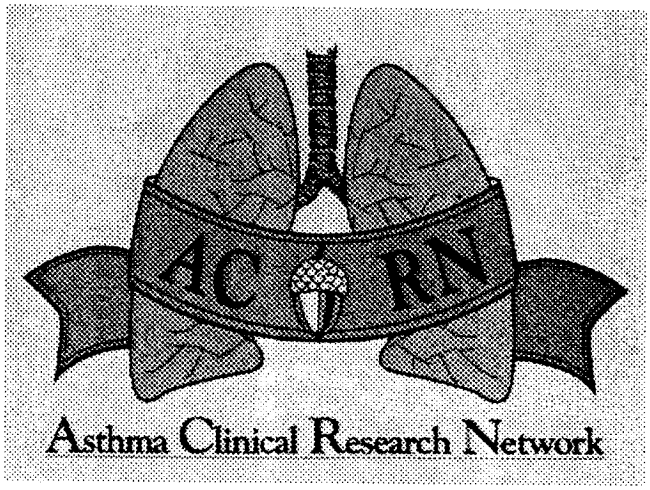


# Dose of Inhaled Corticosteroids with Equisystemic Effects

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# DOSE OF INHALED CORTICOSTEROIDS WITH EQUISYSTEMIC EFFECTS (DICE)

## I. Hypothesis To Be Tested

The primary objective of this trial is to estimate dose-response curves with respect to adrenal suppression for six distinct inhaled corticosteroids. Of secondary interest is the comparison of the dose-response curves, as stated in the following null hypothesis.

Proposed null hypothesis: In patients with mild-to-moderate asthma, there are no differences in the systemic effect as measured by suppression of timed plasma cortisol levels among comparable doses (on a µg per µg basis) of inhaled beclomethasone dipropionate (BDP), budesonide (BUD), flunisolide (FLU), fluticasone propionate (FP) (MDI and dry powder), and triamcinolone acetonide (TAA) when administered via their respective delivery systems (metered-dose inhaler [MDI] plus chamber for FLU, FP-MDI, and BDP; MDI with spacer built-in for TAA; Turbuhaler™ dry powder inhaler device for BUD; and Diskhaler device for dry powder FP). Additionally, there are no differences in systemic effect between the chlorofluorocarbon (CFC) and dry powder preparations of the same inhaled corticosteroid (FP).

## II. Background and Rationale

### A. Introduction

Inhaled corticosteroids (ICS) are being recommended for use in asthma treatment both more frequently and at higher doses than previously (1). Since corticosteroids have multiple potential adverse systemic effects (1), it is essential to be able to compare the different available inhaled steroids and delivery systems with respect to both systemic effects and efficacy as an asthma treatment. While several inhaled steroids (with differing *in vitro* potencies and pharmacokinetic characteristics) and inhaled delivery systems are presently available, and others are expected to be introduced in coming years, *in vivo* systemic effects data comparing these inhaled steroids and delivery systems are lacking.

In this DICE study we propose an experimental paradigm in which inhaled steroids and delivery systems are characterized in terms of systemic effects so that doses which produce "equi-systemic" effects can be subsequently compared in future efficacy trials, including the ACRN efficacy trial entitled "Measuring Inhaled Corticosteroid Efficacy" (MICE). In the DICE trial, adrenal suppression will be used as the primary index of systemic effect. As a network we acknowledge that growth in children and connective tissue parameters are important indicators of systemic absorption, but due to the slow rate of change in these outcome measures, they do not lend themselves to rapid evaluation. We therefore propose to use plasma cortisol profiles (determined over time) which are a sensitive and reproducible indicator of basal adrenal function (2,3) as our index of systemic

steroid effect. Urine cortisol excretion will be a secondary measure of adrenal suppression.

## B. Specific Aims

The specific aims of the combined DICE/MICE projects are four-fold; only the first three will be addressed by the DICE study. We will:

1. Define the dose-systemic effect relationships among different inhaled corticosteroids and delivery systems (if specialized delivery system not incorporated into the ICS system, then an Optichamber (Healthscan) will be used) using overnight adrenal suppression as the primary indicator of systemic effect.
2. Compare the dose-systemic effect relationships of the different inhaled corticosteroids and ascertain equi-systemic doses, or those doses which result in an equivalent degree of systemic effect (cortisol suppression).
3. Determine if other markers of systemic effect can be substituted for the overnight plasma cortisol evaluation so as to simplify future studies that need to measure systemic inhaled corticosteroid effect (urine cortisol).
4. Use the data from this study for dose finding in an evaluation of comparative efficacy of these inhaled corticosteroids and delivery system combinations utilizing the derived equi-systemic doses (the future MICE study).

## C. Research Questions

Although there are a number of inhaled corticosteroids which can be used for asthma therapy, there remains confusion and continued controversy as to the relative efficacy and risk for systemic effects from these agents. Because of this, the choice of inhaled steroid is often made based on convenience (number of µg per actuation, taste, or patient preference) or cost factors. The confusion surrounding the choice of agent will be further compounded by the anticipated introduction of newer and potentially more potent inhaled steroids and newer inhaled drug delivery systems which appear to have enhanced pulmonary drug deposition (and in turn have the potential to alter the efficacy and safety profiles of inhaled steroids). The goal of the DICE trial is to determine whether any inhaled steroid, administered by its respective delivery system (plus chamber for BDP, FLU and FP-MDI), possesses safety advantages over another when compared on an equivalent µg basis and to establish a paradigm that can be used to test subsequent inhaled steroid/delivery systems.

In testing the stated hypothesis, this study will examine patients with asthma severity based on % predicted $FEV_1$ (65-90%) to address the following research questions:

1. Are there dose-response relationships in the suppression of overnight plasma cortisol with the various inhaled corticosteroids and delivery systems?

2. If dose-response relationships exist, at which doses are comparable systemic effects evident as determined by suppression of overnight plasma cortisol?
3. If dose-response relationships exist, which dose produces a 10, 20, 30 or 40% suppression of adrenal steroid secretion (cortisol) for each inhaled steroid and delivery system?

In answering these questions, easier to study markers of systemic effect will be analyzed in parallel for possible use in future studies. The follow up project MICE will compare the clinical efficacy of the different inhaled steroids and delivery system combinations for the treatment of asthma, at equi-systemic doses, i.e., those doses that cause comparable suppression of plasma cortisol, as determined from the DICE study.

## D. Rationale For Choosing These Questions

It is clear from previous work that while inhaled steroids are potent and important anti-inflammatory agents for the treatment of asthma, our understanding of the relative merit of the different ICS preparations is limited. Whether dose-response relationships exist, and whether a plateau of beneficial effects occurs, are also not known. It is generally recognized that there is some risk for systemic adverse effects from inhaled steroids, however, considerable controversy persists over the magnitude for such risks (4). The relative potencies of different ICS preparations and the impact of new delivery systems on the risks for adverse effects are unclear, and the available data provide little information regarding the optimal dose or steroid of choice, if any exists, among the presently available agents (4).

As inhaled steroid therapy is now recommended earlier in the course of treatment of asthma (1), it is important to further our understanding of these medications so they can be used optimally. This is especially important with new and potentially more potent inhaled steroids, as well as the different inhalation delivery systems on the horizon. Further understanding of the differences between the available inhaled steroids, if any, will allow for more rational selection and prescribing. Comparison of the newer agents, BUD and FP, will help determine whether their purported advantages and those determined from drug pharmacokinetics studies, *in vitro* assays, and animal models, translate to clinically significant improvements in their efficacy and safety profiles. The impact of the new dry powder devices on efficacy and risk for adverse effects can also be evaluated using this model.

## E. Limitations On Interpretation

1. The age band will be post-pubertal to 60 years. Thus the results cannot be directly applied to older or younger age groups.
2. The short duration of this study (see study design III.B.) Will not provide information on effects of chronic ICS use, e.g., glaucoma, cataracts and osteoporosis.
3. Efficacy is not an outcome variable. This will be studied in the MICE protocol. Potential of cumulative dose effect (see study design III.B.).

4. The rationale for our dosing schedule and no washout period between doses can be found in III.E.

## III. Protocol Overview

### A. Subjects

This study will require a total of 156 patients with mild to moderate asthma. In order to be able to permit generalizability of the findings to the patient population of interest these patients will be appropriately distributed by gender (approximately 50% female) and by ethnicity (33% ethnic minority). Both heterogeneity of the study group and rapidity of recruitment are greatly facilitated by the involvement of several geographically dispersed study sites in a multi-center collaboration. 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 exclusion criteria. 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% from under-represented minorities (Native Americans, Asian-Pacific Islanders, African Americans, and Hispanics). The ACRN Data Coordinating Center (DCC) will distribute monthly accrual reports for each clinical center, listing subjects entered by age, gender, and ethnicity. This routine monitoring will allow early identification and resolution of potential problems in achieving demographic goals.

### B. Study Design

| Week | 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
|---|---|---|---|---|---|---|---|---|
| | Placebo Run-In | Placebo | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Wash-Out | |
| Visit | 1 | 2* | 3 | 4 | 5 | 6 | 7 | ** |
| | | | ↑ | ↑ | ↑ | ↑ | ↑ | |

* = Randomize ICS or placebo

↑ = Admitted at 6:30 PM for overnight testing

** = Phone call to subject to determine if any adverse events have occurred since discontinuing ICS

Visit 1 - History and physical exam, spirometry (FEV1 65-90% predicted) with reversibility (≥ 12%) or methacholine challenge ($PC_{20}$ ≤ 8 mg/ml), plasma cortisol (> 5 mcg/dl), inhaler use education using OptiChamber (see VI.D.). Pregnancy test for females. Blood for future genetic testing will be obtained. When polymorphisms are established for systemic markers such as adrenal suppression, then analysis will be undertaken and compared to the physiologic responses seen in the DICE Study.

Week 1 - A placebo run-in is a single blind trial for subjects to practice taking scheduled doses (4 puffs bid) for one week and for compliance to be evaluated. AirWatch™ will be used to perform PEFR/$FEV_1$ maneuvers; diary cards will also be used. Data from this week will be used to establish reference values for purposes of determining when the subject is experiencing a significant asthma exacerbation. A compliance evaluation also will be carried out on the basis of these data. Subjects will take their first dose of the run-in placebo during the visit (no time constraints).

Visit 2 - After completing the run-in week, if the subject meets all eligibility criteria, he/she will be randomized to one of the six steroid arms or placebo. Our goal is to obtain supplies to have a distinct double-blind placebo arm at a reduced sample size for each ICS. The OptiChamber will be used for inhaler technique training for the MDI ICS (FLU, BDP, FP-MDI. Similar criteria will be used for TAA (see VI.D.). Subjects randomized to the dry powder arms (FP, BUD) will be trained in proper technique using a performance checklist based on the manufacturers' instructions and the budesonide training device provided by Astra. A placebo inhaler that corresponds to the subject's study arm will be given to the subject and he/she will be formally entered into the protocol. The first dose of this placebo (1 puff bid) must be given prior to 1:30 PM (to allow for flexibility in scheduling Visit 2).

Visits 3- 7 - See III. G.

**C. Randomize To 7 Groups - Parallel Design**

1. Beclomethasone dipropionate (BDP) MDI
2. Budesonide (BUD) dry powder
3. Flunisolide (FLU) MDI
4. Fluticasone propionate (FP) MDI
3. Fluticasone propionate (FP) dry powder
6. Triamcinolone acetonide (TAA) MDI
7. Placebo (consisting of distinct placebos corresponding to each of the six ICS arms)

Randomization will be stratified by gender in order to limit the effect of weight on outcome variables.

**D. Inhaled Steroid Dosing (Bid Hours = 5-10 AM and 9-11 PM)**

For each steroid we will use a "doubling" dose scheme to determine the dose which suppresses the area under the time collected plasma cortisol curve by 10%, termed the cortisol suppressive $(CS)_{10}$ dose. Similarly, we will determine the $CS_{20\text{-}50}$.

1. Beclomethasone (BDP) (84 mcg/puff)
   Starting dose 1P bid = 168 mcg
   Second dose 2P bid = 336 mcg
   Third dose 4P bid = 672 mcg
   Final dose 8P bid = 1344 mcg

**Reasoning:** Most studies on systemic effects of inhaled corticosteroids have been in normal subjects. However, it is difficult to use data obtained by study of normal subjects and apply it to asthmatics, as healthy and asthmatic subjects may have differing adrenal suppression with use of inhaled corticosteroids. Werner, et al. (5) showed in normal males that BDP 1760 mcg/d x 6 days produced a 30% suppression in 24-hour plasma cortisol AUC. Lundback, et al. (6) demonstrated in asthmatics that 1000 mcg/d x 6 weeks caused a 7% suppression of AM cortisol (a very insensitive test of adrenal function).

Using incrementally increasing doses, as described above, we expect to be able to calculate cortisol suppressive doses of $CS_{10}$, $CS_{20}$, $CS_{30}$, and probably a $CS_{40\text{-}50}$. This was demonstrated in our Pilot Protocol.

2. Budesonide (BUD) (100 mcg/puff)
   Starting dose 1P bid = 200 mcg
   Second dose 2P bid = 400 mcg
   Third dose 4P bid = 800 mcg
   Final dose 8 P bid = 1,600 mcg

**Reasoning:** Nikolaizik (3) studied normal subjects using BUD 800 mcg/day x 2 weeks. He measured plasma cortisol q 20 minutes from 10 PM - 7 AM and showed a 37% suppression with this treatment. Werner (5) studied normals treated with 1,800 mcg/day x 6d. He demonstrated a 20% suppression of the 24-hour plasma cortisol AUC. We expect with BUD the $CS_{10\text{-}30}$ will be obtained, and the $CS_{40\text{-}50}$ may also be reached. The upper dose limit for all inhaled steroids used in this study will be 3200 mcg, as clinically the number of patients that use this dose in clinical practice will be rare.

3. Flunisolide (FLU) (250 mcg/puff)
   Starting dose 1P bid = 500 mcg
   Second dose 2P bid = 1,000 mcg
   Third dose 4P bid = 2,000 mcg
   Final dose 8P bid = 4,000 mcg

**Reasoning:** Werner (5) studied normal subjects taking FLU at 2,000 mcg/day and using the AUC for 24-hour plasma cortisol levels showed a 6% suppression. Alternatively, in asthmatics 1,000 and 2,000 mcg/day of FLU for one week has been shown to decrease 24-hour urine free cortisol levels by 15-20%, and 4,000 mcg/day by approximately 46% (7). Since we are using asthmatic subjects a $CS_{10\text{-}30}$ should be obtained.

4. Fluticasone (FP-MDI) (44 mcg/puff)
   Starting dose 1P bid = 88 mcg
   Second dose 2P bid = 176 mcg
   Third dose 4 P bid = 352 mcg
   Final dose 8 P bid = 704 mcg

**Reasoning:** All studies appear to show FP to have marked adrenal suppressive effects. In asthmatics, Clark (8) demonstrated a single dose of 500, 1,000, 1,500, and 2,000 mcg to suppressed AM cortisol (poor test) by 0, 6, 41, and 65%, respectively. In normals, Lonnebo (9) showed that the AUC on 1,000 mcg x 1 yielded 25% suppression and 2,000 mcg x 3.5 days caused a 55% decrease. In normals, Werner (5) demonstrated 1760 mcg/day x 6 days produced a 80% suppression of the AUC. Boorsma (10) in normals at 400, 750, and 2,000 mcg/day x 4 days produced a 21, 39, and 84% suppression (24-hour pooled plasma cortisol). With our schedule we should establish the $CS_{10-40}$.

5. Fluticasone (FP-dry powder) (50 mcg/puff)
   Starting dose 1P bid = 100 mcg
   Second dose 2P bid = 200 mcg
   Third dose 4P bid = 400 mcg
   Final dose 8P bid = 800 mcg

**Reasoning:** Refer to the FP-MDI section in 4 above. In addition, the dry powder and MDI preparations of FP will be compared for differences in adrenal suppressive effects.

6. Triamcinolone (TAA) (100 mcg/puff)
   Starting dose 2P bid = 400 mcg
   Second dose 4P bid = 800 mcg
   Third dose 8P bid = 1,600 mcg
   Final dose 16P bid = 3,200 mcg

**Reasoning:** In normals, Werner (5) showed that TAA 2,000 mcg produced a 25% reduction in the AUC 24-hour plasma cortisol collection. Altman, et al. (11) in asthmatics over 6 months demonstrated at 800 mcg, 1,200 mcg and 1,600 mcg a reduction in ACTH standard dose stimulation test of 15, 16 and 12%, respectively and for 24-hour cortisol urine collection, a 25, 23 and 20% reduction, respectively. With these doses, the $CS_{10-40}$ would most likely be reached.

**Summary of Cortisol Suppressive Doses**

(+ = expect to obtain; ± = may obtain; - = expect not to obtain)

| ICS | $CS_{10}$ | $CS_{20}$ | $CS_{30}$ | $CS_{40}$ | $CS_{50}$ |
|---|---|---|---|---|---|
| BDP | + | + | + | + | + |
| BUD | + | + | + | + | ± |
| FLU | + | + | + | - | - |
| FP | + | + | + | + | + |
| TAA | + | + | + | + | - |

A table of these studies has been formulated (Appendix B, Reference 3, 5-13).

7. Placebo
   Doses will correspond to those of the corresponding ICS arm, in order to maintain the double-blind.

**Reasoning:** On the recommendations of our endocrine consultants and pharmaceutical representatives a placebo arm has been included in the DICE Study. This arm ideally will consist of a small number of distinct placebos corresponding to each of the six ICS arms. This arm will allow for control of miscellaneous factors, such as being in a foreign environment for overnight study and the placebo effect. The placebo arm will include a smaller number of subjects (n=12) than the active treatment arms (n=24 each) because comparisons with placebo are secondary to the main aims of the study.

## E. Reasoning For "Doubling" Doses Without a Washout Period Between Doses

The proposed study will utilize a classic dose-response design in which the dose of the agonist is progressively escalated. While we could have proposed a design in which the doses were administered randomly with washout periods, we think there are scientific and practical drawbacks to such a design. A random design would be subject to the significant possibility of carryover effects when a larger dose of ICS preceded a smaller dose of ICS. In order to eliminate such carryover effects, we would have had to introduce a washout period long enough to assure ourselves that prior effects of the larger dose had waned and that the responsiveness of the HPA axis had recovered. The appropriate length of such a washout period has not been established. Utilizing the classic escalating dose-response design minimizes these uncertainties. Further, we considered that even in the very unlikely case that a carryover effect did exist from prior use of a lower dose of ICS, it would be no greater than any effect that would occur when these medications are used as currently prescribed --- namely for long term, extended use. We therefore saw no advantage to introducing a washout period since it would appear merely to extend the length of this dose-finding study.

## F. Reasoning For Washout Period at Study End

The one week washout period at the end of the study is for safety purposes. Subjects will continue to take peak flow measurements with the Airwatch™ and to complete diary cards. At the end of the washout week the peak flow information stored in the Airwatch™ will be downloaded to the clinical center for review. A call then will be made to the subject to see how they feel in general and with respect to their asthma.

## G. Study Days

1. 8 AM void and discard, then start 8 AM - 8 PM urine collection
2. Between 6:30 and 6:45 PM of the 7th day of placebo or ICS, the subject will report to the Center's designated area for study

3. Dinner between 6:30 and 7 PM (optional)
4. Place 18 g or 20 g catheter for blood draws
5. 8 PM -
   a. Void to complete 8 AM -8 PM urine collection for cortisol
   b. Beginning of 8 PM - 8 AM urine collection for cortisol
   c. Females complete urine pregnancy test
   d. Observed inhaled steroid dose
   e. Start q 1 hour blood draw for cortisol. Last draw is at 8 AM
6. Lights out at 11 PM
7. 8 AM - void to close 8 PM - 8 AM collection for cortisol
8. 8 - 8:30 AM - spirometry on an ATS-approved spirometer
9. Discharge 8:30 AM
10. New dose of ICS given at discharge
11. Other tests on blood for systemic effects: blood osteocalcin - 7 AM sample

## H. Medication Delivered To Subjects

The run-in placebo and the ICS without an extender device (BDP, FLU, and FP-MDI) will use the Optichamber (Healthscan). TAA, which has a built-in spacer, and the dry powder preparations will not use an extender device.

# IV. Inclusion And Exclusion Criteria

## A. Inclusion Criteria

1. Male and female patients post-pubertal up to and including 60 years. Post-pubertal status in adolescents will be determined through a bone age film of the left wrist. Bone age films will be read by radiologists to determine skeletal age using standard tables. Males with skeletal ages of at least 15 years and females with skeletal ages of at least 13 years will be considered post-pubertal and eligible for enrollment. Using these skeletal age thresholds male and female subjects will have achieved 96.8% and 95.8% of their mature height, respectively, using tables by Greulich and Pyle (19). If there is a significant discrepancy between skeletal age and chronological age the judgement of the Principal Investigator should be sought prior to enrollment.
2. History of mild-to-moderate asthma defined as reversible airflow obstruction (12% change in $FEV_1$) or methacholine $PC_{20} \leq 8$ mg/ml, and baseline forced expiratory volume in 1 second ($FEV_1$) 65-90% of predicted. In order to decrease subjects' laboratory visits, the $FEV_1$ reversibility or methacholine requirement can be obtained from measurements within the six months prior to Visit 1. Methacholine results must be obtained using ACRN procedures and software; reversibility results may be obtained using any spirometry system.

3. Morning (prior to 9:30 AM) plasma cortisol concentration of ≥ 5 mcg/dl at enrollment. Samples may be drawn up to one week prior to Visit 1 for cortisol determination.
4. Nonsmoker (less than 10 pack-years and no smoking within the previous year).
5. Ability to provide informed consent, as evidenced by signing a copy of the consent form approved by the Institutional Review Board of the respective study institution.

**B. Exclusion Criteria**

1. Steroid treatment for any condition within the defined intervals prior to enrollment (route)
   a. Oral - None within one year prior to enrollment; maximum of 2 weeks of use between 1 and 2 years prior to enrollment. If subject used any oral steroids between 1 and 2 years prior to enrollment, eligibility must be proven through low dose ACTH Stimulation test (details follow).
   b. Inhaled/Nasal - None within six months prior to enrollment; if subject used any inhaled/nasal steroids between 6 and 12 months prior to enrollment, eligibility must be proven through a low dose ACTH Stimulation test (details follow).
   c. Topical (prescription) - Criteria for inhaled/nasal steroids in b. apply.
   d. Topical (over-the-counter) - None within 2 months prior to enrollment.
   e. Injectable - Criteria for oral steroids in a. apply

   Low dose ACTH Stimulation test for eligibility:

   This test will use a dose of 1.0 mcg Cortrosyn® (ACTH), regardless of body size. Plasma cortisol levels will be measured pretest and at 20 and 30 minutes post-ACTH (14-16). Subjects must achieve a cortisol level > 18 mcg/dl on at least one of the post-ACTH samples to be considered eligible for the DICE study.
2. Current or prior use (within the previous 6 weeks of enrollment) of medications known to significantly interact with steroid disposition, including but not limited to carbamazepine, erythromycin or other macrolide antibiotic, phenobarbital, phenytoin, rifampin, ketoconazole, and sibutramine (Meridia®).
3. Presence of lung disease other than asthma
4. Significant medical illness other than asthma (in particular, thyroid, Cushing's, Addison's, hepatic disease, diabetes, anorexia nervosa or bulimia, glaucoma and cataracts)
5. History of respiratory tract infection within the previous 6 weeks prior to enrollment
6. History of significant exacerbation of asthma within the previous 6 weeks of enrollment

7. History of a life-threatening asthma exacerbation requiring intubation and mechanical ventilation - within 10 years
8. Receiving hyposensitization therapy other than established maintenance regimen
9. Inability, in the opinion of the Study Investigator, to coordinate use of a metered-dose or dry powder inhaler or comply with medication regimens, or inability to comply during the run-in week
10. Pregnancy or lactation
11. Use of oral contraceptives or other hormonal therapy such as Norplant, Depo-Provera, or estrogen replacement therapy (ERT). (Acceptable birth control methods include abstinence, double barrier methods, IUD and surgical sterilization.)
12. Altered day-night cycle
13. BMI > 35
14. HCT at enrollment less than the lower limit of acceptability as specified by the individual clinical center's Institutional Review Board. Samples may be drawn up to 1 week prior to Visit 1 for HCT determination.

### C. Criteria For Assigning Drop-Out Status During Treatment Period

1. Commencement of therapy with any steroid formulation other than study medication, including intranasal and topical steroids
2. Subject becomes pregnant
3. Subject withdraws consent
4. Subject fails to comply with scheduled doses of study drug
5. Subject misses a scheduled visit (and has, therefore, not received the correct dose of ICS for a portion of the study).
6. Subject uses any exclusionary medications listed in Section B.2.

## V. Outcome Variables

### A. Adrenal Suppression

For comparison of adrenal suppression between different doses of individual steroids and between inhaled steroids, changes in AUC plasma cortisol and urine cortisol excretion will be compared. Plasma cortisol concentrations will be measured every hour from 8 PM to 8 AM, and areas under the concentration vs. time curve from time 0 to 12 hours ($AUC_{0-12}$, with time 0 being 8 PM), will be calculated. From these, dose-response relationships (dose vs. % change from the placebo baseline period) will be compared between individual inhaled steroids, and equi-systemic effect doses (i.e., those that cause the same or comparable effect) will be determined. Twenty-four hour (collected from 8 AM - 8 PM and 8 PM - 8 AM), as well as the two 12-hour collections, urine cortisol excretion will be measured, and % change from the placebo baseline period will be used to construct dose-response relationships. These will be compared for the different inhaled corticosteroids.

## B. Secondary Markers of Systemic Effect

Serum Osteocalcin (20)

Although osteocalcin has a circadian variation, the expense of the analysis does not warrant multiple measurements. Standard 7 AM values will be compared (20).

Glaucoma (17)

Although a recent report suggests ICS may be associated with glaucoma (17), the short duration of the DICE study and the cost of the equipment to measure ocular pressures do not warrant this marker to be included in the systemic effect measurements.

**C. AM $FEV_1$** will be measured to determine if a change has occurred on ICS. However, this is an ancillary measurement and not a primary or secondary outcome variable.

## VI. Protocol Information

### A. Recruitment

Each clinical center involved in the ACRN was chosen, in part, based on documentation for subject availability and, to date, there have been no problems in fulfilling the recruitment needs of prior ACRN studies. As this trial requires a limited number of subjects as compared to other ACRN clinical trials, no difficulties in recruitment are anticipated.

Specific recruitment plans of each center are outlined below:

Harvard Clinical Center/Boston

We propose to use the population at Harvard Community Health Plan to achieve our enrollment goals. 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 post-pubertal and < 60 years of age, who had pharmacy benefits and who had received prescriptions for asthma medications were selected. 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. We will contact a fraction of the individuals identified as having mild to 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 Medical and Research Center/Denver

Research subject recruitment has been very successful for all types of asthma patients at the National Jewish Medical and Research Center. The total subjects 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 mild to moderate category. National Jewish 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 $FEV_1$s range from 30-110% of predicted.

a. Denver General Hospital

Dr. Michael Hanley, Acting Head of Pulmonary Medicine, is supporting our efforts by helping us to recruit from the asthmatic patient population at Denver Health Medical Center. 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.

University of Wisconsin/Madison

The Allergy Research Program of the University of Wisconsin maintains a file of potential subjects with mild to moderate asthma 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. Approximately 85% of subjects in this database have "mild to moderate" asthma. 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 Clinic patient population. Also, the U.W. Adolescent Clinic, U.W. Sports Medicine Clinic, U.W. Student Health, V.A. Allergy Clinic, and Northeast Family Practice Clinic are additional sources for potential study subjects.

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 85% of asthmatics in this database have "mild to 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 a given study will be identified by the database, and personal contact will be made by the study coordinator for the purpose 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 patient waiting areas of the Pulmonary Medicine and Allergy Clinics at the major teaching hospitals of UCSF (Moffitt-Long, San Francisco General Hospital, Ft. Miley V.A. 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. To date, we have screened well over 1,000 subjects for our database.

## B. Drug Supplies

Drug supplies for this study will consist of BDP, FLU, FP and TAA MDIs, BUD Turbuhalers™, and FP Diskhalers, as well as albuterol MDIs. The run-in will utilize BDP placebo MDIs. Medications will be supplied by each respective pharmaceutical manufacturer or purchased, if necessary.

## C. Compliance And Monitoring

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

1. Diary card: At each visit the symptom diary card will be reviewed with the patient. Limitations are accuracy of subject's recall and honesty in completing the diary.
2. The AirWatch™ peak flow meter with diary recording will be used to record peak flows (PEF) and $FEV_1$, and to serve as a check of compliance in general, as date and time are electronically recorded. Subjects will be instructed to take study drug between 5 and 10 AM and between 9 and 11 PM, immediately following measurement of PEF. The timestamp provided by the AirWatch will allow for monitoring the subject's compliance with dosing schedules.
3. Due to prior failure and poor reliability of the Chronolog device, it will not be used in this trial. Also, this device cannot be used with all MDIs to be studied. The number of doses or "clicks" remaining in each 200-dose Turbuhaler™ will be counted for an estimate of BUD usage. The number of used and unused FP dry powder disks (Rotadisks) will be used to estimate FP (dry powder) usage. A dose counter (Doser) will be used for the MDI inhaled steroids. Clinic Coordinators will use these data to aid in compliance assessments with subjects at each clinic visit. The limitation of these methods is that there is no indication of whether the subject actually inhaled the medication ("dose-dumping" phenomenon). If 4 or more of the 14 weekly dose actuations are missed or consist of an incorrect number of puffs, the subject will be dropped from the study.

4. Watches with dual alarms will be set at the specific dosing times to remind subjects to use their ICS medication. This worked well in the ACRN BAGS Study.

## D. Inhalation Technique

1. For dry powder ICS [budesonide (Pulmicort) and fluticasone (Flovent)], the budesonide (Astra) training device will be used and scored as follows:

   a. Medication activation via knob turning to hear a click and initiate light - 1 point.
   b. Proper mouth seal and initiation of inspiration 2nd light - 1 point.
   c. Rapid deep inhalation to activate all of the remaining 3 lights - total of 3 points (1 for each light).
   d. Breath hold >5 seconds - 1 point.
   e. Six of six points are needed for each of two consecutive, separate breaths.
   f. Since the fluticasone Diskhaler device is different than budesonide, subjects randomized to fluticasone will require additional instruction on how the device itself works.

2. For triamcinolone (Azmacort), there is a built in spacer. Technique is scored the same as for the OptiChamber (see below).

3. For fluticasone (Flovent) MDI, beclomethasone (Vanceril), and flunisolide (Aerobid), the OptiChamber will be used.

   a. Coordinator primes the OptiChamber with 12 puffs of the ICS.
   b. Subject shakes canister and puts it into the OptiChamber (1 point).
   c. Subject first actuates the canister (1 point).
   d. Inspiration begins <u>after</u> actuation but within 2 seconds of actuation (1 point).
   e. Inspiration is slow, i.e., no whistle (1 point).
   f. Inspiration is to total lung capacity (1 point).
   g. Breath hold is > 5 seconds (1 point).
   h. Six of six points are needed for each of two consecutive, separate breaths.

4. At each clinic visit the subject must be reminded that only one actuation from the inhaler device is allowed per each inspiration, i.e., no double, triple, etc. actuations for a single inspiration.

## E. Risks/Benefits

This study compares the systemic effects of various doses of different inhaled steroids for the treatment of asthma. While not a minor concern, the degree of systemic effects anticipated with the doses to be studied should not pose any greater risk as compared to conventional asthma treatment. Since most of these subjects will be placed

on ICS, we expect their asthma to be under better control. However, to ensure the safety of individuals whose asthma worsens during the study period, specific criteria from the ACRN's Beta-agonist Trial (BAGS) for assigning "treatment failure" status, and for initiating appropriate asthma therapy will be used (Appendix A). There will be no direct benefit to the patients participating in this study. The results may be of potential benefit to the entire group of patients with asthma as it may lead to a better definition of guidelines for asthma therapy.

### F. Anticipated Results

It is anticipated that dose-response relationships for each inhaled steroid will be observed for suppression of plasma cortisol concentrations. Data will be compared, and doses for each inhaled steroid which result in a similar degree of adrenal suppression will be calculated. These equi-systemic doses will then be used to for evaluating comparative efficacy in the treatment of asthma (future study--MICE).

## VII. Adverse Events

### A. Definitions

An adverse event shall be defined as any detrimental change in the patient's condition, whether it is related to an exacerbation of asthma or to another unrelated illness. Adverse events related to asthma exacerbations will be managed according to rescue algorithms outlined in the BAGS trial (Appendix A).

An adverse event is deemed serious if it suggests a significant hazard contraindication, side effect, or precaution. Serious adverse events include any experience that is fatal or life-threatening, is permanently disabling, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose. Serious adverse events must be reported to the DCC within 72 hours of notification. Once notified, the DCC will disseminate information about the event to the Data Safety and Monitoring Board and to the Steering Committee.

### B. Adverse Events Unrelated to Asthma

Adverse events due to concurrent illnesses other than asthma may be grounds for withdrawal if the illness is considered significant by the Study Investigator or if the patient is no longer able to effectively participate in the study. Patients experiencing minor intercurrent illnesses may continue in the study provided that the nature, severity, and duration of the illness are recorded and that any unscheduled medications required to treat the illness are also recorded. Examples of minor intercurrent illnesses include acute rhinitis, sinusitis, upper respiratory infections, urinary tract infections, gastroenteritis, and injuries. Medications are allowed for treatment of these conditions (except steroids and certain antibiotics, See IV. B.2) in accordance with the judgment of the responsible study physician. If a subject develops a febrile illness (defined as having a fever over 100° F) during the study, overnight visits for determination of cortisol levels should be rescheduled

within the visit window, if possible. If an overnight study visit cannot be rescheduled for a time after the fever has resolved and within the visit window, the subject may continue in the study but must not be admitted for cortisol studies. In this case the subject should come into the ACRN Clinical Center on the regular visit date to obtain new drug supplies, record adverse events, and handle other administrative tasks. The subject will have an incomplete study visit, as no outcome data will be collected.

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

- Description of the illness
- Dates of illness
- Treatment of illness and dates (medications, doses, and dose frequency)
- Whether emergency treatment or hospitalization was required
- Treatment outcome
- Actual timing of event in relationship to last dose of the study medication

## C. Adverse Events Related to Asthma Exacerbations

**Definition** - for this protocol, an asthma exacerbation is defined as the development of an increase in symptoms of cough, chest tightness, and wheezing in association with one or more of the following:

- An increase in "as needed" or PRN albuterol use of $\geq$ 8 puffs per 24 hours over baseline use (baseline defined as average daily use during the run-in week) for a period of 48 hours or $\geq$ 16 total puffs per 24 hours for a period of 48 hours
- A fall in PEF of $\geq$ 35% from baseline (defined as the AM PEFR average during the run-in week)

We do not anticipate significant asthma exacerbations in this protocol as the population is mild and we are adding ICS to the treatment program for the majority of subjects. However if this does occur, then the BAGS study protocol for treatment will be undertaken (Appendix A).

## D. Study Center Visits Following Exacerbations

*If a subject receives systemic steroids for an exacerbation or any other steroid other than the study drug, the patient will be considered dropped from the study* and will return for a Termination Visit following resolution of the exacerbation. Because this protocol is specifically focused to determine systemic effects of inhaled corticosteroids and other administered steroids would interfere with this analysis, the intent to treat paradigm will not be followed. If the subject has not been treated with any other steroids, regular follow up evaluations will continue according to the protocol.

### E. Criteria for Discontinuing Subjects Due to Asthma Exacerbations

**Drop-Out Status** - Any subject requiring systemic steroids for an asthma exacerbation during the treatment period will be assigned drop-out status. In addition, subjects may be assigned drop-out status during the treatment period if the subject is treated with any other form of steroid (except study drug) or drugs listed in IV.B.2., becomes pregnant, withdraws consent to participate, or fails to comply with scheduled doses of study drug or the study visit schedule.

## VIII. Cost, Liability, And Payment

All tests will be performed without cost to the participating subjects. Since this is a trial comparing established asthma treatments, liability for patient care costs incurred by patients during the course of the trial will in most cases be borne by the patient or their insurer. Details of the National Institutes of Health policies concerning this issue can be found in NIH Documents #5305 and 6352-2, Research Patient Care Costs Supported by NIH Sponsored Agreements, which are in the ACRN Manual of Operations.

Each patient will be paid an amount determined by their local center for study reimbursement. For patients who drop out, reimbursement will be pro-rated for the length of time they stayed in the study.

## IX. Data Recording

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

## X. Statistical Design And Analysis

### A. Data Collection And Data Management

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

The DCC will be responsible for generating the data collection forms based on input from the clinical centers. Once the data collection forms have been filled out and reviewed, the Clinic Coordinator will log into the DCC computer system and enter the data within 3 days of the patient visit. The advantage of this distributed data entry system is that the Clinic Coordinators will review the data a second time as they are entering it, which serves

as another level of quality control. The data base management system will have range checks and validation checks programmed into it for a second level of quality control. Forms will then be forwarded to the DCC for the second data entry and filing, which will be performed within 3 days of receipt. The DCC will be responsible for identifying problem data and resolving inconsistencies. Once the quality control procedures are complete, new study data will be integrated into the primary study database.

## B. Masking

Due to the different doses (requiring various numbers of actuations) and inhalation systems used with the various inhaled steroids to be studied, specifically conventional MDIs with and without a spacer and the Turbuhaler™ device, this study will be very difficult to mask completely. However, due to the inclusion of a placebo arm consisting of placebos corresponding to each of the six ICS arms we will attempt to make this a double-blind study to the extent possible, pending acquisition of the necessary placebo supplies. This will allow for determination of any perceived placebo effect. In addition, because each subject receives the placebo for his/her randomized study drug during the first week of the treatment period (single-blind) unlabeled drug will be obtained and repackaged to maintain this blind. The central laboratory at the National Jewish Medical and Research Center that performs the plasma cortisol concentrations and other assays will be blinded. Also, the investigators will be blinded to each subject's results over the course of the trial.

## C. Randomization

When a subject 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 subject requires randomization. After entering the pertinent information with respect to clinical center, gender, and eligibility criteria, the Clinic Coordinator will be asked to verify that all of the entered information is correct. If so, the Clinic Coordinator will be given a drug packet number for the subject's treatment arm assignment based on randomization stratified by Clinical Center and gender. In order to maintain security of the randomization schedules, the data manager of the DCC will receive automatically a notice from the ACRN network server that a subject has been randomized. If no follow-up information is forthcoming on such a subject, the data manager will contact the Clinic Coordinators concerning the status of the subject.

## D. Statistical Analysis

The primary response variable in this study is the AUC for overnight hourly plasma cortisol (see Section V.A). The objective of the statistical analysis is to fit a dose-response curve and estimate the doses that yield cortisol suppression (CS) between 10% and 40% within each of the 6 ICS treatment arms and the placebo arm. Comparisons of the 6 ICS treatment arms with respect to their dose-response curves is of secondary interest.

Because each subject will receive increasing doses of an inhaled corticosteroid, the statistical model must account for the presence of correlated data. Therefore, the chosen models will fall within the realm of linear and nonlinear mixed-effects models and restricted

maximum likelihood estimation (REML) will be applied for the purposes of estimation (18). A model that worked well for the DICE Pilot Study was the exponential decay model:

$$\text{(Response at dose d)/(Response at baseline)} = \exp(\alpha+\beta^{*}\log_2(d)+\gamma^{*}\text{gender})$$

$$\begin{cases} d = 1, 2, 4, 8 \text{ puffs b.i.d.}, \\ \text{gender} = -1 \text{ (male)}, +1 \text{ (female)} \end{cases}$$

The $CS_{100p}$, $0 < p < 1$, in this model is

$$CS_{100p} = 2^{**}[\{\log(1-p)-\alpha\}/\beta]$$

The asymptotic distribution of the REML estimators is multivariate normal so the delta method can be applied to attain the asymptotic distribution of a particular $CS_{100p}$ or a joint set of $CS_{100p}$'s. This approach also can be adapted to compare the dose-response curves of the 6 inhaled corticosteroid groups.

## E. Sample Size

The objective of the sample size calculation is to determine the sample size, n, for each ICS treatment arm such that the 95% confidence interval for the $CS_{100p}$ is sufficiently narrow. Thus, the sample size must be large enough to guarantee a relative amount of precision in the interval estimate of the $CS_{100p}$.

The following 95% confidence intervals for the $CS_{10}$, $CS_{20}$, $CS_{30}$, and $CS_{40}$, resulted from the DICE Pilot Study:

| | $CS_{10}$ (puffs/d) | $CS_{20}$ (puffs/d) | $CS_{30}$ (puffs/d) | $CS_{40}$ (puffs/d) |
|---|---|---|---|---|
| Inhaler A (n = 11) | (0.4, 4.8) | (0.6, 6.8) | (0.8, 10.2) | (1.4, 17.2) |
| Inhaler B (n = 11) | (1.6, 6.8) | (2.4, 9.6) | (3.4, 15.2) | (5.0, 27.0) |
| Inhaler C (n = 10) | (0.8, 3.6) | (1.4, 4.6) | (2.4, 6.6) | (4.0, 10.8) |

If the sample size were doubled to n=24 for each ICS arm (allowing for 20% drop-out), then an approximately 30% improvement in confidence interval length occurs:

| | $CS_{10}$ (puffs/d) | $CS_{20}$ (puffs/d) | $CS_{30}$ (puffs/d) | $CS_{40}$ (puffs/d) |
|---|---|---|---|---|
| Inhaler A | (0.6, 3.2) | (0.8, 4.6) | (1.2, 7.2) | (2.0, 11.8) |
| Inhaler B | (2.0, 5.6) | (3.0, 8.0) | (4.2, 12.2) | (6.4, 21.0) |
| Inhaler C | (1.0, 2.8) | (1.6, 3.8) | (2.8, 5.6) | (4.6, 9.4) |

Therefore, a sample size of n=24 is proposed for each ICS arm. An additional 12 subjects will be randomized to a placebo arm, yielding a total sample size of 156.

## DICE Protocol In Tabular Form

| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Phone Contact |
|---|---|---|---|---|---|---|---|---|
| Week | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Window (Days) | | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 |
| Dispense Medications | Run-in Placebo & Rescue | Steroid Placebo | Dose 1 Steroid | Dose 2 Steroid | Dose 3 Steroid | Dose 4 Steroid | | |
| Informed Consent | X | | | | | | | |
| Randomization | | X | | | | | | |
| Medical History | X | | | | | | | |
| Long Physical Exam | X | | | | | | | |
| Blood Draw for Genetic Analysis | X | | | | | | | |
| Am Cortisol | X | | | | | | | |
| Hematocrit | X | | | | | | | |
| Spirometry | X | | X | X | X | X | X | |
| Methacholine Challenge | X* | | | | | | | |
| B-agonist Reversibility Test | X* | | | | | | | |
| Pregnancy Test | X | | X | X | X | X | X | |
| Airwatch QC | X | | | | | | X | |
| Dispense/Review Diary Cards | X | X | X | X | X | X | X | X |
| Technique Assessment | X | X | | | | | | |
| Medication Compliance Assessment | | X | X | X | X | X | X | |
| Adverse Events Assessment | | X | X | X | X | X | X | X |
| Overnight Hospitalization | | | X | X | X | X | X | |

* Either a methacholine challenge or a reversibility test may be performed at Visit 1 to meet eligibility requirements if documentation of past results is unavailable.

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## Appendix A Adverse Events Related to Asthma Exacerbations

### A.1 Definition

For this protocol, an asthma exacerbation is defined as the development of an increase in symptoms of cough, chest tightness, and wheezing in association with one or more of the following:

- An increase in "as needed" ß-agonist use of ≥ 8 puffs per 24 hours over baseline use (baseline defined as average daily use over the run-in week) for a period of 48 hours or ≥ 16 puffs per 24 hours for a period of 48 hours.

- A fall in PEFR of ≥ 35% from reference levels (reference level will be defined as the average AM peak flow during the run-in week of the protocol).

Patients developing asthma exacerbations during the treatment period will be managed according to the following rescue algorithms. Patients developing asthma exacerbations during the run-in period will be removed from the study.

### A.2 Rescue Algorithms

Rescue algorithms will be applied in cases where an exacerbation as defined in Section A.1 fails to resolve or PEFR is not improved to > 65% of reference level within 48 hours after increasing PRN albuterol use. Rescue algorithms are based on recommendations from the NAEP Guidelines for Diagnosis and Management of Asthma (NHLBI Publication No. 91-3042, 1991). Albuterol and oral prednisone are the principal medications for rescue management and patients will be instructed in their use for home management. For severe acute episodes of asthma, treatment will be administered according to the best medical judgment of the treating physician.

### A.2a Home Care

Asthma exacerbations will be recognized by an increase in symptoms and by a corresponding drop in PEFR 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 PEFR to ≤ 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 sooner, if needed. Patients will be instructed to use the "PRN MDI" for treatment.

- If the PEFR 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.

- Failure of albuterol to control or maintain PEFR > 65% reference level may necessitate the use of steroids (see below) in which case the subject achieves DICE dropout status (See Section IV.C.).

**A.2b Physician's Office or Emergency Room Treatment**

- Patients will be assessed by history, physical examination, and by physiological monitoring including spirometry or PEFR. If the patient's PEFR 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 PEFR 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 2c.

- If symptoms persist and PEFR 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 (60 mg prednisone orally; methylprednisolone 60 mg iv bolus). Monitoring of PEFR or spirometry should continue every hour. Within 4 hours of treatment, a decision should be made regarding patient disposition.

- If PEFR increases to > 65% reference level within 4 hours, the patient can be discharged to continue treatment at home. Home treatment should include a 8-day course of prednisone (see below).

- If PEFR 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 PEFR 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.

### A.2c Prednisone Treatment

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

- For follow-up management after discharge from the physician's office, emergency room, or hospital for an acute exacerbation.

- For home management if the patient is taking ≥ 16 puffs albuterol per 24 hours over a 48 hour period and, despite this therapy, PEFR remains < 65% reference level before albuterol use and the daily sum of the symptom scores in the same period is > 8.

- For home management when the daily sum of the symptom scores is >10 for 48 hours or longer and the patient is taking ≥ 16 puffs of albuterol.

- When PEFR 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.

## B. Clinical Center Visit Following Exacerbations

A follow-up evaluation will occur to assess the subject's asthma status and to determine if he/she must be dropped from the study.

## APPENDIX B: Adrenal Suppression Studies with ICS

| Author (Ref.) | Subjects | Measurement | Drugs | Dose & Schedule | Results (% Suppression) |
|---|---|---|---|---|---|
| Nikolaizik (3) | NL, M (8), F (10) | Cortisol q 20 min from 10 PM - 7 AM | BUD (Placebo 4M, 2F) | 400 x 1 8 PM (2M, 4F)<br>400 bid x 2 wks (2M, 4F) | Single Dose / 2 wks<br>BUD 40% / 37% |
| Werner (5) | NL, M (60) | 24-h plasma cortisol AUC Q 4 h | BID<br>FLU 1000<br>TAA 1000<br>BDP 880<br>FP 880<br>BUD 900 | Day 1 - Placebo at 10 PM<br>Day 2 - dose at 10 PM<br>Day 3 - dose bid<br>Day 4 - dose bid<br>Day 5 - dose bid<br>Day 6 - last dose 10 PM | Single Dose / 2 wks<br>FLU 2000 8% / 6%<br>TAA 2000 19% / 25%<br>BDP 1760 18% / 30%<br>FP 1760 35% / 80%<br>BUD 1800 17% / 20% |
| Lundback (6) | Asthmatics on ICS<br>M (306)<br>F (279) | AM Cortisol | FP<br>BDP | FP 500 per day MDI x 6 wks<br>FP 500 per day Disk x 6 wks<br>BDP 1000 per day MDI x 6 wks | FP MDI - 1%<br>FP Disk - 4%<br>BDP - 7% |
| McCubbin (7) | Asthmatics<br>M (13)<br>F (13) | 24-h Urinary Cortisol | BDP<br>TAA<br>FLU | 400 x 1 week then 800 then 1600<br>800 x 1 week then 1600 then 3200<br>1000 x 1 week then 2000 then 4000 | BDP - 15, 10, 12<br>TAA - 10, 5, 45<br>FLU - 15, 15, 46 |
| Clark (8) | Asthmatics<br>M (7)<br>F (5) | 8 AM Cortisol<br>ACTH Levels<br>10-h Urinary Cortisol | BUD<br>FP | 400, 1000, 1600, 2000 at 10 PM<br>500, 1000, 1500, 2000 at 10 PM<br>x-over, single dose | Cortisol / ACTH / Urine<br>BUD<br>400 -8 4 24<br>1000 4 8 57<br>1600 16 12 50<br>2000 26 14 47<br>FP<br>500 -7 3 59<br>1000 6 19 51<br>1500 41 32 81<br>2000 65 44 77 |
| Lonnebo (9) | NL, M (24) | 20 h plasma cortisol ~ Q 2 h | BUD 800<br>FP 1000 | Single dose 10 PM<br>3 - 1/2 days bid<br>x-over, 1 - wk washout | Single Dose / 3.5 days<br>BUD 26% / 34%<br>FP 25% / 55% |

**Definitions:**

NL = Normal
M = Male
F = Female
BUD = Budesonide
FLU = Flunisolide
TAA = Triamcinolone acetonide
BD = Beclomethasone dipropionate
FP = Fluticasone propionate

APPENDIX B: Adrenal Suppression Studies with ICS

| Author (Ref.) | Subjects | Measurement | Drugs | Dose & Schedule | Results (% Suppression) |
|---|---|---|---|---|---|
| Boorsma (10) | NL, M (12) | Suppression of 24 h pooled Plasma cortisol<br>? - None from 10 PM - 6 AM | BUD<br>FP<br>(Placebo) | 200 bid, 400 bid, 1000 bid<br>200 bid, 375 bid, 1000 bid<br>4 d each dose, 3 d washout | BUD 1%, 3%, 27%<br>FP 21%, 39%, 84% |
| Altman (11) | Asthmatics<br>M (100)<br>F (43)<br>No Steroids x 30 d | ACTH Stim<br>24-h urine | TAA | TID x 2 wks then BID for 6 months<br>400 bid<br>600 bid<br>800 bid | Max. Suppression<br>ACTH Stim. / Urine<br>800 15% 25%<br>1200 16% 23%<br>1600 12% 20% |
| Grahnen (12) | NL, M (25) | Cortisol - $AUC_{20}$<br>10 PM - 6 PM<br>Urine Cortisol 24 h | BUD<br>FP<br>FP | 800, 10 PM single dose BUD<br>250, 500, 1000 10 PM x 1 FP<br>1000 x 3.5 days FP | BUD<br>800 7%<br>FP<br>250 7%<br>500 19%<br>1000 27%<br>1000 x 3.5 d 65% |
| Grove (13) | NL, M (5)<br>F (4) | Am Cortisol<br>ACTH Stimulation<br>Osteocalcin<br>Urine Calcium | BUD<br><br>FP | 400 bid x 1 wk<br>800 bid x 1 wk<br>750 total (? how at bid dose)<br>750 bid x 1 wk | AM Cortisol / ACTH Stim. / Osteo Ca / U<br>BUD<br>800 11 8 9 8<br>1600 13 15 12 4<br>FP<br>750 6 9 5 25<br>1500 -3 10 7 27 |

**Definitions:**

| | | | |
|---|---|---|---|
| NL | = Normal | FLU | = Flunisolide |
| M | = Male | TAA | = Triamcinolone acetonide |
| F | = Female | BD | = Beclomethasone dipropionate |
| BUD | = Budesonide | FP | = Fluticasone propionate |