

Salmeterol vs. Placebo in the Treatment of Moderate-Persistent Asthma in an Ethnically Diverse Urban Teaching Hospital

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A. Study Purpose and Rationale

Asthma is one of the most common diagnoses made in the outpatient setting. It is estimated that up to 16 million adults in the United States have asthma¹ with higher incidence in ethnic minorities. Despite the frequency of this diagnosis, patients often have poorly controlled symptoms, especially in urban areas. As a marker of poor symptom control, it is estimated that up to 25% of patients with asthma report Emergency Room (ER) visits each year for asthma exacerbations.² Despite this sobering statistic, less than 1/2 of eligible patients are on optimal medication management.² The current standard of care for patients with moderate-persistent asthma is an inhaled corticosteroid (ICS) plus a long acting β_2 agonist (LABA)³. This official recommendation comes with a caveat since short acting β_2 agonists have been shown to contribute to excess asthma mortality in several historical case series^{4,5,6} and clinical trials^{7,8}. The same concern has recently been extended to salmeterol^{9,10}. The SMART study¹⁰ in particular found increased risk of asthma related death in African-Americans. This persuaded the US Food and Drug Administration (FDA) to place a "black box warning" on medications that contained salmeterol. Despite this concern, uses of salmeterol and salmeterol containing products have grown in recent years as other studies have shown improved control of asthma when added to a stable regime of inhaled corticosteroid^{11,12,13} with minimal increased risk. Some suggest that genetic differences may be responsible for the differences in efficacy found in between certain ethnic groups^{14,15}.

With this background in mind, it is my intention to study the use of salmeterol when added to an ICS in a population of moderate persistent asthmatics at a major urban teaching hospital in New York City. This population in particular includes many people of Hispanic ancestry, a population that has been historically overlooked in clinical trials.

B. Study Design and Statistical Analysis

The current study under consideration is a double-blind, placebo controlled, prospective study of salmeterol in moderate-persistent adult asthmatics. Patients will be randomized into two arms: ICS + Placebo or ICS + Salmeterol. Randomization will occur in blocks of 6. Subjects will be followed for a total of one year. The primary outcome of interest is ER visits for asthma exacerbation.

Number of subjects: 246 are needed in each group (492 total). Due to the concern over attrition (estimated at 10%), I will recruit 542 patients for this study. The power analysis is based on the χ^2 statistic, assuming a power of 80% at an α of 0.05.

Statistical Analysis: All statistics will be based on the intention-to-treat principal. Risk or potential benefit of the study drug will be analyzed by the Relative Risk calculation and 95% confidence intervals around that risk, with an alpha set for 0.05. Time to drop-out and time to primary endpoint will be analyzed by the Kaplan-Maier curve.

C. Study Procedure

Subjects will be recruited by their own physicians, primarily from the resident run "Associates in Internal Medicine"(AIM) outpatient clinic, or the fellow-run Pulmonary clinic. If a subject currently meets the clinical definition for moderate persistent asthma³ and not currently taking a long-acting β_2 agonist they will be considered for study participation.

- **Visit 0: (0 Weeks)** Eligible and interested study subjects sign informed consent. Baseline demographic data is collected including age, gender, self-described race or ethnicity, educational level, and annual household income. An initial physical exam is done by the study coordinator. Complete spirometry is ordered if not done within the past 6 months. Since the national guidelines³ stipulate the use of moderate dose ICS for all patients with moderate persistent asthma, subjects are started on this medication if not already on it.
- **Visit 1: Randomization (4 weeks):** Subjects will be given an ICS inhaler or a combination ICS + salmeterol inhaler. Subjects and study personnel will be blinded as to which inhaler they are receiving. Study subjects will be taught how to use the inhaler and will be asked to demonstrate its use to ensure understanding. Subjects will be asked to keep a diary of their asthmatic symptoms, recording the number of rescue inhaler sprays they use per week.
- **Visit 2: (8 weeks):** Data collection and compliance assessment: All subjects will undergo a physical examination and peak flow measurement. Use of current asthma and non-asthma medications will be recorded. Subjects will be asked whether they have had any ER visits for asthma exacerbations, and if so, which hospital. Subjects will submit their empty inhalers for inspection, since the drug delivery device contains a numerical indicator of number of spent inhalations. Finally, subjects will be queried about adverse events.
- **Visit 3 (16 weeks):** Data collection, compliance assessment (see above)
- **Visit 4 (24 weeks):** Data Collection, compliance assessment (see above)
- **Visit 5 (32 weeks):** Data Collection, compliance assessment (see above)
- **Visit 6 (38 weeks):** Data Collection, compliance assessment (see above)
- **Visit 7: (42 weeks):** Data Collection, compliance assessment (see above)
- **Visit 8 (48 weeks):** Data Collection, compliance assessment (see above)
- **Visit 9 (54 weeks):** Data Collection, compliance assessment, and Study Wrap-up. All study related medication will be collected. Complete office spirometry will be repeated. Patients will be consented for a peripheral blood draw to determine 13₂ gene receptor polymorphism genotyping.

D. Study Drug

Salmeterol SEREVENT DISKUS (salmeterol xinafoate inhalation powder) contains salmeterol xinafoate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component of the formulation is salmeterol base, a highly selective beta₂-adrenergic bronchodilator. The chemical name of salmeterol xinafoate is 4-hydroxy-[[[6-(4-phenylbutoxy)hexyl]amino] methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate. Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the empirical formula is C₂₅H₃₇NO₄• C₁₁H₈O₃. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water. Adverse reactions to salmeterol are similar in nature to reactions to other selective beta₂-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm; headache; tremor; nervousness; and paradoxical bronchospasm¹⁶

E. Medical Device

N/A

F. Study Questionnaires

N/A

G. Study Subjects

Inclusion:

- Diagnosis of moderate-severe persistent asthma

- clinically requiring ICS for asthma control
- age >18

Exclusion

- Pregnant/Lactating
- Allergy to salmeterol
- Contraindication to inhaled corticosteroid
- Concurrent use of β -blockers

H. Recruitment of Subjects

Subjects will be recruited by residents and clinical fellows practicing at Columbia Presbyterian Medical Center. Since subjects are recruited directly from their regular outpatient provider, it is assumed that the primary physician agrees that the patient is suitable for the study, *as* stipulated by CPMC policy.

I. Confidentiality of Study Data

Study data will be held strictly confidential. All data will be collected by trained study personnel and kept in locked file cabinets when not in use. In addition, computer programs that contain data will be password protected. Finally, all study material will be kept separate from the regular hospital chart. Data will only be viewed by qualified study personnel, but in some situations, adverse reactions may be reportable to government officials working for the Federal Drug Administration. (FDA)

J. Potential Conflict of Interest

None reported

K. Location of the Study

This study will be conducted in the outpatient clinic setting. This consists of Vanderbilt Clinic, second floor, AIM East (1150 St. Nicholas Ave.) - first floor, and ACNC clinic 181st street. Occasionally, other outpatient venues (such *as at* the Allen Pavilion) may be used.

L. Costs to Subjects

Patients are not expected to incur any additional costs by participating in the study. If a patient's asthma worsens and hospitalization is required, the financial responsibility for this visit will fall to the patient and their insurance company. If patients are directly harmed by their participation in the study, certain compensation may be available.

M. Minors *as* Research Subjects

We will not enroll patients under age 18 in this study.

N. Radiation or Radioactive Substances

We will not use radiation or radioactive substances in this study.

O. References

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