Tiotropium Bromide as an Alternative to Increased Inhaled Corticosteroid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroids

**TALC and BASALT Trials:** The TALC and BASALT (Best Adjustment Strategy for Asthma over Long Term) trials are complementary studies that share a common 4-week run-in period. Asthmatics who are controlled on low-dose inhaled corticosteroids (ICS) during the common run-in are enrolled in BASALT; patients who are sub-optimally controlled on low-dose ICS and, therefore, require additional treatment to gain asthma control are enrolled in TALC.

**Why this study?** National and international asthma treatment guidelines recommend ICS as the initial controller therapy for all severities of asthma that warrant daily treatment with a controller. When treatment with low-moderate doses of ICS is not sufficient to gain and maintain asthma control, guidelines suggest adding a second controller, rather than escalating the ICS dose to high levels.

Therapeutic options for an additional controller include a long-acting beta-agonist, a leukotriene modifier, and theophylline. It is generally agreed that adding a long-acting beta-agonist provides the greatest benefit. However, long-acting beta-agonists may not be an appropriate choice for all patients. Recent data have suggested that some asthmatics might be at increased risk for severe adverse events (severe asthma episodes, death) when taking salmeterol. These concerns were the topic of a FDA Public Health Advisory (November 18, 2005). Tiotropium bromide might prove to be an effective alternative to long-acting beta-agonists for use in combination with ICS. This study will provide preliminary data on the usefulness of tiotropium bromide as an add-on agent in patients with inadequate asthma control who are taking an ICS.

**Primary Objectives:** This is an exploratory trial to determine if the addition of tiotropium bromide is superior to doubling the dose of an inhaled corticosteroid in patients with moderately severe asthma who are not adequately controlled on a lower dose of inhaled corticosteroid alone (primary exploratory research hypothesis). This study is also designed to determine if the addition of tiotropium bromide is not inferior to the addition of a long-acting beta-agonist in patients with moderately severe asthma who are not adequately controlled on a lower dose of inhaled corticosteroid alone (secondary exploratory research hypothesis). The primary outcome is improvement in lung function (AM peak flow and forced expiratory volume in one second (FEV$_1$)). Secondary outcomes include indices of asthma control.
(asthma symptoms, asthma control days, Asthma Control Questionnaire, Asthma Symptom Utility Index, asthma exacerbations) and quality of life and biomarkers of inflammation (exhaled nitric oxide, exhaled breath pH, exhaled breath biological mediators, sputum eosinophilia).

**Eligibility Criteria:** Potential participants are nonsmoking men and women 18 years of age and older with a history of physician-diagnosed asthma. They must have no significant medical illnesses other than asthma and allergies. Subjects must meet pulmonary function eligibility criteria at Visit 1 that include a minimum baseline FEV\(_1\) of 40% of predicted normal and either a methacholine challenge or albuterol reversibility test to verify airway hyperresponsiveness. Subjects must also demonstrate a need for daily controller therapy as shown by either a prescription for or use of a controller during the past year, or symptoms more than twice a week if not on an asthma controller. Following the 4-week run-in period on standardized low-dose inhaled corticosteroid, subjects qualify for the TALC protocol if they have FEV1 \(\geq\) 40% of predicted normal and either of the following:

- Prebronchodilator FEV\(_1\) \(\leq\) 70% predicted
- Score on the ACRN Asthma Evaluation Questionnaire (see protocol Appendix 1) of 2 or 3 on any 1 (or more) of the 3 questions. This corresponds to: symptoms 6 or more days per week and/or rescue inhaler use 6 or more days per week and/or nocturnal awakenings for asthma two nights per week or more.

**Study Design:** The TALC trial is an exploratory 52-week, randomized, double-blind three-period cross-over study encompassing 15 study visits. The TALC protocol uses a common 4-week run-in period with the BASALT protocol to maximize patient recruitment for these complementary studies. At Visit 1 eligible subjects enter a common run-in period during which they will receive open-label, low-dose ICS (1xICS; beclomethasone dipropionate HFA 80 mcg BID) for 4 weeks. At the conclusion of the run-in period, patients who are not well controlled on low-dose ICS will be allocated to the TALC trial and will enter the randomized, double-blind, three-period crossover portion of the trial.

TALC subjects will be randomized to receive a defined sequence (order) of the following three treatment regimens: 1) ICS alone at twice the dose (2xICS) used in the common run-in period; 2) ICS at the same dose (1xICS) used in the run-in period plus tiotropium bromide (18 mcg of dry powder administered once daily in the morning); 3) ICS at the same dose (1xICS) used in the run-in period plus a long-acting beta-agonist (salmeterol 50 mcg BID). Subjects will receive each regimen for 14 weeks of double-blind, placebo-controlled treatment followed by a 2-week open-label wash-out period on 1xICS. Subjects will be given open-label albuterol for use as rescue therapy. Once randomized, intention-to-treat principles will apply.

**What are the benefits and risks for society and the participants?**

If the addition of tiotropium bromide to low-dose ICS is found to be superior to doubling the dose of ICS and non-inferior to the combination of long-acting beta-agonist and low dose ICS, then a safe and effective alternative to a long-acting beta-agonist may have been identified. This will be especially important for patients who experience adverse effects of long-acting beta-agonists.

For each subject enrolled in the study the following medications will be provided without charge: albuterol rescue inhalers, tiotropium bromide, inhaled corticosteroids, and long-acting beta-agonists. Subjects will receive a peak flow meter to monitor their lung function during the trial. They will be instructed on the identification of worsening symptoms and will have action plans to guide management of their asthma. ACRN physicians/coordinators will be
available 24 hours/day, 7 days/week to provide advice for subjects. In addition, asthma education and clinic evaluations will be offered during the study. Subjects will be compensated for their time and effort. There is no long-term benefit to the participant for joining this study.

Risks of study participation include risks associated with study procedures as outlined in the consent document and possible drug-related side effects. In addition, taking long-acting beta-agonists could potentially make some people’s asthma worse. A series of rescue algorithms is in place to treat asthma symptoms and exacerbations.