote risk of aseptic necrosis of the hip or clavicular head. We propose to survey subjects for development of these complications by checking blood pressure and urine glucose and by inquiring about new symptoms. In addition, patients will be given cards instructing them to contact a study coordinator if they develop symptoms of polyuria, polydypsia, headache, restlessness, blurred vision, or fatigue. Subjects who develop significant complications from the intense course of treatment at the end of the run-in period will not be randomized to one of the three treatment arms. At the end of this run-in period, before randomization but after the subject's first experience with the first course of intense combined therapy in this study, subjects will be reminded of their freedom to withdraw consent to participate.

An extremely remote risk of treatment with a leukotriene receptor antagonist is the development of Churg-Strauss syndrome. The most recent reports to the pharmaceutical companies and the FDA suggest that the incidence of Churg-Strauss syndrome is 40-60 per million patient-years of exposure. Depending on the data base reviewed, this is either equal to, or at most 4 times, the incidence in asthmatics. Most of the cases reported have occurred in patients with moderate or severe asthma requiring inhaled or oral corticosteroids. In fact, such cases have now been reported with fluticasone and had been previously reported with the cromoglycates. While, it is not yet known whether the reported relationship between leukotriene modifiers and these Churg-Strauss-like reports is causal, or results simply from increased case finding and possible concomitant tapering or oral corticosteroid therapy, in either case, the risk for our subjects is extremely low.

In view of the fact that the total cumulative exposure time to a leukotriene antagonist in our study is less than 200 patient years, combined with the fact that we are studying only mild asthmatics, we estimate that the chances of detecting even one case of such a disease in our patients is substantially less than one in several thousand. Therefore, we now propose not to screen specifically for Churg-Strauss disease but rather to use a standard adverse events screening questionnaire. We nevertheless will educate the coordinators and investigators about signs and symptoms of incipient Churg-Struass disease such as unexplained shortness of breath, fever, gastrointestinal complaints, rash, or joint pains so that a physician will interview any patient reporting these complaints to decide whether further evaluation is necessary.

There may be no direct benefit to the patients participating in this study, apart from the provision of asthma care, medications, and education about asthma. The results may be of potential benefit to all patients with asthma as it may lead to a clearer definition of guidelines for the treatment of asthma.

XIV. ANTICIPATED RESULTS AND SIGNIFICANCE

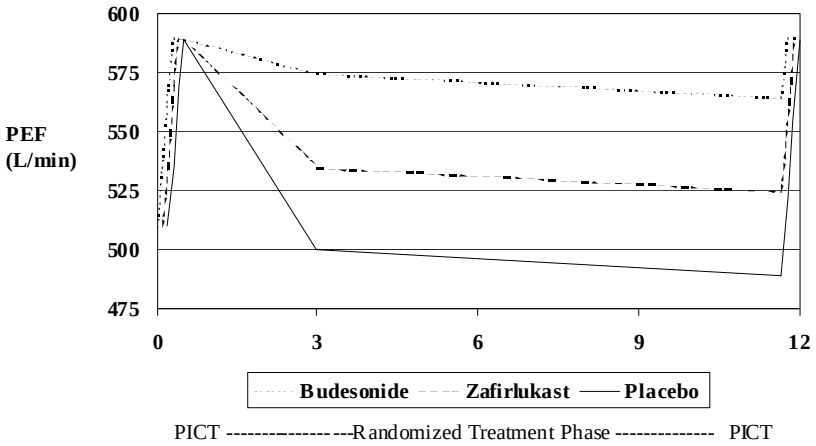
We anticipate that our results will confirm the results of previous placebo-controlled studies of inhaled corticosteroids and of leukotriene antagonists in patients with mild/moderate asthma. That is, we expect our results to show the two active treatments to cause significantly greater improvements than are seen in the placebo group in AM Peak Flow and FEV_1. However, based on review of the data from Haahtela and colleagues[6], we expect that the initial improvement in airway function will stabilize. Thus, we suspect that there may be no clinically significant fall in peak expiratory flow over the six months from study month 6 to month 12. We expect our results will also show that the active treatments will cause small but significantly greater improvements in asthma control and in the number of courses of inhaled budesonide and oral prednisone taken “as needed,” over the 12 months of active treatment. Some of these differences will likely be apparent as early as the first return visit (three months) after treatment is started. Based on the results of previous studies, we expect the improvements in these outcomes to be greater in the group treated with inhaled budesonide than in the group treated with zafirlukast, but we are not sure of this, for all subjects will have no more than mild, persistent asthma, and there is thus little range of improvement possible. While we expect the number of unscheduled office visits, Emergency Department visits, and hospitalizations to be greater in the placebo group than in the other two groups, we expect the absolute number of these events to be small, for we believe prompt initiation of inhaled corticosteroid treatment of symptomatically mild exacerbations of asthma and of prednisone for more severe attacks to be effective. We, thus, anticipate that the estimated reduction in medical costs associated with these events will be modest, and may be insufficient to offset the

additional costs of continuous treatment.

If our results indeed conform to these expectations, they will suggest that the additional expense of regular therapy for mild persistent asthma cannot be justified by an offsetting reduction in the costs for treatment of asthma exacerbations. Our analysis of the impact of the three treatments on subjective ratings of the severity of asthma, such as the number of symptom free days, of the "asthma symptom utility index," and of "asthma related quality of life" may then provide additional information. Because asthma mild enough to meet the criteria for "mild, persistent asthma" does not much interfere with social or physical function, the maximal possible improvements in these measures of the impact of asthma are small, and because we further expect the education in self-management given to all subjects (necessary to instruct them in the symptom-based action plan) to reduce asthma's impact even in the group assigned to receive continuous placebo, we think any greater improvement in either of the two active treatment groups may be insignificant. Even if such a difference is found, we think it may be insufficiently large to justify the expense of continuous treatment for patients with such mild disease.

These anticipated findings will bring to the front the putative consequences of "delaying" anti-inflammatory therapy on the development of irreversible airflow obstruction, attributed to "airway wall remodeling." Examining this alleged consequence of delaying therapy is the purpose of our assessing the PEF and FEV_1 measured after repeated treatment with albuterol and again after an intense 10-16 day course of combined therapy with oral and inhaled corticosteroids and a leukotriene receptor antagonist and after repeated treatment with albuterol. Assessing these indicators of airflow obstruction will enable us to determine whether any differences in AM PEF or FEV_1 after the active treatments reflect "irreversible" changes in airway caliber, presumed to be due to "airway wall remodeling." While we are aware that the development of such irreversible changes in the airways may be minimal over 12 months, such differences have been reported by Haahtela et al from a study only six months longer than the study here proposed.[3] We have powered this study to detect the differences reported by Haahtela in the delayed and early intervention groups estimating the variability of PEF from our own observations is previous trials of subjects with asthma of similar severity. We in fact expect that the variability of the PICT indices will be smaller and thus may have sufficient power to detect even smaller differences.

The graph below illustrates a possible outcome of this study.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PICT ----------Randomized Treatment Phase ---------- PICT

We know of no study that has assessed whether treatment-related differences in pulmonary function persist after brief, intense anti-inflammatory therapy. We will use the values for mean change and variability in PEF and FEV_1 after a period of intense combined therapy for estimation of the sample size and duration of possible future studies of the effects of different treatment regimens on the development of persistent changes in airway caliber.

In addition to assessing the question of persistence of treatment-related differences, we will be able to assess whether patients with mild persistent asthma actually experience a progressive decline in pulmonary function. Based on our current sample size we should be able to detect a 13 L/min decline in pulmonary function over one year. Failure to detect such a small change in pulmonary function in our patients would suggest that data suggesting a progressive decline may not be applicable to a mild persistent group of asthmatics as defined by the NAEPP.

A likely outcome of our study is that the declines in AM PEF and FEV_1 will vary among individual subjects. This is suggested by the wide variances reported for the declines in tests of maximal airflow in the groups not treated with an inhaled corticosteroid in previous studies. In Agertroft, et al's study[2], the mean change in FEV_1 in the control patients (not treated with inhaled budesonide), expressed in terms of % predicted FEV_1 per year, was –1.17%, with a range from –8.1% to +5.8%. The comparable change in the budesonide treated group were a mean of +3.88% and a range from +2.5% to +5.2%. Similarly, Haahtela, et al, reported that the trend in FEV_1 over two years of treatment with terbutaline was –0.20L/yr when expressed as the mean change but was only –0.03L/yr as the median change. In the group treated with budesonide for two years, the mean fall in FEV_1 was –0.06L/yr with a median change of –0.06L/yr.[6] This dissociation of mean and median change in the terbutaline-treated group implies the existence of a subgroup who deteriorated steeply. We believe that it is important to determine whether this subgroup is large enough among patients with mild, persistent asthma to justify treatment all such patients with continuous anti-inflammatory therapy.

If large falls in AM PEF or FEV_1 indeed occur in some subjects and persist despite intense combined treatment, our study will permit a search for possible markers of risk of this outcome. We anticipate that the subjects in the placebo group who have the highest initial values for exhaled NO, sputum eosinophil%, ECP level, and bronchial reactivity (lowest PC_{20}) at baseline, and/or the greatest falls in AM PEF and FEV_1 over the first three months of blinded treatment, will have the greatest falls in AM peak flow. These subjects will probably also require the most "as needed" courses of inhaled corticosteroid treatment. We also anticipate that the subjects who have persistently abnormal values of these indices despite receiving regular treatment with an ICS or a LT-antagonist will also have greater falls in the PEF and FEV_1 after the PICT and will

require more frequent courses of inhaled corticosteroid treatment than will the subjects in whom these indices of airway inflammation are within the normal range.

This analysis of predictors of individual deterioration in AM PEF and FEV_1 over the 12 months of randomized treatment will be extended to include study of differences at genetic loci thought possibly to be related to differences in asthma severity (e.g, IL-4 and 5 promoter loci). In addition, we plan to analyze whether greater deteriorations in pulmonary function are related to differences in evidence of atopy (as reflected by elevated serum IgE and positive skin tests).

In addition to addressing these issues, this study will also give us the chance to examine whether regular use of a leukotriene receptor antagonist is as effective as an inhaled corticosteroid in controlling symptoms and in preventing declines in airway function after a PICT in subjects with mild, persistent asthma. It is widely assumed that airway remodeling is a consequence of inflammatory activity in the airway, and it is not clear that oral leukotriene pathway antagonists are as effective as inhaled corticosteroids in inhibiting airway inflammation. Some information about their relative efficacy as anti-inflammatory agents will come from our studies of their effects on exhaled NO levels and eosinophil percent in induced sputum samples. We will thus be able to compare the anti-inflammatory activity of the two classes of therapy and will further be able to analyze whether differences in anti-inflammatory activity have any relationship to differences in improving asthma control or in preventing declines in airway function after a PICT.

Finally, just as we anticipate little evidence of benefit in these asthmatic subjects treated with placebo, a low dose of an ICS, or a low dose of an LT-antagonist, we also expect little toxicity. Our assessment of the evidence linking osteoporosis, cataracts, or glaucoma to inhaled corticosteroid treatment has dissuaded us from measuring bone density or performing eye examinations in this study. We also plan not to measure adrenal function. The likelihood of a positive finding in a young group of subjects (the mean age of subjects enrolled in previous ACRN studies has been 28-32 years) treated with a low dose of an ICS seems to us too low to justify the expense and subject inconvenience entailed.

XV. ADVERSE EVENTS AND TREATMENT FAILURES

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.

A. Adverse Events Related to Asthma:

Asthma exacerbations will be managed according to the symptom-guided management plan described above (Section V). Subjects who experience a >20% drop in baseline FEV_1 (Visit 1) during the run-in will be terminated from the study.

B. Adverse Events Unrelated to Asthma

Adverse events due to concurrent illnesses other than asthma may be grounds for stopping study treatment if the illness is considered significant by the study investigator or if the patient is no longer able to effectively participate in the study. Even in these subjects, every attempt will be made to measure the PICT PEF and FEV_1, 12 months after entry into the study. Patients experiencing minor intercurrent illnesses will continue the study drugs 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, gastroenteritis, acute injury or illnesses expected to resolve entirely with treatment; e.g. community acquired pneumonia, arthroscopic knee surgery, appendicitis. Medications are allowed for treatment of these conditions in accordance with the judgement 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:

- Description of the illness
- Dates of illness
- Treatment of illness and dates (medications, doses, and dose frequency)
- Whether emergency treatment or hospitalization was required
- Treatment outcome
- Whether the illness is considered unrelated, possibly related, or probably related to the medications or procedures of the study.

C. Treatment Failure

The criteria for treatment failure are any of the following:

1. Requirement for > 4 courses of an ICS for worsening asthma in a 12 month period.
2. Requirement of > 2 courses of an oral corticosteroid in a 12 month period.
3. Requirement for > 1 emergency department visit or hospitalization for asthma

exacerbation in a 12 month period; i.e. two or more of either event within a year.

4. Requirement for admission to an intensive care unit for severe asthma exacerbation.

Additional open treatment for asthma will be given to all subjects who meet these criteria. This treatment may consist of an inhaled corticosteroid and a long-acting β-agonist, or other "long-term controller" therapy selected at the discretion of a physician investigator or of a subject's personal physician. Study medications will be continued, and the subjects will continue participating in all study visits at the discretion of the treating physician. Because the "intense combined therapy" given during the PICT is expected only to improve asthma, every attempt will be made to give this course of treatment at the end of the planned 12 months of randomized treatment to all subjects, even if they have been switched to "open" treatment by a physician and have not continued to take study medications.

Subjects meeting the criteria for treatment failure will not be dropped from the primary analyses of all study outcomes, based on "intent to treat." Comparisons will be made of the number of subjects meeting "treatment failure" criteria in the three treatment groups. In addition, secondary analyses of all study outcomes will be made of subjects completing the three investigated treatments, ignoring data collected after a change in treatment due to treatment failure.

D. Criteria for Discontinuing Patients

Patients may be dropped from the study for withdrawal of consent. For subjects who withdraw consent for unanticipated changes in residence, employment, or scholastic status, every effort will be made to gather data on all customary endpoints, including the PICT FEV_1 measured after 10-16 days of intense combined therapy. When possible, we will attempt to retain subjects who change residence by funding travel expenses to the nearest ACRN site.

Despite assurance of the use of a reliable form of contraception for the course of the study, we anticipate that some women may become pregnant. Should this occur, the subject will suspend all study medications and be treated according to the judgement of her physician (consultation with a study physician will be offered) until delivery. The subject will be asked to re-enroll in the study either six weeks after delivery (if not nursing) or after completing nursing. From the point of re-entry, study medications and procedures will be resumed until the end of the anticipated 12 months of randomized treatment or for 6 months, whichever is longer.

XVI. COST, LIABILITY, AND PAYMENT

Study medications will be provided, and all tests will be performed without cost to the participating patients. 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 National Institutes of Health policies concerning this issue can be found in NIH Documents #5305 and 6352-2, Research Patient Care Costs Supported by NIH Sponsored Agreements, which are in the ACRN Manual of Operations. Each patient will be paid an amount determined by their local center for study reimbursement. For patients who drop out, reimbursement will be pro-rated for the length of time they stayed in the study.

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