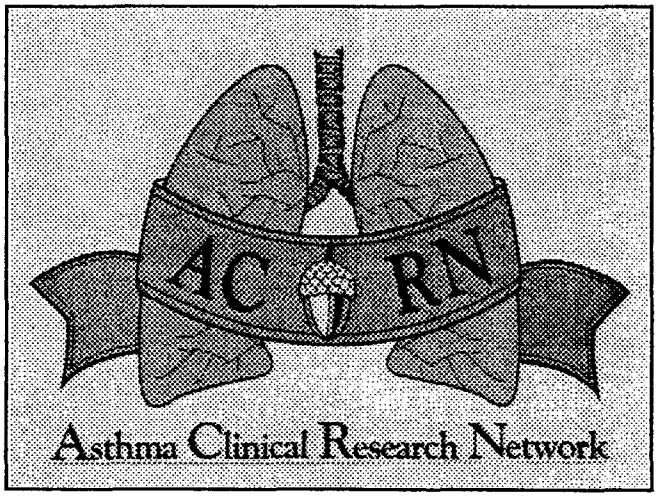

Salmeterol ± Inhaled Corticosteroids (SLIC)

Study Protocol

Version 3.4

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I. HYPOTHESIS TO BE TESTED

Proposed Research Hypothesis: In patients with moderate asthma whose symptoms are suboptimally controlled by using an inhaled β-agonist on an "as needed" basis and an inhaled corticosteroid on a scheduled basis, the addition of the long acting β-agonist, salmeterol, on a scheduled basis will permit a reduction in dose, and/or elimination of, inhaled corticosteroids over time without a concomitant increase in asthmatic symptoms, or a decrease in the protection against methacholine-induced bronchoconstriction.

II. BACKGROUND AND RATIONALE

A. Introduction

In developing protocols to ascertain the relative safety of chronic beta agonist therapy in moderate asthma, members of the ACRN Steering Committee were concerned that the group of asthmatic patients who could be considered to have moderate disease were too heterogeneous to construct a single study that would yield meaningful information for all within this group. Indeed, many patients with moderate disease are adequately controlled with inhaled corticosteroid (ICS) doses $\leq$ 400 μg/day, whereas others require higher doses of ICS with additional bronchodilator support in the form of sustained released theophylline or long acting inhaled or oral β-agonists. Further, pulmonary function as measured using either spirometry or peak flow meters may vary widely both from an inter and intrapatient standpoint. Thus, to safely address questions regarding the proper placement of chronic bronchodilator therapy in asthma, more than one protocol appeared to be required.

To this end, the Steering Committee focused their efforts on designing two studies that would share a common run in phase, but permit the randomization of the patients into two separate protocols based on both levels of pulmonary function measured acutely as well as their stability following six weeks of ICS therapy. These two protocols have been given the acronyms **SOCS** (salmeterol *off* corticosteroids) and **SLIC** (salmeterol ± inhaled corticosteroids). Patients whose disease activity was more on the mild end of the moderate category would be entered into the SOCS protocol, whereas patients whose disease activity was more on the moderate to severe end of the moderate category would be enrolled in the SLIC protocol presented herein.

The rationale for evaluating issues revolving around the use of anti-inflammatory therapy and chronic beta agonists has been well described in the SOCS protocol[1-5] and elsewhere[6] and therefore will not be further elaborated on here. As a background for the design of the SLIC protocol, the Steering Committee was intrigued by two recent reports comparing the effects of adding inhaled salmeterol to a constant dose of an ICS vs more than doubling the dose of ICS in patients with moderate asthma whose disease control was suboptimal.[7,8] Greening et al.[8] enrolled over 400 asthmatic patients who still had symptoms despite maintenance treatment with 200 μg of beclomethasone dipropionate (BDP) twice daily. These patients were then randomly assigned to two groups: Salmeterol (42 μg twice daily) with BDP (200 μg twice daily), and higher-dose BDP (500 μg twice daily). The protocol was conducted over a period of six months. The mean morning peak expiratory flow (PEF) increased from baseline in both groups, but the increase was significantly greater in the salmeterol/BDP group than in the higher-dose BDP group at all time points. Mean evening PEF also increased with salmeterol/BDP but not with higher-dose BDP. There were significant differences in favor of salmeterol/BDP in circadian variation of PEF (all time points), in use of rescue bronchodilator (albuterol), and daytime and night-time symptoms (at some time points). There was no significant difference between the groups in adverse effects or exacerbations of asthma indicating

that, in this group of patients, regular β_2-agonist therapy was not associated with any risk of deteriorating asthma control over 6 months.

Woolcock and colleagues, in a preliminary report, also noted that the addition of salmeterol to a stable ICS regimen was better than increasing the dose of ICS in terms of improving PEF and nocturnal awakenings.[7] In addition, they were unable to find any adverse effects of chronic salmeterol therapy on measurements of airway hyperresponsiveness either during therapy or in a two week washout period. Although patients receiving salmeterol reported a higher incidence of tremor, the group receiving the higher doses of ICS demonstrated a statistically significant reduction in AM plasma cortisol levels. Taken together, these studies would argue that the addition of salmeterol to an acceptable dose of ICS stabilizes asthmatic symptoms and improves pulmonary function to a greater extent, and with the potential for fewer serious side effects, than does a higher dosage of ICS. Indeed, the current recommendations in the international guidelines for the treatment of asthmatic patients in the moderate category (based on the following categories: mild episodic, mild persistent, moderate, severe) involve the introduction of a long acting bronchodilator if symptom control is not adequate on anti-inflammatory therapy alone. These recommendations, along with the observations of Greening[8] and Woolcock[7], would indicate that the combination of salmeterol (or perhaps SR theophylline) and an inhaled corticosteroid should be considered the standard of care for this patient population.

However, once improvement in clinical symptoms is achieved with this regimen, the next logical question which needs addressing is "what is appropriate 'step down' treatment in these patients?" For example, in either the Greening or Woolcock study populations, would it have been possible to add salmeterol to a stable ICS regimen to improve symptom control, pulmonary function, and perhaps quality of life[9], and then begin carefully tapering the dose of ICS while maintaining all of these parameters stable? Since some have argued that chronic beta agonist therapy treats the symptoms while not treating the underlying disease (inflammation)[10,11], the concept of tapering ICS while continuing chronic beta agonist therapy may seem paradoxical. However, recent work by Gardiner et al. would refute the concept that salmeterol worsens underlying asthmatic inflammation.[12] Employing a double-blind crossover placebo controlled protocol, they performed bronchoalveolar lavage before and after eight weeks of salmeterol therapy in nine asthmatic patients receiving ICS. Evaluating a number of markers of airway inflammation (e.g. CD_4 and CD_8 lymphocyte counts, HLA-DR expression, numbers of epithelial cells, eosinophils, neutrophils, and mast cells, and levels of albumin and tryptase), they found that salmeterol had no effects on any of these parameters. Thus, following the chronic administration of salmeterol, the patients improved clinically without any evidence of a deterioration in the underlying inflammatory disease process. Taken together, all of this intriguing background information strongly supports a more comprehensive evaluation of the issue of ICS tapering in patients stabilized and/or improved following the initiation of salmeterol.

B. Specific Aims

The specific aims of this study are as follows:

To determine if the addition of salmeterol to the maintenance therapy of patients with moderate asthma will:

1. Improve and stabilize measurements of pulmonary function (FEV_1, AM PEFs).

2. Permit a significant reduction in maintenance inhaled corticosteroid treatment without a significant deterioration in either symptom control or measurements of pulmonary function.

3. Achieve #1 and #2 above without any significant deterioration in measurements of the bronchoprotective effect of salmeterol to methacholine inhalation over time.

This study also is designed to examine the safety and efficacy of methacholine challenge in the evaluation of subjects with moderate asthma.

C. Research Questions

In patients with moderate asthma receiving inhaled corticosteroids for maintenance therapy, the addition of the long acting β-agonist, salmeterol, has been shown to improve pulmonary function and symptom control to a greater extent than does increasing the dose of inhaled corticosteroids 2.5 fold.[8] In addition, salmeterol administered for a period of 8 weeks in patients receiving inhaled corticosteroids has been demonstrated to improve pulmonary function without changing markers of inflammation in bronchoalveolar lavage fluid.[12] Taken together, these data would indicate that symptom control in asthma can be improved by the use of a maintenance beta agonist without the risks of significantly worsening the underlying disease process. If this is indeed true, the following questions will no doubt be asked of and by physicians caring for patients with moderate asthma:

1. In patients with moderate asthma whose disease is suboptimally controlled even when receiving regularly scheduled inhaled corticosteroid therapy, does the addition of salmeterol consistently and significantly improve pulmonary function?

2. Following the initiation of maintenance salmeterol, can the dose of inhaled corticosteroids subsequently be reduced and possibly eliminated without a deterioration in symptoms or pulmonary function? That is, is corticosteroid reduction appropriate and safe step down therapy in this clinical situation?

3. If corticosteroid dose reduction is achievable without any change in symptom control, are there any subtle adverse effects that clinicians need to be concerned about? Since the diminution of the bronchoprotective effects of beta agonists following chronic administration may be one such consequence[14], will the use of salmeterol with or without inhaled corticosteroid produce such a decrease of this effect that will correlate with any clinical markers of worsening disease?

4. In short, can salmeterol be safely used as a steroid-sparing medication?

In addition to issues related to salmeterol therapy in moderate asthma, two additional questions regarding the safety and efficacy of methacholine challenge will be addressed:

5. Is there a difference in the frequency of asthma exacerbations following clinic visits at which methacholine challenge is performed, compared with visits at which it is not?

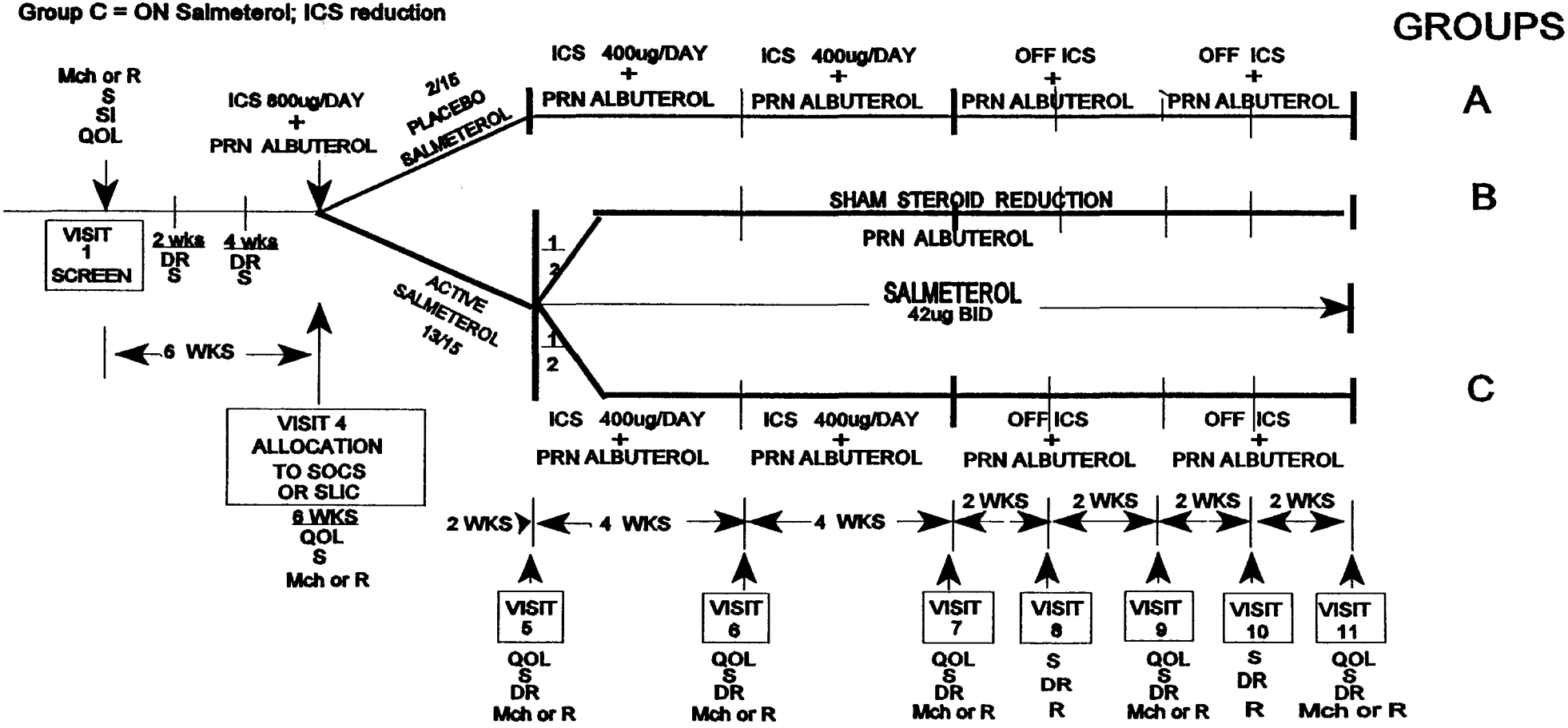
6. How does PC_{20} compare with other measures of asthma outcome, such as AM and PM PEF, FEV_1, symptom scores, rescue beta-agonist use, and quality of life scores?

L. Protocol Overview

Mch = Methacholine responsiveness
S = Spirometry
QOL = Quality of life questionnaire
R = Reversibility with bronchodilator
SI = Sputum induction/analysis
DR = Diary Review

SLIC PROTOCOL

Group A = OFF Salmeterol; ICS reduction
Group B = ON Salmeterol; no ICS reduction
Group C = ON Salmeterol; ICS reduction



This will be a 24 week, randomized, double-blind, prospective multi-center trial evaluating the ability of salmeterol to permit a stepwise reduction in inhaled corticosteroids in patients with moderate asthma. All patients with moderate asthma who meet the inclusion and exclusion criteria will receive both a methacholine bronchoprovocation (if baseline FEV_1 $\geq$ 55% predicted) followed by a sputum induction with hypertonic saline (if post-albuterol FEV_1 > 60% predicted). They will then be treated for a six week run-in period with a uniform dose of ICS (triamcinolone acetonide 400 μg BID) and prn use of the intermediate acting β_2-agonist, albuterol. Beginning with the run-in period, subjects will record in a daily diary their daytime and nighttime symptoms (dyspnea, wheeze, cough, each scored 0-3), AM and PM PEFs, albuterol use, and intercurrent illnesses and hospitalizations. At the end of the run-in period, patients will be randomized within either the SOCS or SLIC protocol based on FEV_1 measurements at the week six visit, and the stability of their PEF measurements during the preceding two weeks. (See diagram, page 24) Patients with greater airflow limitation (FEV_1 $\leq$ 80% predicted), or greater pulmonary function instability (variability > 20% but FEV_1 > 80% predicted), will be selected for the SLIC protocol. At the end of the six-week run-in period, patients will be randomized in a 2:13 ratio to placebo BID (Group A) and salmeterol 42 µg BID (Group B/C), respectively, for a period of two weeks. At the end of week eight, patients in Group B/C will be classified into subgroup I (FEV_1 > 80% and PEF variability over previous two weeks $\leq$ 20%) and subgroup II [FEV_1 $\leq$ 80% predicted or (FEV_1 > 80% predicted and PEF variability over previous two weeks > 20%)]. Then a stratified randomization will take place within each subgroup such that patients in Group B/C will be randomized to Group C (a two step dose reduction/elimination in ICS if they meet safety criteria) (800 → 400 μg at week 8, and 400 → 0 μg at week 16), and Group B (a sham stepwise reduction). All patients in Group A will also undergo a two step dose reduction identical to Group C. After qualifying for SLIC, all patients will receive 2 puffs of salmeterol (42μg) (single blind); one hour later, if their FEV_1 $\geq$ 55% predicted, methacholine bronchoprovocation will be performed. They will visit the clinical center every 2-4 weeks for an interval history and physical examination, diary review, quality of life measurements, and spirometry (see detailed schematic). At all subsequent visits patients in Groups A, B and C will receive 2 puffs of salmeterol (single blind) and, at designated visits, this will be followed one hour later by methacholine bronchoprovocation if their baseline FEV_1 $\geq$ 55% predicted. Sputum induction for analysis of markers of inflammation will not be performed at any subsequent visit. Patients will be assigned treatment failure status if their pulmonary function, beta agonist use, or symptom control significantly worsens as defined by a set of strict criteria. If this occurs prior to the scheduled end of the study, the patients may be rescued using a steroid burst algorithm, while at the same time increasing their dose of triamcinolone acetonide to the baseline dose of 800 μg/day. The patients will continue to be followed and all scheduled visits and testing will occur but no further inhaled corticosteroid dose reductions will be attempted. Patients will continue to take their study salmeterol (or placebo) unless the physician can document that treatment failure status was causally related to taking this medication. Glaxo, Inc. has kindly agreed to supply active and placebo canisters for albuterol (Ventolin®) and salmeterol xinofoate (Serevent®), and Rhône-Poulenc Rorer has graciously consented to supply active and placebo canisters for triamcinolone acetonide (Azmacort®) to be used in this protocol.

III. INCLUSION AND EXCLUSION CRITERIA

A. Inclusion Criteria (at visit 1)

1. Male and female subjects, between the ages of 12 and 65 years.

2. For patients not already taking inhaled corticosteroids:
   a) $FEV_1 \leq 80\%$ of predicted.
   b) Documentation from preceding 6 months of $\geq 12\%$ increase in FEV_1 after aerosolized albuterol.

3. For patients already taking inhaled corticosteroids:
   a) $FEV_1 \geq 40\%$ of predicted.
   b) If FEV_1 is 40-80% of predicted, patient must:
      - provide documentation from preceding 6 months of $\geq 12\%$ increase in FEV_1 after aerosolized albuterol

      OR

      - document from the preceding 6 months or demonstrate a 20% reduction in FEV_1 in response to a concentration of inhaled methacholine ≤ 8 mg/ml (PC_{20} $FEV_1 \leq 8$ mg/ml).
   c) If FEV_1 is > 80% of predicted, patient must document from preceding 6 months or demonstrate a 20% reduction in FEV_1 in response to a concentration of inhaled methacholine $\leq$ 8mg/ml (i.e., $PC_{20}FEV_1 \leq$ 8mg/ml).

4. Ability to provide informed consent, as evidenced by signing a copy of the consent form approved by the Committee on Human Research of the study institution.

5. Non-smoker (total lifetime smoking history $\leq$ 10 pack - years; no smoking for at least 1 year).

6. No smokeless tobacco use for at least one year.

B. Exclusion Criteria (at Visit 1)

1. Use of any drugs listed in Table 1 during the designated washout period prior to Visit 1, or intention to take the drug during the study.

Table 1. Drugs to be withheld throughout the study	Washout prior to Visit 1
Inhaled Steroids, except as provided in study	None
Oral Steroids	≥ 6 weeks
Cromolyn/Nedocromil	≥ 6 weeks
Oral beta-adrenergic agonists	≥ 1 week
Monoamine oxidase inhibitors	≥ 4 weeks
Tricyclic antidepressants	≥ 4 weeks
Beta-adrenergic blockers	≥ 4 weeks
ACE inhibitors	≥ 4 weeks
Inhaled beta-adrenergic agonists (intermediate-acting, e.g., albuterol, terbutaline, metaproterenol, pirbuterol, bitolterol), except provided in study	≥ 8 hours
Salmeterol, except as provided in study	≥ 48 hours
Anticholinergics	≥ 48 hours
Short-acting theophylline (e.g., Slophyllin® tablets)	≥ 12 hours
Long-acting theophylline (e.g., Theo-Dur®, Slo-BID®)	≥ 24 hours
Ultra long-acting theophylline (e.g., Theo-24®, Uniphyl®)	≥ 48 hours
Antihistamines (except for Astemizole and Loratidine, see below)	≥ 72 hours
Astemizole, Loratidine	≥ 72 hours *
Zafirlukast (Accolate)	> 6 weeks
Zileuton (Zyflo)	> 6 weeks

Drugs withheld prior to pulmonary function and/or methacholine challenge, per MOP	Specified time period
Albuterol	≥ 6 hours
Salmeterol Study Drug	≥ 12 hours
Terfenadine (Allegra)	≥ 48 hours
Chlorpheniramine (ChlorTrimeton)	> 48 hours
Methylxanthine-containing foods or beverages (e.g., coffee, tea)	≥ 8 hours
Alcohol-containing foods or beverages	≥ 8 hours

* Since these medications may remain in the body for weeks following administration, it is recommended that prick skin testing with histamine be performed in patients who are currently on treatment. If a flare ≥ 5mm develops following testing, the patient would be eligible for study participation. If not, the patient would need a longer washout period (possibly weeks) prior to retesting and enrollment.

2. Medication use: Chronic use of any medication other than β-agonists and inhaled corticosteroids, except oral contraceptives and other hormonal forms of contraceptives (i.e. DepoProvera®, Norplant®), estrogens/progesterone replacement therapy for post-menopausal women, vitamins, nasal beclomethasone (2 puffs each

nare, BID) at a stable dose throughout the entire study (see MOP), acetaminophen, non-steroidal anti-inflammatory medications (e.g., aspirin, naproxen, ibuprofen), thyroid replacement medications, terfenadine, anticholesterol medication, or medium and low potency topical cutaneous steroids.
Allowable medications also include:

a. calcium supplements
b. nasal saline spray
c. topical eye preparations for allergic eye symptoms (e.g. antihistamines, NSAIDs, or antiallergic compounds)
d. diuretics
e. specific antihypertensives (e.g. calcium channel blockers, clonidine, etc.)
f. antibiotics for acne
g. stool softeners, psyllium
h. acyclovir
i. chlorpheniramine (48 hour washout)
j. pseudoephedrine (48 hour washout)

3. Lung disease other than asthma.

4. Established diagnosis of vocal cord dysfunction.

5. Significant medical illness other than asthma.

6. History of respiratory tract infection within the previous 6 weeks.

7. History of a significant exacerbation of asthma in the previous 6 weeks (see section VI for definition of significant exacerbation and guidelines for treatment).

8. History of life-threatening asthma requiring treatment with intubation and mechanical ventilation within the past 10 years.

9. Hyposensitization therapy other than an established maintenance regimen.

10. Inability, in the opinion of the investigator or clinic coordinator, to coordinate use of a metered dose inhaler (MDI).

11. Changes of ischemic heart disease or arrhythmia on screening ECG (not excluded for occasional, $\leq$ 3/min, atrial or ventricular premature contractions, or clinically insignificant sinus bradycardia).

12. Pregnancy. If potentially able to bear children, not using an acceptable form of birth control (see ACRN MOP, Appendix One).

13. Inability, as evidenced through biological quality control testing, to correctly use an AirWatch™ device for recording peak flow measurements.

C. Inclusion Criteria For Randomization (at Visit 4)

1. Prebronchodilator FEV_1 • 80% of predicted.
2. If FEV_1 is > 80% predicted, average variability $\frac{PM - AM}{1/2\ (PM+AM)}$ in PEF > 20% during the final two weeks of the run-in period (weeks 5 and 6).

3. Ability of the subject to measure his/her AM and PM PEFR on schedule using the AirWatch device, to appropriately mark the measurements using the post-medication marker, and to accurately transcribe the PEFR measurements onto his/her diary cards at least 85% of the time during the last two weeks of the run-in.

D. Exclusion Criteria For Randomization (at Visit 4)

1. Significant exacerbation of asthma during the run-in period (see section VI for definition of significant exacerbation and guidelines for treatment).

2. Inability to comply with regular use of MDI (use of scheduled MDI less than twice/day on more than 12 days in the run-in period), as reflected by the diary card.

3. Failure to record peak flow measurements and symptoms in a symptom diary on average more than two days/week during the run-in period.

4. Any changes with regard to any of the exclusion criteria identified for visit 1 (see Section IIIB above).

5. Use of an average of • 16 puffs of albuterol per 24 hours during last week of run-in (week 6).

6. Prebronchodilator FEV_1 < 55% of predicted normal.

E. Criteria for Stratification into Two Subgroups (based on severity of airway obstruction and/or PEF stability) (Subgroups I and II) at Visit 5

Criteria for stratification into ***Subgroup I:***

1. FEV_1 is > 80% predicted and PEF variability $\frac{PM - AM}{1/2(PM+AM)}$ in previous two weeks is ≤ 20%.

Criteria for stratification into ***Subgroup II:***

1. $FEV_1 \leq 80\%$ of predicted.
2. If FEV_1 is > 80% predicted, average variability $\frac{PM-AM}{1/2(PM+AM)}$ in PEF > 20% during the previous two weeks.

F. Criteria For Assigning Treatment Failure Status During Double-blind Treatment Period (weeks 7-24)

Treatment failure status will be defined as the occurrence of one or more of the following:

*At-home measurements:**

1. PREbronchodilator PEF ≤ 65% of baseline on any 2 of 3 consecutive scheduled measurements.

   Baseline is defined as the average prebronchodilator AM PEF value recorded during the last two weeks of the run-in (weeks 5 and 6).

2. POSTbronchodilator AM PEF ≤ 80% of baseline.

   For postbronchodilator AM PEF value, subject may take ≥ 6 puffs of albuterol within 1 hour (2-4 puffs every 20 minutes).

   Baseline is defined as the average prebronchodilator AM PEF value recorded during the last two weeks of the run-in (weeks 5 and 6).

3. An increase in PRN albuterol use of 8 puffs per 24 hours over baseline use for a period of 48 hrs or ≥ 16 puffs/24 hrs for 48 hrs.

   Baseline is defined as average daily use during the last two weeks of the run-in (weeks 5 and 6).

* Patients will be instructed to contact the ACRN study site immediately should any of these events occur.

In-clinic measurements:

1. POSTbronchodilator $FEV_1 \leq 80\%$ of the baseline POSTbronchodilator value obtained at Visit 4. All values obtained one hour post-salmeterol (single blind).

2. PREbronchodilator FEV_1 values on 2 consecutive sets of spirometric determinations which are $\leq$ 80% of the baseline PREbronchodilator value obtained at Visit 4. This would involve the following comparisons:

   Visit 6 and Visit 5
   Visit 7 and Visit 6
   Visit 8 and Visit 7
   Visit 9 and Visit 8
   Visit 10 and Visit 9
   Visit 11 and Visit 10

   ADDENDUM: As an addendum to these criteria, the subject will also be a treatment failure if the following set of circumstances occurs:

   If the prebronchodilator FEV_1 value at Visit 5 or later is $\leq$ 80% of the PREbronchodilator value obtained at Visit 4, the patient should be given albuterol ($\geq$ 6 puffs in one hour) to assess the degree of reversibility in his/her airflow obstruction. These values must be reported to the physician responsible for the care of the ACRN patient on that day. If the physician determines that the subject's response to the bronchodilator is satisfactory, and the patient's clinical condition is stable, the patient may continue in the study, provided he/she returns to the ACRN study site in 24-96 hours for repeat spirometry. In addition, the clinic coordinator or designee shall telephone the patient every 24 hrs to assess his/her condition. Prior to leaving the clinic, the patient should receive the usual doses of his/her study medications; no additional procedures scheduled for that study day shall be performed. At the additionally scheduled visit within the next 4 days, the repeat spirometric PREbronchodilator FEV_1 value must be > 80% of PREbronchodilator value obtained at Visit 4; if not, the patient will be considered a treatment failure at that time. If spirometric values are within the acceptable range, all procedures for the previously scheduled visit shall be performed according to the MOP and the patient will continue on his/her study medications.

Additional Treatment Failure Criteria:

1. Any use of oral or parenteral corticosteroids related to the treatment of the patient's asthma.

2. Occurrence of a significant exacerbation during the double-blind period.

3. Need for emergency treatment at a medical facility that is related to, or complicated by, the patient's asthma and which results in corticosteroid treatment or hospitalization for an acute asthma exacerbation.

4. Physician clinical judgment for safety reasons.

G. Criteria for Inhaled Corticosteroid Dose Reduction

1. The inhaled corticosteroid dose will be reduced from 800 to 400 μg at visit 5 and from 400 to 0 μg on visit 7, unless the patient has met the criteria for treatment failure status on the day of their visit or in the interval since their last visit.

2. If patients meet criteria for treatment failure status, their dose of inhaled corticosteroids will be increased to the dose they were receiving at visit 4 (800 µg/day) delivered by an open-label inhaler. Study inhalers of corticosteroids (or its placebo) will be returned to the clinical center. If they meet the criteria detailed in Section VI, they will be treated with appropriate rescue algorithms for an asthma exacerbation. Study inhalers of salmeterol (or placebo) will be continued unless the physician can document that treatment failure status was causally related to taking this medication. They will continue to participate in the study until its termination (intent-to-treat analysis), but no further reductions in inhaled corticosteroid dose will be attempted during this time period. For safety reasons, all subjects will be seen within one week (± 3d) from the day they were categorized as achieving treatment failure status. Following this "safety" visit, subsequent protocol visits will continue in accordance with the visit schedule established at Visit 1 (see SOCS/SLIC MOP for details concerning possible replacement of scheduled protocol visits with treatment failure related visits).

IV. OUTCOME VARIABLES

The primary outcome variable will be the time to treatment failure. It will be evaluated using a Kaplan-Meier survival analysis. Secondary outcome indicators will include comparisons of FEV_1, mean peak flow variability (PM-AM peak flow difference normalized by the average of the AM and PM peak flow), methacholine airway responsiveness following premedication with salmeterol (evaluation of bronchoprotective effect), asthma symptom scores, quality of life, and rescue medication use at visits 5-11 to those obtained at visit 4.

Daily data obtained from post-randomization diary cards will be summarized and analyzed as averages. Because subjects are instructed to withhold their study salmeterol (or placebo) for 12 hours prior to a visit, the affected peak flow values will be excluded.

V. PROTOCOL

A. Subjects

1. **Sample size.** This trial has a target sample size of 150 randomized patients, with 20 in Group A, 65 in Group B, and 65 in Group C. See section X.F for the derivation of this sample size.

2. **Subjects.** This study will require a total of 150 randomized subjects with moderate asthma. Patients will be recruited from the "standing" populations of the participating centers, by advertisement, and by referral from participating physicians. Patients will meet the inclusion criteria specified herein and not possess any of the exclusion criteria. Both heterogeneity of the study group and rapidity of recruitment are greatly facilitated by the involvement of several geographically dispersed study centers in a multi-center collaboration. For the randomization that occurs at visit 5, there will be stratification according to ethnic group, gender, and age. Each center can recruit no more than 25% of patients from the 12-18 years age group. Every attempt will be made by each center to enroll approximately equal numbers of patients of either gender and to include in their enrolled patients at least 33% (at least a total of 50 patients) from under-represented minorities (Native Americans, Asian-Pacific Islanders, African-Americans, and Hispanics) in order to permit generalizability of the findings to the patient population of interest. The 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 problems in achieving demographic goals.

B. Recruitment

Each clinical center involved in the ACRN was chosen based on documentation for patient availability, among other things. It is, however, worthy to note the specific plans of each center.

Harvard Clinical Center/Boston

1. Need

Approximately 30 patients with moderate asthma are needed to fulfill the recruitment needs of this study at this center. We propose to use the population at Harvard Community Health Plan to achieve our enrollment goals.

2. Potential Participants Stratified by Severity

To assess the number of potential participants, computerized pharmacy records of all individuals who had been Plan members for at least 3 months, who were between 12 and

65 years of age, who had pharmacy benefits and who had received prescriptions for β-agonists plus inhaled steroids were selected. Such individuals were also retained in this category if they received concurrent prescriptions for one other asthma medication such as theophylline, cromolyn, or nedocromil. Severe asthma was operationally defined as being extant in those individuals who had received prescriptions for β-agonists plus 2 or more asthma drugs where one of these agents was oral or inhaled steroids. Prescription frequency was not considered when assigning severity categories between moderate and severe patients; failure to consider this may have resulted in an inappropriate assignment of severity category.

3. Results
9,885 asthmatic individuals were identified of whom 7,588 (76.7%) met the definition of mild asthma, 1,883 (19.0%) met the criteria for moderate asthma and 414 (4.3%) met the criteria for severe asthma.

4. Recruitment strategy
We will contact a fraction of the 1,883 individuals identified as having moderate asthma by the pharmacy search by letter. In this solicitation, attention will be paid to postal zip code to achieve the needed minority patients.

National Jewish Center/Denver

Research subject recruitment has been very successful for all types of asthma patients at the National Jewish Center for Immunology and Respiratory Medicine. The total of 30 subjects with one-half being female and one-third minority population will come from the following areas.

1. National Jewish Center 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 approximately 50% are in the moderate 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 40% are in the moderate category. Ninety-seven additional children were seen in follow-up. The National Jewish Center has 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 Center Asthma Research Pool. There are over 200 asthma patients (not followed in the NJC outpatient clinic) that have participated in our research studies. Many of these subjects have been through various medication studies and bronchoscopies with lavage/biopsies. Their FEV_1s range from 30-110% of predicted.
a. Denver Health Medical Center - Dr. Michael Hanley, Acting 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. Carol Welch, acting Pulmonary Director, will support this grant. The VA hospital has a large outpatient clinic of patients with asthma, but not chronic obstructive pulmonary disease.
c. Denver Kaiser Permanente HMO. Dr. Timothy Collins is the Director of Pulmonary Medicine and Dr. William Marsh is the Director of Allergy at Kaiser. Drs. Collins and Marsh have been actively involved in supporting research at NJC in the past by referring us patients. Their groups will continue to play an active role.
d. Dr. Jay Markson is a pediatrician in a large inner city clinic and will support this grant by recruitment of patients.

University of Wisconsin/Madison

The Allergy Research Program of the University of Wisconsin maintains a file of potential subjects with moderate asthma (FEV_1 40-80%) who are interested in future research participation. These individuals have been screened and/or participated in previous asthma studies. The following information is maintained: birth date, gender, ethnic background, age of asthma diagnosis, childbearing status, atopic status (including results of skin testing if performed previously), concurrent medical history, asthma and non-asthma medications. This database of subjects will be used as the primary source of recruitment for this protocol. If additional subjects are needed, they will be recruited via U.W. Human Subjects committee-approved, newspaper advertising and from the U.W. Allergy Clinics (Pediatric and Adult) patient population. Also, the U.W. Adolescent Clinic, U.W. Sports Medicine Clinic, U.W. Student Health, V.A. Allergy Clinic, Northeast Family Practice Clinic, Wingra Family Practice Clinic and Verona Family Practice Clinic will serve as other patient sources, in cooperation with the patient's primary physician. Referrals from the private allergy clinics in town will also be sought. Radio and television advertising may be utilized. Approved recruitment ads will be posted in churches, community centers, grocery stores, and U.W. Student Organization headquarters. Recruitment of women and minorities from the available pool will be emphasized. To improve the recruitment of people of color, especially African-Americans, a part-time community liaison has been hired to assist. This population is being targeted by placing advertisements and articles in community newspapers and journals. Community-based programs have been established in order to increase awareness about the University of Wisconsin Allergy Research Program's studies and to develop trust within the community. In addition, work is being done to try to eliminate any barriers that might prevent someone from participating such as lack of transportation.

Harlem Prevention Center/New York

Central Harlem has a residentially stable population of approximately 115,000 of whom 98% are African American or Hispanic, and 53% are women. The prevalence of asthma in Central Harlem is 3-4 times that in the U.S. population. Harlem Hospital and its network

of community-based clinics, together comprise the Northern Manhattan Network. Through the Network, the Harlem Asthma Research Center (HARC) has identified more than 2,000 asthmatic patients who are in stable primary care relationships, and established collaborative arrangements with their primary care providers.

The Harlem Asthma Research Center will initially recruit participants in ACRN clinical trials through this network of collaborating providers. While the Center will specifically target people of color, it will never turn anyone away.

The investigators anticipate no difficulty in recruitment of women. Accrual of participants will be monitored for all protocols. If targeted approaches are needed, the HARC will consider strategies which have been used successfully to recruit and sustain the participation of women in this community. These have included provision of transportation, meals, child care, home visits, utilizing peer educators, the formation of a woman's support group, culturally appropriate education efforts and linkages to support services.

Primary care physicians from the Northern Manhattan Network will approach their patients about their willingness to participate in the clinical trials. If they are interested, the screening and all follow-up visits will take place at the Harlem ACRN Clinical Center. Because asthma clinical trials will require procedures that are not performed routinely in primary care offices, appropriate procedures will be followed so that patients participate fully in ACRN protocols while staying in contact with their primary care providers as needed.

Thomas Jefferson Medical College/Philadelphia

All patients with a diagnosis of asthma currently cared for in the outpatient offices of the Division of Pulmonary Medicine and General Internal Medicine and the Departments of Family Medicine and Pediatrics are listed in a computerized data-base. Approximately 23% of asthmatics in this database have "moderate" asthma. Terminals located at each clinic site are linked to the ACRN file server located in the study coordinator's office. Patients fulfilling every criteria for this study will be identified in the database, and personal contact will be made by the study coordinator for purposes of explaining the study and enlisting their participation. If on initial contact, the patient agrees, they will return to the study center to verify entry qualifications and further discuss the study.

University of California/San Francisco

Our approach to recruiting subjects with asthma for research studies relies heavily on community advertising. We place advertisements in editions of the San Francisco Chronicle and Examiner, in small neighborhood newspapers, and on bulletin boards on the UCSF campus, in community health centers, and at campuses of colleges and universities in the Bay Area. We also place advertisements on two popular radio stations (one "soft rock" station; one "soul" station). Finally, we place fliers in the waiting areas of the

Pulmonary Medicine and Allergy clinics at the major teaching hospitals of UCSF (Moffitt-Long, San Francisco General Hospital, Ft. Miley VA Hospital, and Mt. Zion Hospital). Responses to these advertisements are made to a dedicated telephone number equipped with voice mail. We have hired a full-time recruiter to respond to each inquiry and to obtain basic information about the subject's demographics and about the severity, duration, required treatment, and frequency of symptoms of asthma. Subjects who pass this telephone screen and who are interested in proceeding are scheduled for a screening appointment in the laboratory. We have obtained permission from our institutional review board to perform basic, simple screening tests on potential research subjects to determine if they qualify for research studies. These tests include a focused medical history, spirometry, prick skin testing with allergen mixes common to Northern California, and methacholine challenge.

To improve our recruitment of ethnic minorities, especially African-Americans, we have opened a second, "satellite" research site in space leased by the UCSF General Clinical Research Center (GCRC) at Summit Hospital in Oakland, CA. This site was established by Dr. Curtis Morris, GCRC Director, for a study of the effects of potassium supplementation on hypertension in African-Americans. Dr. Morris has generously allowed us to consult with his clinical research staff for identification of the publications, radio stations, physician practices, community health centers, and census tracts where they have been most successful in recruiting people of minority ethnicity for research studies. People who call to express interest are screened by telephone and by a characterization visit, as described above, except that all procedures are performed at the satellite research site.

To date, we have screened well over 500 subjects for our database. Of those screened at the Moffitt-Long site, less than 10% are members of ethnic minorities. Over 60% of those screened at the Oakland satellite are of this category.

C. Drug Supplies

Drug supplies for this study will consist of the inhaled corticosteroid, triamcinolone acetonide (delivery of 100 μg/puff), to be supplied by Rhône-Poulenc Rorer, salmeterol xinolate (21 μg/puff) and albuterol (90 μg/puff) to be supplied by Glaxo, Inc. Both companies will supply matching placebo canisters. The ACRN will contract with ProClinical, Inc. to work with the DCC to ensure proper blinding and coding of drugs (see Section X.B.). The participation of the pharmaceutical companies in this protocol is limited to the provision of drugs and placebos. They have not participated in the design of the study.

D. Compliance and Monitoring

In order to determine subject compliance with study drug usage, information recorded on subjects' diary cards regarding number of puffs taken from each inhaler each day will be reviewed at each visit. Limitations of this mechanism for monitoring compliance are accuracy of the subject's recall and honesty.

E. Visit Structure

Visit 0, Prescreening

Subjects will be interviewed prior to protocol entry (either by phone or in person) regarding their asthma and medical history. Specifically, the current status of asthma control, use of asthma and non-asthma medications, and health status in the previous 6 weeks will be determined. An overview of the goals of the study and the visit structure and procedures involved will be presented. If the patient appears to fulfill entry criteria, is interested in study participation, and is not taking oral corticosteroids or inhaled nedocromil or cromolyn, Visit 1 may be scheduled. If the patient is taking one of these asthma medications regularly, a pre-study visit must be scheduled, informed consent obtained, and the patient evaluated by the study investigator as to the appropriateness of drug withdrawal for the 6 weeks prior to Visit 1. If warranted, the investigator may request additional pre-study visits for evaluation of asthma stability during this 6 week period.

Visit 1, Week 0

Patients will visit their clinical center after having had verbal contact with one of the study investigators, or their representatives, concerning the general goal and outline of the trial. On this first visit, written Informed Consent will be obtained, using a document which has been approved by the ACRN as well as by the local IRB. A medical history, physical examination, allergy skin testing, vital signs, spirometry, and 12-lead electrocardiogram will be obtained. Urine will be obtained for a pregnancy test in females and blood will be drawn for determination of serum electrolytes and for DNA extraction and possible subsequent genetic analysis. (see Section V.F for timetable of visits and data collected).

If the individual qualifies for the study based on these data, the Quality of Life Questionnaires will be administered, and methacholine challenge and sputum induction will be performed. The Quality of Life Questionnaires (Juniper and SF-36) will always be administered prior to methacholine challenge and sputum induction. Methacholine challenge will always be performed prior to sputum induction.

Allergy skin testing, spirometry, methacholine challenge, and sputum induction will be administered according to protocols outlined in the ACRN MOP. All data will be recorded electronically and on forms supplied by the ACRN.

If, based on the information gathered to this point, the patient meets the specific entry criteria, he/she will be entered into the (run-in phase of the) trial, and genetic analysis will be performed on the blood sample. Patients will be given an "open label" regular use inhaler (triamcinolone acetonide, 100μg/puff)) to be used 4 puffs twice a day, a peak flow measuring device (AirWatch™), and an albuterol "open-label" inhaler to be used for rescue treatment. Prior to distribution, the AirWatch readings will be checked using a Jones-Flow Volume calibrator. Only AirWatches whose readings are within a specified range of the Jones will be distributed. Patients will be taught how to use their AirWatches and MDI's. They will be instructed to measure peak flow and then use their corticosteroid inhaler immediately upon arising and at bedtime (between 2000 and 0100 hrs.). The use of diary cards will be explained and patients will be given an appropriate supply. Patients will be instructed to mark peak flow values obtained less than 2 hours after use of inhaled albuterol by circling them on their diary cards. Patients will be instructed to return to the clinical center in 2 weeks.

Visit 2, Week 2

Patients will return to the clinical center at the same time of day as on week 0. If scheduling permits, all subsequent visits will occur within a ± 2-hour window on the study day. Spirometry will be obtained. The patient's AirWatch will be tested against the Jones-Flow Volume calibrator and will be replaced if it does not meet defined quality control standards. Adverse events will be assessed and recorded using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; AirWatch data will be uploaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording. Guidelines will be reviewed as needed. Open label inhaled corticosteroid and albuterol will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks.

Visit 3, Week 4

Patients will return to the clinical center at the same time of day as on week 0, ± 2 hours. Spirometry will be obtained. The patient's AirWatch will be tested against the Jones-Flow Volume calibrator and will be replaced if it does not meet defined quality control standards. Adverse events will be assessed and recorded using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; AirWatch data will be uploaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording. Guidelines will be reviewed as needed. Open label inhaled corticosteroid and albuterol will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks.

Visit 4, Week 6

Patients will return to the clinical center at the same time of day as on week 0, ± 2 hours. Quality of life questionnaires will be administered. Urine will be obtained for a pregnancy test in females. The patient's AirWatch will be tested against the Jones-Flow Volume calibrator and will be replaced if it does not meet defined quality control standards. Adverse events will be assessed and recorded using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; AirWatch data will be uploaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording. Guidelines will be reviewed as needed.

If at this time, in the opinion of the clinical center personnel, the patient understands and can follow the protocol adequately to participate in the study, pulmonary function will be performed and the patient's peak flow data over the past two weeks reviewed. If the prebronchodilator FEV_1 is $\leq$ 80% and $\geq$ 55% of predicted, or if it is > 80% predicted but the peak flow variability in the previous week is > 20%, the patient is eligible for the SLIC protocol. All other patients are potentially eligible for the SOCS protocol. Further testing with regard to sputum induction and/or methacholine challenge testing will be performed based on the following flow diagram.

Diagram for Methacholine Bronchoprovocation and Sputum Induction At Visit 4

Since sputum induction will not be performed in the SLIC Protocol, two different strategies for methacholine bronchoprovocation will be employed at visit 4 once the patient has been assigned to either SOCS or SLIC.

Perform baseline spirometry and calculate PEF variability from diary cards
(If FEV_1 > 80% predicted)

↙ ↘

FEV_1 > 80% predicted and
PEF variability ≤ 20%
in past 2 weeks (weeks 5 & 6)

↓

Eligible for **SOCS**

↓

Perform methacholine bronchoprovocation per protocol in MOP

↓

Randomize Patient

↓

Perform sputum induction per protocol in MOP

*This timing of the methacholine challenge in relationship to salmeterol dosing is important in evaluating bronchoprotection properties. [14, 15]

** Patients will be advised that an FDA-approved bronchodilator medication will be administered at this time, without specifically identifying its precise generic or trade name (single blind).

FEV_1 is 55 to 80% of predicted or
FEV_1 >80% predicted but
PEF variability > 20%
in past 2 weeks (weeks 5 & 6)

↓

Eligible for **SLIC**

↓

Give 2 puffs of salmeterol (42 μg) **
from MDI

↓

Wait 1 hour *

↓

If FEV_1 < 55% predicted, stop the visit and make one attempt to reschedule methacholine challenge within the visit window

If FEV_1 ≥ 55% predicted,
perform methacholine bronchoprovocation per protocol in MOP

↓

Randomize Patient

↓

Dispense Study Medications

↓

No sputum induction performed.
Continue with Visit 4 procedures on SLIC checklist.

If the patient continues to meet the inclusion criteria for the study, and fulfills the criteria for randomization, the ACRN DCC will be contacted and the patient will be randomized to either active salmeterol (13/15) (treatment Group B/C) or placebo salmeterol (2/15) (treatment Group A). Based upon this randomization, all patients will receive a coded, double-blind "regular use" inhaler to be taken twice a day (salmeterol or placebo). They will also receive two additional coded, double-blind inhalers to be taken twice daily at the same time the other blinded inhaler is taken. The inhalers will contain triamcinolone and the patients will be instructed to take two puffs of each inhaler twice daily. All patients will receive open label albuterol inhalers, to be used as needed for rescue treatment. Thus, each patient will receive a total of 4 inhalers. Prednisone tablets will also be provided. New diary cards will be issued. Based on data obtained in the previous two weeks, values for lower limits of acceptable peak flow measurements (prebronchodilator PEF < 65% of the mean value of AM prebronchodilator PEF recorded for the two weeks (weeks 5 and 6) prior to Visit 4 on any 2 of 3 consecutive scheduled measurements) will be calculated for each individual. They will be instructed to contact the study center immediately if peak flow measurements fall outside the acceptable range. They will also be instructed as to the level of rescue medication use which would be in excess of acceptable limits, and the need to contact the study center immediately if usage exceeds these limits. Patients will be asked to withhold their rescue inhaler for 6 hours and their salmeterol (or placebo) inhaler for at least 12 hours (to facilitate both AM and PM patient visits and to maximize the consistency of the time at which methacholine bronchoprovocation is performed in relationship to salmeterol dosing) prior to all future visits. Patients will be instructed to return to the clinical study center in 2 weeks.

Telephone Call, Week 7

Patients will be contacted by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, to answer any questions that may arise, and to assure that their asthma is under adequate control, as assessed by the patient. The coordinator will attempt to determine whether the patient is showing signs of treatment failure. Specifically, the coordinator will inquire about rescue β-agonist use, peak flow measurements and symptoms. If it is determined that the patient fulfills criteria for treatment failure, they will be advised to visit the study center within 24 hours for evaluation and initiation of treatment as specified by ACRN protocol (see section VI). Otherwise, arrangements will be made for the patient to return to the clinic in 1 week.

Visit 5, Week 8

Patients will return to the clinical center at the same time of day as on week 0, ± 2 hours. Quality of life questionnaires will be administered. Spirometry will be obtained. The patient's AirWatch will be tested against the Jones-Flow Volume calibrator and will be replaced if it does not meet defined quality control standards. Adverse events will be assessed and recorded using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; AirWatch data will be uploaded. Clinical center

personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording. All patients should have withheld their rescue inhaler for at least 6 hours and their salmeterol (or placebo) inhaler for at least 12 hours prior to the visit. Following baseline spirometry, all patients will receive 2 puffs of salmeterol (42 μg) (single blind). One hour later, if the postbronchodilator $FEV_1 \geq 55\%$ predicted, methacholine bronchoprovocation will be performed. If the postbronchodilator $FEV_1 < 55\%$ predicted, one attempt will be made to schedule the subject for retesting within the visit window, and the current visit will be stopped. If the subject cannot be rescheduled, all remaining visit procedures, with the exception of the methacholine bronchoprovocation, will be carried out and the visit completed. Guidelines for peak flow safety limits and rescue medication use will be reviewed. Patients will be randomized into their final study treatment groups. Those on active salmeterol at Visit 5 will be randomized to receive either the ICS reduction (Group C) or the sham reduction (Group B), whereas patients on placebo salmeterol at Visit 5 (Group A) will all undergo the ICS reduction. Patients in Group A will undergo a sham randomization in order to preserve all levels of blinding. Patients will receive two new coded, double-blind "steroid" inhalers to be taken 2 puffs twice daily. They will also receive a new "salmeterol" inhaler (placebo in Group A, active drug in Groups B and C) and will be further instructed to maintain at a dose of 2 puffs twice daily. Following methacholine bronchoprovocation, 2 puffs of albuterol will be administered. Open label albuterol will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks.

If patients meet criteria for treatment failure status, their dose of inhaled corticosteroids will be increased to the dose they were receiving at visit 4 (800 μg/day) delivered by an open-label inhaler. Study inhalers of corticosteroids (or its placebo) will be returned to the clinical center. If they meet the criteria detailed in Section VI, they will be treated with appropriate rescue algorithms for an asthma exacerbation. Study inhalers of salmeterol (or placebo) will be continued unless the physician can document that treatment failure status was causally related to taking this medication. They will continue to participate in the study until its termination (intent-to-treat analysis), but no further reductions in inhaled corticosteroid dose will be attempted during this time period. For safety reasons, all subjects will be seen within one week (± 3d) from the day they were categorized as achieving treatment failure status. Following this "safety" visit, subsequent protocol visits will continue in accordance with the visit schedule established at Visit 1 (see SOCS/SLIC MOP for details concerning possible replacement of scheduled protocol visits with treatment failure related visits).

Drug Swap Visit, Week 10

Patients will return to the clinical center 2 weeks after Visit 5. The "salmeterol" inhaler will be exchanged during this visit. Diary cards will be reviewed to determine whether the patient is showing signs of treatment failure. Specifically, the coordinator will inquire about rescue β-agonist use, peak flow measurements and day and nocturnal symptoms. If it is

determined that the patient fulfills criteria for treatment failure, a treatment failure visit will be completed and study medications will be adjusted accordingly.

Visit 6, Week 12

Patients will return to the clinical center at the same time of day as on week 0, ± 2 hours. Quality of life questionnaires will be administered. Spirometry will be obtained. The patient's AirWatch will be tested against the Jones-Flow Volume calibrator and will be replaced if it does not meet defined quality control standards. Adverse events will be assessed and recorded using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; AirWatch data will be uploaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording. All patients should have withheld their rescue inhaler for at least 6 hours and their salmeterol (or placebo) inhaler for at least 12 hours prior to the visit. Following baseline spirometry, all patients will receive 2 puffs of salmeterol (42 μg) (single blind). One hour later, if the postbronchodilator $FEV_1 \geq 55\%$ predicted, methacholine bronchoprovocation will be performed. Guidelines for peak flow safety limits and rescue medication use will be reviewed. If the patient does not meet criteria for treatment failure, they will receive two new coded, double-blind "steroid" inhalers to be taken 2 puffs twice daily. They will also receive a new "salmeterol" inhaler (placebo in Group A, active drug in Groups B and C) inhaler and will be further instructed to maintain at a dose of 2 puffs twice daily. Following methacholine bronchoprovocation, 2 puffs of albuterol will be administered. Open label albuterol will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks.

If patients meet criteria for treatment failure status, their dose of inhaled corticosteroids will be increased to the dose they were receiving at visit 4 (800 μg/day) delivered by an open-label inhaler. Study inhalers of corticosteroids (or its placebo) will be returned to the clinical center. If they meet the criteria detailed in Section VI, they will be treated with appropriate rescue algorithms for an asthma exacerbation. Study inhalers of salmeterol (or placebo) will be continued unless the physician can document that treatment failure status was causally related to taking this medication. They will continue to participate in the study until its termination (intent-to-treat analysis), but no further reductions in inhaled corticosteroid dose will be attempted during this time period. For safety reasons, all subjects will be seen within one week (± 3d) from the day they were categorized as achieving treatment failure status. Following this "safety" visit, subsequent protocol visits will continue in accordance with the visit schedule established at Visit 1 (see SOCS/SLIC MOP for details concerning possible replacement of scheduled protocol visits with treatment failure related visits).

Drug Swap Visit, Week 14

Patients will return to the clinical center 2 weeks after Visit 6. The "salmeterol" inhaler will be exchanged during this visit. Diary cards will be reviewed to determine whether the

patient is showing signs of treatment failure. Specifically, the coordinator will inquire about rescue β-agonist use, peak flow measurements and day and nocturnal symptoms. If it is determined that the patient fulfills criteria for treatment failure, a treatment failure visit will be completed and study medications will be adjusted accordingly.

Visit 7, Week 16

Patients will return to the clinical center at the same time of day as on week 0, ± 2 hours. Quality of life questionnaires will be administered. Spirometry will be obtained. The patient's AirWatch will be tested against the Jones-Flow Volume calibrator and will be replaced if it does not meet defined quality control standards. Adverse events will be assessed and recorded using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; AirWatch data will be uploaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording. All patients should have withheld their rescue inhaler for at least 6 hours and their salmeterol (or placebo) inhaler for at least 12 hours prior to the visit. Following baseline spirometry, all patients will receive 2 puffs of salmeterol (42 μg) (single blind). One hour later, if the postbronchodilator $FEV_1 \geq 55\%$ predicted, methacholine bronchoprovocation will be performed. Guidelines for peak flow safety limits and rescue medication use will be reviewed. If the patient does not meet criteria for treatment failure, they will receive two new coded, double-blind "steroid" inhalers to be taken 2 puffs twice daily (in Groups A and C, these will be placebo inhalers; in Group B, these will be active inhalers). They will also receive a new "salmeterol" inhaler (placebo in Group A, active drug in Groups B and C) and will be further instructed to maintain at a dose of 2 puffs twice daily. Following methacholine bronchoprovocation, 2 puffs of albuterol will be administered. Open label albuterol will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks.

If patients meet criteria for treatment failure status, their dose of inhaled corticosteroids will be increased to the dose they were receiving at visit 4 (800 μg/day) delivered by an open-label inhaler. Study inhalers of corticosteroids (or its placebo) will be returned to the clinical center. If they meet the criteria detailed in Section VI, they will be treated with appropriate rescue algorithms for an asthma exacerbation. Study inhalers of salmeterol (or placebo) will be continued unless the physician can document that treatment failure status was causally related to taking this medication. They will continue to participate in the study until its termination (intent-to-treat analysis), but no further reductions in inhaled corticosteroid dose will be attempted during this time period. For safety reasons, all subjects will be seen within one week (± 3d) from the day they have been categorized as achieving treatment failure status. Following this "safety" visit, subsequent protocol visits will continue in accordance with the visit schedule established at Visit 1 (see SOCS/SLIC MOP for details concerning possible replacement of scheduled protocol visits with treatment failure related visits).

Telephone call, Week 17

Patients will be contacted by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, to answer any questions that may arise, and to assure that their asthma is under adequate control, as assessed by the patient. The coordinator will attempt to determine whether the patient is showing signs of treatment failure. Specifically, the coordinator will inquire about rescue β-agonist use, peak flow measurements and symptoms. If it is determined that the patient fulfills criteria for treatment failure, they will be advised to visit the study center within 24 hours for evaluation and initiation of treatment as specified by ACRN protocol (see Section VI). Otherwise, arrangements will be made for the patient to return to the clinic in 1 weeks.

Visit 8, Week 18

Patients will return to the clinical center at the same time of day as on week 0, ± 2 hours. Following baseline spirometry, all patients will receive 2 puffs of salmeterol (42μg) (single blind). One hour later postbronchodilator spirometry will be obtained (i.e., salmeterol reversibility testing). The patient's AirWatch will be tested against the Jones-Flow Volume calibrator and will be replaced if it does not meet defined quality control standards. Adverse events will be assessed and recorded using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; AirWatch data will be uploaded. Clinical center personnel will review the appropriateness of the timing of the medication use, peak flow recording and symptom recording. If the patient does not meet criteria for treatment failure, they will receive two new coded, double-blind "steroid" inhalers to be taken 2 puffs twice daily. They will also receive a new "salmeterol" inhaler (placebo in Group A, active drug in Groups B and C) and will be further instructed to maintain a dose of 2 puffs twice daily. Open label albuterol will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks.

If patients meet criteria for treatment failure status, their dose of inhaled corticosteroids will be increased to the dose they were receiving at visit 4 (800 μg/day) delivered by an open-label inhaler. Study inhalers of corticosteroids (or its placebo) will be returned to the clinical center. If they meet the criteria detailed in Section VI, they will be treated with appropriate rescue algorithms for an asthma exacerbation. Study inhalers of salmeterol (or placebo) will be continued unless the physician can document that treatment failure status was causally related to taking this medication. They will continue to participate in the study until its termination (intent-to-treat analysis), but no further reductions in inhaled corticosteroid dose will be attempted during this time period. For safety reasons, all subjects will be seen within one week (± 3d) from the day they were categorized as achieving treatment failure status. Following this "safety" visit, subsequent protocol visits will continue in accordance with the visit schedule established at Visit 1 (see SOCS/SLIC MOP for details concerning possible replacement of scheduled protocol visits with treatment failure related visits).

Telephone call, Week 19

Patients will be contacted by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, to answer any questions that may arise, and to assure that their asthma is under adequate control, as assessed by the patient. The coordinator will attempt to determine whether the patient is showing signs of treatment failure. Specifically, the coordinator will inquire about rescue β-agonist use, peak flow measurements and symptoms. If it is determined that the patient fulfills criteria for treatment failure, they will be advised to visit the study center within 24 hours for evaluation and initiation of treatment as specified by ACRN protocol (see Section VI). Otherwise, arrangements will be made for the patient to return to the clinic in 1 week.

Visit 9, Week 20

Patients will return to the clinical center at the same time of day as on week 0, ± 2 hours. Quality of life questionnaires will be administered. Spirometry will be obtained. The patient's AirWatch will be tested against the Jones-Flow Volume calibrator and will be replaced if it does not meet defined quality control standards. Adverse events will be assessed and recorded using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; AirWatch data will be uploaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording. All patients should have withheld their rescue inhaler for at least 6 hours and their salmeterol (or placebo) inhaler for at least 12 hours prior to the visit. Following baseline spirometry, all patients will receive 2 puffs of salmeterol (42 μg) (single blind). One hour later, if the postbronchodilator $FEV_1 \geq 55\%$ predicted, methacholine bronchoprovocation will be performed. Guidelines for peak flow safety limits and rescue medication use will be reviewed. If the patient does not meet criteria for treatment failure, they will receive two new coded, double-blind "steroid" inhalers to be taken 2 puffs twice daily. They will also receive a new "salmeterol" inhaler (placebo in Group A, active drug in Groups B and C) and will be further instructed to maintain a dose of 2 puffs twice daily. Following methacholine bronchoprovocation, 2 puffs of albuterol will be administered. Open label albuterol will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks.

If patients meet criteria for treatment failure status, their dose of inhaled corticosteroids will be increased to the dose they were receiving at visit 4 (800 μg/day) delivered by an open-label inhaler. Study inhalers of corticosteroids (or its placebo) will be returned to the clinical center. If they meet the criteria detailed in Section VI, they will be treated with appropriate rescue algorithms for an asthma exacerbation. Study inhalers of salmeterol (or placebo) will be continued unless the physician can document that treatment failure status was causally related to taking this medication. They will continue to participate in the study until its termination (intent-to-treat analysis), but no further reductions in inhaled corticosteroid dose will be attempted during this time period. For safety reasons, all subjects will be seen within one week (± 3d) from the day they were categorized as

achieving treatment failure status. Following this "safety" visit, subsequent protocol visits will continue in accordance with the visit schedule established at Visit 1 (see SOCS/SLIC MOP for details concerning possible replacement of scheduled protocol visits with treatment failure related visits).

Telephone call, Week 21

Patients will be contacted by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, to answer any questions that may arise, and to assure that their asthma is under adequate control, as assessed by the patient. The coordinator will attempt to determine whether the patient is showing signs of treatment failure. Specifically, the coordinator will inquire about rescue β-agonist use, peak flow measurements and symptoms. If it is determined that the patient fulfills criteria for treatment failure, they will be advised to visit the study center within 24 hours for evaluation and initiation of treatment as specified by ACRN protocol (see Section VI). Otherwise, arrangements will be made for the patient to return to the clinic in 1 week.

Visit 10, Week 22

Patients will return to the clinical center at the same time of day as on week 0, ± 2 hours. Following baseline spirometry, all patients will receive 2 puffs of salmeterol (42 μg) (single blind). One hour later postbronchodilator spirometry will be obtained (i.e., salmeterol reversibility testing). The patient's AirWatch will be tested against the Jones-Flow Volume calibrator and will be replaced if it does not meet defined quality control standards. Adverse events will be assessed and recorded using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; AirWatch data will be uploaded. Clinical center personnel will review the appropriateness of the timing of the medication use, peak flow recording and symptom recording. If the patient does not meet criteria for treatment failure, they will receive two new coded, double-blind "steroid" inhalers to be taken 2 puffs twice daily. They will also receive a new "salmeterol" inhaler (placebo in Group A, active drug in Groups B and C) and will be further instructed to maintain a dose of 2 puffs twice daily. Open label albuterol will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks.

If patients meet criteria for treatment failure status, their dose of inhaled corticosteroids will be increased to the dose they were receiving at visit 4 (800 μg/day) delivered by an open-label inhaler. Study inhalers of corticosteroids (or its placebo) will be returned to the clinical center. If they meet the criteria detailed in Section VI, they will be treated with appropriate rescue algorithms for an asthma exacerbation. Study inhalers of salmeterol (or placebo) will be continued unless the physician can document that treatment failure status was causally related to taking this medication. They will continue to participate in the study until its termination (intent-to-treat analysis), but no further reductions in inhaled corticosteroid dose will be attempted during this time period. For safety reasons, all subjects will be seen within one week (± 3d) from the day they have been categorized as

achieving treatment failure status. Following this "safety" visit, subsequent protocol visits will continue in accordance with the visit schedule established at Visit 1 (see SOCS/SLIC MOP for details concerning possible replacement of scheduled protocol visits with treatment failure related visits).

Telephone call, Week 23

Patients will be contacted by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, to answer any questions that may arise, and to assure that their asthma is under adequate control, as assessed by the patient. The coordinator will attempt to determine whether the patient is showing signs of treatment failure. Specifically, the coordinator will inquire about rescue β-agonist use, peak flow measurements and symptoms. If it is determined that the patient fulfills criteria for treatment failure, they will be advised to visit the study center within 24 hours for evaluation and initiation of treatment as specified by ACRN protocol (see Section VI). Otherwise, arrangements will be made for the patient to return to the clinic in 1 week.

Visit 11, Week 24

Patients will return to the clinical center at the same time of day as on week 0, ± 2 hours. Quality of life questionnaires will be administered. Urine will be obtained for a pregnancy test in females. Spirometry and a 12-lead ECG will be obtained. Blood will be drawn for determination of serum electrolytes. The patient's AirWatch will be tested against the Jones-Flow Volume calibrator. Adverse events will be assessed and recorded using the protocol outlined by the ACRN. Diary cards will be collected; AirWatch data will be uploaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording. All patients should have withheld their rescue inhaler for at least 6 hours and their salmeterol (or placebo) inhaler for at least 12 hours prior to the visit. Following baseline spirometry, all patients will receive 2 puffs of salmeterol (42μg) (single blind). One hour later, if the postbronchodilator $FEV_1 \geq 55\%$ predicted, methacholine bronchoprovocation will be performed. A final physical examination will be performed and all inhalers will be collected. The patient will resume outpatient therapy based on recommendations made by either ACRN-associated physicians or by the patient's regular physician depending on the preference of the patient.

Treatment Failure Visit

In the event of a "treatment failure" (see section III.F), patients will be instructed to come into the Clinical Center as soon as possible, preferably within 72 hours and ideally within 24 hours, in order to have their condition assessed. At this time, the patient will complete Quality of Life Questionnaires, undergo spirometry, and complete a physical exam with adverse events assessment. If the examining physician feels it is safe for the patient to continue, salmeterol reversibility testing will also be performed. Peak flow measures and rescue inhaler use will be reviewed on the diary cards. Any non-study drugs taken prior

to this visit will be documented. If patients meet criteria for treatment failure status, their dose of inhaled corticosteroids will be increased to the dose they were receiving at visit 4 (800 μg/day) delivered by an open-label inhaler. Study inhalers of corticosteroids (or its placebo) will be returned to the clinical center. Study inhalers of salmeterol (or placebo) will be continued unless the physician can document that treatment failure status was causally related to taking this medication.

If they meet the criteria detailed in Section VI, they will be treated with appropriate rescue algorithms for an asthma exacerbation. Trial salmeterol will be continued during exacerbations unless the treating physician considers it appropriate to suspend such therapy until the exacerbation resolves. Reinstitution of trial salmeterol will occur when the exacerbation has resolved at the discretion of the investigator. A record of all medications, dosages, and frequency of occurrence will be kept during exacerbations (see Section VI for additional information regarding the medical management of significant asthma exacerbations).

They will continue to participate in the study until its termination (intent-to-treat analysis), but no further reductions in inhaled corticosteroid dose will be attempted during this time period. For safety reasons, all subjects will be seen within one week(± 3d) from the day they were categorized as achieving treatment failure status. Following this "safety" visit, subsequent protocol visits will continue in accordance with the visit schedule established at Visit 1 (see SOCS/SLIC MOP for details concerning possible replacement of scheduled protocol visits with treatment failure related visits).

F. Protocol In Tabular Form

ICS = Inhaled corticosteroid MDI; AS = Active salmeterol MDI;
PS = Placebo salmeterol MDI; β = albuterol MDI

Variable	Run-in (ICS)					Double-Blind Treatment									Treatment Failure
Visit	1	2	3	4		5	Drug Swap	6	Drug Swap	7	8	9	10	11	
Week	0	2	4	6	6→8	8	10	12	14	16	18	20	22	24	
Window		±3 days	±3 days	±3 days		-2 +3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	
Group A	ICS	ICS	ICS	ICS ⟨ PS / ICS		PS ↓ICS	PS ↓ICS	PS ICS Same	PS ICS Same	PS Off ICS	PS Off ICS	PS Off ICS	PS Off ICS		PS ICS
Group B	ICS	ICS	ICS	ICS ⟨ AS / ICS		AS No ↓ ICS	AS No ↓ ICS	AS No ↓ ICS	AS No ↓ ICS	AS No ↓ ICS	AS No ↓ ICS	AS No ↓ ICS	AS No ↓ ICS		AS ICS
Group C	ICS	ICS	ICS	ICS ⟨ AS / ICS		AS ↓ICS	AS ↓ICS	AS ICS Same	AS ICS Same	AS Off ICS	AS Off ICS	AS Off ICS	AS Off ICS		AS ICS
"As needed" treatment	β	β	β	β		β	β	β	β	β	β	β	β		β
Randomization				X		X									
Informed Consent	X														
Medical History	X														
Long Physical Exam	X													X	X
Short Physical Exam		X	X	X		X		X		X	X	X	X		
Allergy Skin Test	X														
Spirometry	X	X	X	X		X		X		X	X	X	X	X	X
ECG	X													X	
Pregnancy Test	X			X										X	

Variable	Run-In (ICS)					Double-Blind Treatment									Treatment Failure
Visit	1	2	3	4		5	Drug Swap	6	Drug Swap	7	8	9	10	11	
Week	0	2	4	6	6→8	8	10	12	14	16	18	20	22	24	
Electrolytes	X													X	
Adverse Events Assessment		X	X	X		X		X		X	X	X	X	X	X
Steroid Reduction Groups A & C Sham Reduction Group B						X				X					
Review Peak Flow Data		X	X	X		X		X		X	X	X	X	X	X
BIOQC and Peak Flow Performance Check	X														
Peak Flow QC	X	X	X	X		X		X		X	X	X	X	X	X
Dispense/Review Diary Cards	X	X	X	X		X		X		X	X	X	X	X	X
Methacholine Challenge	X			X		X		X		X		X		X	
Salmeterol Reversibility Testing											X		X		X
Sputum Induction	X														
Quality of Life Questionnaires	X			X		X		X		X		X		X	X
Genetic Analysis Blood Draw	X														
Dispense/Collect Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Prednisone				X											

G. Risks/Benefits

This study evaluates the potential for the long acting beta agonist, salmeterol, to provide a mechanism by which inhaled corticosteroid dosages can be decreased in patients with moderate asthma without significantly affecting pulmonary function, symptom control, or quality of life. Biologic and physiologic correlates of these clinical parameters will be assessed using measurements of methacholine bronchial responsiveness. The benefits of adding salmeterol to a regimen of inhaled corticosteroids have already been demonstrated in two large multicenter trials[7] [8], and, based on this information and recommendations within the international guidelines, this combination therapy could be considered standard of care for the treatment of moderate asthma. This protocol is designed to evaluate the logical extension of these results: is it possible that salmeterol could act as an "inhaled corticosteroid-sparing" agent in patients with moderate asthma thereby providing a means for safe and effective step down treatment in this group of patients?

The benefits of this evaluation revolve around the fact that, although inhaled corticosteroids are less toxic than oral forms when administered on a chronic basis, the potential for adverse effects increases with escalating dosages. Applying "safe" inhaled corticosteroid dosing strategies derived from group mean data can be risky, especially in children and elderly patients.

The risks of this protocol should mainly involve those randomized to group A, since they will be receiving placebo salmeterol and undergo a stepwise reduction in their inhaled corticosteroid dose. Thus, this group appears to be at an increased risk of having an asthma exacerbation compared to those randomized to either Group B or C. However, from observations made by previous investigators evaluating steroid reduction outcomes in more severe asthmatic patients (on chronic oral prednisone)[13], the "placebo" effect of daily patient monitoring and frequent clinic visits can be significant. Moreover, a multicenter trial in which inhaled corticosteroids were abruptly stopped in a group of patients with moderate asthma (baseline FEV_1 approximately between 70% - 75% predicted while receiving inhaled corticosteroids) has been performed[19]. Although treatment failure was used as a major outcome criteria and occurred in 60% of patients in the placebo group, no serious adverse events were reported. Since the treatment failure criteria used in the SLIC protocol are in many respects more strict than in this previous study, significant adverse events should be minimized. Finally, if the ultimate clinical outcome of Groups B and C were identical and Group A was not available for comparison, the design of the study could not distinguish if these comparable results were related to the beneficial effects of salmeterol versus the fact that the patients being evaluated had lower inhaled corticosteroid requirements than had been estimated initially. Therefore, this group is an important component of the study and the frequent clinic visits and telephone contacts should minimize any significant adverse outcomes.

A fourth study group on placebo salmeterol and in whom corticosteroids would not be tapered (sham reduction) was not included due to the fact that two previous observations[7] [8] failed to demonstrate that even a doubling dose of inhaled corticosteroids was significantly more effective than the introduction of salmeterol therapy. It is also conceivable that the underlying inflammation felt to be important in asthma may increase but remain unrecognized by the patient while they are receiving salmeterol therapy. Although controversial, this adverse effect may be related, at least in part, to reports that chronic use of salmeterol may result in a loss of the initial degree of bronchoprotection from irritant challenges. For this reason, repetitive methacholine challenges will be performed following premedication with salmeterol in an attempt to correlate changes in bronchoprotection over time with clinical outcomes. Both the timing of methacholine challenge testing in relationship to salmeterol dosing and the presence or absence of concomitant corticosteroid treatment may influence the bronchoprotective effect. In patients not receiving inhaled corticosteroids and challenged one hour after salmeterol, a significant loss of the bronchoprotective effect was noted over an 8 week chronic treatment period with salmeterol[14]. In contrast, when patients (some of whom were receiving inhaled corticosteroids) were challenged 12 hours following chronic salmeterol dosing for the same time interval, no loss of the bronchoprotective effect to methacholine provocation could be demonstrated[15]. Thus, to maximize the potential of observing an adverse effect of chronic salmeterol therapy on these physiologic measurements, a one hour time interval for evaluation was chosen for this protocol.

H. Anticipated results

It is anticipated that patients randomized to Groups A and B will have treatment failure rates of 50 - 60%[19] and 5%[8], respectively, as they approach the end of the randomization period. Since no data are available to calculate comparable values for Group C, a rate which would be considered clinically significant was developed by the ACRN Steering Committee. The committee agreed that a reduction in the treatment failure rate of Group A by more than 50% would be clearly clinically relevant, and the value of 20% was therefore used to calculate the sample size for the various study populations. (see Section X.F for a more detailed discussion)

VI. ASTHMA EXACERBATIONS

A. Definition

During the course of the study, patients may experience an exacerbation of asthma. An exacerbation of asthma is characterized by an increase in symptoms of cough, chest tightness, and wheezing and it is generally associated with a fall in PEF. It is recognized, however, that the PEF may be improved by use of a bronchodilator and that increased bronchodilator use may, in this case, be more reflective of the exacerbation than PEF. An exacerbation may be brief and self-limited, or it may be of sufficient severity as to warrant documentation as a significant asthma exacerbation. Although any increase in symptoms or changes in PEF should be carefully monitored by the patient, the clinic coordinator, and the physician, alterations in asthma stability will be considered as constituting a significant asthma exacerbation when PEF does not increase to > 65% of reference levels, or symptoms are not satisfactorily relieved, after the first 60 minutes of rescue beta agonist (albuterol) use. Albuterol may be used at a dose of 2-4 puffs every 20 minutes during this one hour time period. For the SLIC protocol, the reference point for PEF comparisons will be as follows:

During run-in period (weeks 1 - 6):	Weeks 1-2: Predicted PEF obtained from spirometry software at Visit 1
	Weeks 3-6: Mean value of AM prebronchodilator PEF recorded during the first 2 weeks of the run-in (weeks 1 and 2)
During double-blind treatment (weeks 7 - 24):	Mean value of AM prebronchodilator PEF recorded during the last 2 weeks of the run-in period (weeks 5 and 6)

In addition, a significant asthma exacerbation will be identified if patients have a significant increase in symptoms associated with either:

An increase in "as needed" β-agonist use of ≥ 8 puffs per 24 hours over baseline use for a period of 48 hours,

Baseline defined during run-in period:	Average daily use during the first two weeks of the run-in period.

Baseline defined during double-blind period: Average daily use during the last two weeks of the run-in period.

or

Use of ≥ 16 puffs of "as needed" β-agonist per 24 hours for a period of 48 hours.

Once a significant asthma exacerbation has occurred, the patient should contact the clinic coordinator and/or be evaluated at the study site or the nearest medical emergency facility as quickly as possible.

Since less-significant changes in symptoms and/or PEF may precede more severe alterations in asthma stability, a series of rescue algorithms has been developed to address the various clinical presentations that may occur (Section VI 2). Once any of these rescue interventions leads to the administration of oral or parenteral corticosteroids, the patient will also be considered to have developed a significant asthma exacerbation. In addition, if in the opinion of the treating physician, corticosteroid therapy is warranted regardless of any antecedent measurements of pulmonary function (PEF, FEV, etc.), value for symptom score, or frequency of rescue beta agonist use, the patient will be considered to have developed a significant asthma exacerbation. It should be noted that although any patient who has developed a significant asthma exacerbation will also achieve treatment failure status, it is possible that a patient may meet the criteria for treatment failure status even though he/she does not meet the criteria for having developed a significant asthma exacerbation.

The time in which a significant asthma exacerbation develops in relationship to the schedule of the SLIC protocol will affect the manner in which future clinic visits, medication adjustments, and diagnostic studies are scheduled or performed.

- Patients developing significant asthma exacerbations during the run-in period will be removed from the study. Once the exacerbation has resolved, the patient may be considered for re-enrollment, starting again at visit 1 and undergoing randomization into either SOCS or SLIC.

- Significant asthma exacerbations which occur following randomization (double-blind treatment phase) will be recorded and the patient considered a treatment failure. During medical management of the exacerbation, trial salmeterol or placebo will be continued, unless the treating physician considers it appropriate to suspend such therapy until the exacerbation resolves. Reinstitution of trial medications (salmeterol or placebo) will occur when the exacerbation has resolved at the discretion of the investigator.

Trial triamcinolone or placebo will be stopped during exacerbations, and open label triamcinolone acetonide [400 μg (4 puffs) BID] restarted unless the treating physician considers it appropriate to suspend such therapy until the exacerbation resolves. This reinstitution of triamcinolone will occur when the exacerbation has resolved at the discretion of the investigator. A record of all medications, dosages, and frequency of occurrence will be kept during exacerbations. Additional visits and procedures will be scheduled according to guidelines for treatment failure visits (Section E, Visit Structures).

B. Rescue Algorithms

Rescue algorithms will be applied in cases where postbronchodilator PEF falls $\geq$ 35% below baseline and is not improved to > 65% of reference level within 48 hours after increasing as needed albuterol use. Rescue algorithms are based on recommendations from the NAEP Guidelines for the Diagnosis and Management of Asthma (NHLBI Publication No. 91-3042, 1991). Albuterol and oral prednisone are the principal medications for rescue management, therefore, patients will be instructed in their use for home management and supplies of both will be provided throughout the study. For severe acute episodes of asthma, treatment will be administered according to the best medical judgment of the treating physician.

1) Home Care:

Asthma exacerbations will be recognized by an increase in symptoms and by a corresponding drop in PEF below reference level. Patients will be educated to recognize exacerbations as early as possible to facilitate prompt treatment and to lessen morbidity.

- Patients who recognize increased symptoms and/or a fall in PEF to $\leq$ 65% reference level will use albuterol by MDI, 2-4 puffs every 20 min up to 60 min if needed, and then every 4 hours, or less, if needed. Patients will be instructed to use the as needed inhaler for treatment.

- If the PEF does not increase to > 65% reference level or if symptoms are not improved after the first 60 min of therapy, the patient should contact the investigator, their primary physician or seek care in the emergency department. This sequence of events constitutes a significant asthma exacerbation.

- Failure of albuterol to control or maintain PEF > 65% reference level may necessitate the use of corticosteroids (see below).

2) Physician's Office or Emergency Room Treatment:

- Patients will be assessed by history, physical examination, and by physiological monitoring including spirometry or PEF. If the patient's PEF or FEV_1 is less than 25% predicted or if the patient shows evidence of altered mental status, cyanosis, labored breathing, or use of accessory muscles, sampling of arterial blood for respiratory gas analysis is indicated, with appropriate action taken depending on the results obtained.

- When treated in the physician's office or the hospital emergency room, patients should initially be given albuterol by nebulization (0.5 cc of 0.5% solution) every 20 min over the first 60 min.

- If the PEF increases to > 65% reference level after the first 60 min, the patient can be discharged to continue treatment at home. Prednisone may be administered at the discretion of the physician to augment therapy (see VIF).

- If symptoms persist and PEF remains < 65% reference level, nebulized albuterol should be continued as often as every hour and further treatment with oral or parenteral corticosteroids should be considered (prednisone, 60 mg orally; methylprednisolone, 60 mg iv bolus). Monitoring of PEF or spirometry should continue every hour. Within 4 hours of treatment, a decision should be made regarding patient disposition.

- If PEF increases to > 65% reference level within 4 hours, the patient can be discharged to continue treatment at home. Home treatment should include an 8-day course of prednisone (VI.2.c).

- If PEF remains > 40% but < 65% reference level, an individualized decision should be made to hospitalize the patient for more aggressive therapy or to continue therapy at home with a course of prednisone.

- If PEF is < 40% reference level after repeated albuterol treatments, the patient should be admitted to the hospital unless, in the physician's best judgment, alternative treatment could suffice.

3) Prednisone Treatment:

In this protocol, prednisone will be used when acute exacerbations cannot be controlled by albuterol therapy. Indications for prednisone therapy may include the following:

- To achieve stable control of symptoms and optimize pulmonary function once treatment failure status is achieved.
- For follow-up management after discharge from the physician's office, emergency room, or hospital for an acute exacerbation.
- An increase in "as needed" β-agonist use of ≥ 8 puffs per 24 hours over baseline use (baseline defined as average daily use over last 2 weeks of run-in period) for a period of 48 hours, or
- Use of ≥ 16 puffs of "as needed" β-agonist per 24 hours for a period of 48 hours.
- When PEF falls to < 50% reference level despite albuterol treatment.

The dose of prednisone used during an acute exacerbation shall consist of 60 mg as a single dose every day for 3 days, followed by a 10 mg/day taper over the next 5 days. The decision to initiate or to continue a course of prednisone beyond 8 days is left to the discretion of the physician.

C. Adjustment of Trial Medications During Asthma Exacerbations

Trial salmeterol or placebo will be continued during exacerbations which occur during the double-blind treatment period, unless the treating physician considers it appropriate to suspend such therapy until the exacerbation resolves. Reinstitution of trial medications (salmeterol or placebo) will occur when the exacerbation has resolved at the discretion of the investigator. Trial triamcinolone or placebo will be stopped during exacerbations, and open label triamcinolone acetonide [400 μg (4 puffs) BID] restarted unless the treating physician considers it appropriate to suspend such therapy until the exacerbation resolves. Reinstitution of open-label triamcinolone will occur when the exacerbation has resolved at the discretion of the investigator. A record of all medications, dosages, and frequency of occurrence will be kept during exacerbations. By definition, the development of a significant asthma exacerbation in SLIC constitutes treatment failure status.

Patients developing asthma exacerbation during the ***run-in period*** will be removed from the study. Once the exacerbation has been resolved, the patient may be considered for re-enrollment, starting again at Visit 1 and undergoing randomization into either SOCS or SLIC as previously described.

D. Study Center Visits Following Exacerbations

For safety reasons, all subjects will be seen within one week (± 3d) from the date of the exacerbation. Following this "safety" visit, subsequent protocol visits will continue in accordance with the visit schedule established at Visit 1 (see SOCS/SLIC MOP for details concerning possible replacement of scheduled protocol visits with treatment failure related visits).

E. Criteria for Discontinuing Patients Due to Asthma Exacerbations

1. Treatment Failure Status

Criteria for assigning treatment failure status during the double-blind treatment period are described in **Section IIF**. Patients who are assigned "treatment failure" status will continue to participate in the data gathering aspects of the protocol until the time they would have completed the trial. (see Section III, G.2.)

2. Drop-out Status

Patients may be assigned "drop-out" status during the double-blind treatment period if they become pregnant or if the patient withdraws consent. In addition to the usual reasons for withdrawing consent (moving to another region, inconvenience, etc.), it will be noted if a patient withdraws consent due to the lack of satisfaction with the quality of the asthma control. At this visit, study termination procedures will be conducted, all study medications stopped, and the patient will begin a treatment plan at the direction of the examining physician. See the SOCS/SLIC MOP for further details regarding early study termination.

F. Asthma Exacerbations as Outcom ı Variables

During exacerbations, the following variables ıill be recorded and used as outcome variable measures:

- Hospitalization
- Emergency Department Visits
- Unscheduled physician/clinic visits
- Number of subjects having an exacerbatioı as defined by prednisone use
- Treatment failure

VII. ADVERSE EVENTS

A. Definitions

Both clinical and laboratory adverse events will ɔe documented and reported. An algorithm for identifying, recording, and follow-ι p of all adverse events has been developed (refer to Appendix I). A clinical adverse ɜvent is any unintended worsening in the structure (signs) or function (symptoms) of the ƚ ody, whether or not considered to be drug-related. This includes any side effect, injury, ɔr sensitivity reaction, as well as any intercurrent event. A laboratory adverse event is ɜ ny clinically important worsening in a test variable which occurs during the course of the s udy, whether or not considered to be drug-related. Only conditions that appear or beɛ ome worse after study entry will be recorded.

B. Potential Clinical Adverse Events

1. Asthma Exacerbations

   Since inhaled corticosteroid therapy wil be first reduced and then eliminated in 2 of the 3 study populations, it is a ıticipated that asthma exacerbations will occur. The protocol contains ɜ number of "safety nets" including frequent visits, phone calls, and well described rescue algorithms so that exacerbation can be recognized early ınd appropriately treated by both the patient and the ACRN medical support ɜtaff. Once an exacerbation requiring oral or parenteral corticosteroid treatı ıent has occurred, the patient will be placed back on their initial dose of inhaı ɘd corticosteroid and continued to be followed per the visit schedule designaı ɘd in the protocol. This event will be recorded as a significant asthma exacɘ bation rather than an adverse event. Information and data gained as a reɜ ult of these subsequent visits will be utilized in the "intent to treat" analy ɜis. Should asthma exacerbations become too frequent or too severe following randomization, the ACRN principal investigator may elect to ɾ rop the patient from further study participation. Study termination pr ɔcedures will be completed. Any complication resulting from an asƚ ıma exacerbation (pneumothorax, pneumomediasternum, mechanical vɛ ntilation, etc.) will be recorded as an adverse event in addition to the dɛ cumentation also recorded for the significant asthma exacerbation. (Seɛ SOCS/SLIC MOP for further details regarding early study termination).

2. Other Medical Complications from Thɾ rapy

   Complications from chronic salmeterol herapy have been reported to occur in about 12% of patients compared to 23% in patients receiving scheduled albuterol, and 20% of patients only rɾ ceiving albuterol on a PRN basis[4].

Headache, tremor, and occasional achycardia are the most commonly reported adverse effects. Significant e ectrocardiographic disturbances with salmeterol have not been noted[4]. Ora candidiasis and hoarseness are two of the more commonly reported sid effects in patients receiving chronic inhaled corticosteroid therapy. The se problems can be minimized with proper mouth rinsing and the use o f spacer devices (which Azmacort® contains), respectively. Any adverse effects felt to be drug related will be documented, thoroughly evaluated, and treated appropriately. (Refer to Manual of Operations) Persistent p alpitations will be further evaluated electrocardiographically. The deve opment of any clinically significant abnormal rhythm or other cardiac abno rmality will be evaluated by the ACRN principal investigator, and a decision as to whether or not the patient will remain in the study will be made by h m/her.

3. Unrelated Medical Complication

Clinical adverse events due to inter urrent illnesses may be grounds for withdrawal if the illness is considered ignificant by the investigator or if the patient is no longer able to effectiv ely participate in the study. Patients experiencing minor intercurrent illnesse s may continue in the study provided that the nature, severity, and duratio of the illness are recorded and that any unscheduled medications required to treat the illness are also recorded. Examples of minor intercurrent illne ses include acute rhinitis, sinusitis, upper respiratory infections, urinary tract infections, and gastroenteritis. Medications are allowed for treatment o f these conditions in accordance with the judgment of the responsible physi ian.

C. Procedures and Reporting

All possible adverse events related to drug a dministration will be explained to the patient verbally and in the written consent form. Terminated patients will be followed through the end of the study and u ntil drug-related adverse events are resolved.

Documentation of an adverse event will be r corded on the Clinical or Laboratory Adverse Event Report Form and will include he following information:

Description of the condition
Dates of condition
Treatment of condition (medications, doses, dates)
Whether hospitalization or emergency treatm ent was required
Treatment outcome
Relationship of the adverse event to the stud y medication(s)
Severity of the event

VIII. COST, LIABILITY AND PAYMENT

All tests will be performed without cost to the participating patients. Each patient will receive an honorarium for study participation determined by their local center. For patients who drop out, payments will be pro-rated for the length of time they stayed in the study, but payments will not be made until the study would have been completed had the patient not dropped out.

IX. DATA RECORDING

Recording of all data including the informed consent, history, physical examination, results of allergy skin testing, vital signs, electrocardiograms, results of pregnancy tests, adverse events, confirmation of medication dispensation, methacholine challenge testing, and quality of life testing will be recorded on forms prepared by the ACRN DCC. 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 will be transmitted electronically to the DCC. All data will be stored and analyzed at the DCC.

X. STATISTICAL DESIGN AND ANALYSIS

A. Data Collection and Data Management

Each center will have a computer configuration tha includes an X-terminal, a post-script printer, and a modem. This will give each center th capability of logging directly into the DCC computing system over the Internet, with the r odem as a back-up if the connection is not possible. Though this set-up is installed prim rily to allow for distributed data entry into a centralized database on the ACRN project sen er at the DCC, menu options will also include sending electronic mail, downloading study d ocuments such as forms and reports, and viewing a calendar of ACRN events. A sophisti ated security system will limit access to qualified personnel and prevent corruption of th study database.

The DCC will be responsible for generating the data collection forms based on input from the SLIC Forms Subcommittee. Once the data col ection forms have been filled out and reviewed, the Clinic Coordinator will log into the DCC computer system and enter the data within 3 days of the patient visit. The advantage of th s distributed data entry system is that the Clinic Coordinators will review the data a seco nd time as they are entering it, which serves as another level of quality control. However, t ne Clinic Coordinators will not be able to query their own data. The database manageme t 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 an d filing. The DCC will be responsible for identifying problem data and resolving incon istencies. Once the quality control procedures are complete, new study data will b e integrated into the primary study database.

Results from lung function tests will be sent dire tly to the DCC via a modem in the computer attached to the spirometer.

B. Masking

Careful procedures are required in order to m aintain triple-masking of the study participants, Clinical Center personnel, and DCC personnel as to whether individual patients are taking (1) salmeterol or its placebo, an d (2) full or reduced doses of ICS.

In order to mask the treatment arms with respect to IC S reduction and sham ICS reduction, it is necessary for each patient to receive two ICS (active and/or placebo) canisters. Subjects in the sham reduction arm will receive tw canisters of active drug. Therefore, all SLIC subjects will receive two ICS canisters (activ and/or placebo) and will take 2 puffs BID from each.

Treatment medication for each patient will be pa kaged together and labeled with a unique number. The contents of the packages will b e known only to limited personnel at the DCC. These packages will be delivered to the Clinic Coordinators. Triple-masking,

i.e., masking of the DCC personnel in addition to the study participants and Clinical Center personnel, will be employed so that the statistical analyses are not biased by preconceived notions. Until the time of manuscript preparation, DCC personnel will identify the randomized groups as X, Y, and Z and only limited personnel within the DCC will know the identity of X, Y, and Z.

In order to decrease the likelihood of incorrect drug distribution, each coded package designated for a study participant will have a sheet of removable labels attached to it. When the Clinic Coordinator retrieves a package for the study participant, he/she will remove one of the labels and attach it to the data collection form prior to mailing the form to the DCC. The Clinic Coordinator will initial across the label to indicate that he/she checked to make sure the appropriate package was distributed to the participant.

C. 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, the Clinic Coordinator will be asked to verify that all of the information has been reviewed carefully and the patient is eligible. 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 automatically receive 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.

As described in Section IID, this protocol requires randomization of patients on two occasions. Patients at Visit 4 are randomized to either active salmeterol (13/15) or placebo salmeterol (2/15). Patients on active salmeterol at Visit 5 are randomized to receive the ICS reduction (Group C) or the sham ICS reduction (Group B), whereas the placebo salmeterol patients (Group A) will undergo the ICS reduction.

D. Stratification

The randomization scheme will be stratified according to center because differences among clinical centers typically yield a large amount of variability. In addition, each Clinical Center will be restricted to enroll no more than 25% of its target sample size of patients to be between the ages of 12 and 18.

Within subgroup I and subgroup II (see Section IID for definitions) of each clinical center an adaptive randomization scheme at Visit 5 will be invoked in order to balance the treatment arms with respect to the following strata:

ethnic group (white, black, Hispanic, native American, Asian, Other)
gender (male, female)
age (adolescent, adult)

The strata of a particular patient are noted and the marginal frequencies of these strata are summed for each treatment arm. Then the patient is assigned to that treatment arm which has the smallest sum of marginal frequencies[16].

E. Statistical Analysis

The primary response variables in this study are time and occurrence of treatment failure after visit 5, where treatment failure is defined in Section III. Kaplan-Meier survival curves will be constructed for the three treatment arms. Statistical tests, such as the logrank test and the generalized Wilcoxon test, will be applied to compare the survival curves of the groups.

In addition, a proportional hazards regression analysis will be applied, which allows for comparing the survival curves of the groups in the presence of other covariates. In this type of analysis the hazard function at time t is modelled as

$$h(t; \mathbf{x}) = h_0(t)\exp(\mathbf{x}^T\xi)$$

where
$h_0(t)$ is the unspecified baseline hazard,
$\mathbf{x} = [x_1 \ldots x_k]^T$ is a vector of explanatory variables, and
$\xi = [\xi_1 \ldots \xi_k]^T$ is a vector of unknown parameters.

The vector **x** will include indicator variables for treatment assignment, Clinical Center, and treatment × center interactions. The assumption of proportional hazards is important for the logrank test and the proportional hazards regression. This will be assessed via graphical procedures (comparing log survival plots) and statistical tests (including time-dependent covariates in the proportional hazards regression and testing for significance).

Safety of methacholine challenge will be examined by analyzing the frequency of adverse events following clinic visits at which methacholine challenge is performed, compared with the frequency following visits at which it is not. McNemar's test will be applied for this purpose because of the correlated responses within each subject. The efficacy of methacholine challenge will be analyzed by correlating PC_{20} with other measures of asthma outcome, such as AM and PM PEF, FEV_1, symptom scores, rescue beta-agonist use, and quality of life scores. Correlation coefficient estimates and confidence intervals, specifically designed for longitudinal data, will be calculated for this purpose. Daily data obtained from post-randomization diary cards will be summarized and analyzed as

averages. Because subjects are instructed to withh ld their study salmeterol (or placebo) for 12 hours prior to a visit, the appropriate peal flow values prior to the visit will be excluded.

F. Sample Size Calculation

The primary comparison of interest in this trial s testing whether the time-to-failure responses for Groups B and C are significantly lifferent. Schoenfeld [17] described a formula for sample size calculations based on a prop ortional hazards regression for a time-to-failure response. For a one-sided test in a two-a med trial, the total number of failures required is

$$4(z_{1-\beta} + z_{1-\alpha})^2/\{\log(\Delta)\}^2$$

where
z_γ represents the 100γ percentile from the standar l normal distribution,
α is the Type I error rate,
β is the Type II error rate,
p_1 is the proportion randomized to treatment arm # l (Group C),
p_2 is the proportion randomized to treatment arm #2 (Group B in the primary case and Group A in the secondary case), and
Δ is the hazard ratio of the two treatment arms.

If exponential distributions are assumed for Grou ps B and C, then the corresponding hazard functions and their ratio is constant and no a function of time. Letting θ_1 and θ_2 denote the proportion of failures in treatment arm #1 and #2, respectively, and letting T denote the length of the trial, then the hazard funct ons are $-\log(1-\theta_1)/T$ and $-\log(1-\theta_2)/T$, respectively, and the hazard ratio is $\Delta = \log(1-\theta_1)/\log(1-\theta_2)$.

Chervinsky, et al[19] reported a 60% failure rate fo a similar group of patients receiving placebo, so we assume that $\theta_A = 0.60$. Greening, t al[8] reported a 5% failure rate for a similar group of patients receiving salmeterol anc ICS, so we assume that $\theta_B = 0.05$. Although it is anticipated that $\theta_A > \theta_C > \theta_B$, there s no report in the literature as to an anticipated failure rate for Group C. As such, a rate which would be considered clinically significant was discussed at length by the ACRN Steering Committee. The committee agreed that a reduction in the treatment failure rate of Group A by more than 50% would be clearly clinically relevant in this patient populati n. Therefore, failure rates less than 30% were assumed for Group C in order to calc late the sample size. The Steering Committee also recognized that the eventual choic of a precise failure rate for Group C needed to reflect the relative numbers of asthmatic patients with moderate asthma within the entire asthmatic population in the United State s (approximately 25% of the total) in order to set realistic recruitment goals for this disea e severity category. After numerous discussions with input from various individuals, the St ering Committee agreed that a 20% treatment failure rate for Group C would be the be t choice to address both the clinical

relevance of any observed differences and the patient population disease severity restraints.

It is not of interest to detect failure rates in the other direction, i.e., $> \theta_B > \theta_C > \theta_A$, so one-sided tests are used. One interim analysis is planned for this trial when approximately one-half of the randomized patients have completed the trial. Therefore, a significance level of $\alpha = 0.029$ (see Pocock[18]) will be invoked at each analysis. Using $\beta = 0.20$ (80% statistical power) and allowing for a 10% withdrawal rate, a total of 130 randomized patients are needed in Groups B and C. In order to perform the secondary comparison of Group B versus Group A, the target sample size for Group A will be 20 randomized patients. This comparison of Group C versus Group A will have 80% statistical power based on the assumed failure rates of 20% and 60%, respectively. Thus, the required sample size for this trial is 150 randomized patients.

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