Participant Information and Consent Form

Title of Study:	Tiotropium efficacy against allergen induced early asthmatic responses
Protocol #:	UofS BIO REB #1959
Principal Investigator:	Dr. Donald Cockcroft, MD, FRC(P)C Department of Medicine Division of Respirology, Critical Care and Sleep Medicine University of Saskatchewan 306-844-1446
Co-Principal Investigator:	Dr. Beth Davis, PhD Department of Medicine Division of Respirology, Critical Care and Sleep Medicine University of Saskatchewan 306-844-1444
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Introduction:

You are invited to take part in this clinical research study because you have been diagnosed with allergic asthma and you are between 18 and 65 years of age.

Your participation is entirely voluntary. If you decide to participate, you are still able to withdraw at any time. If you choose not to participate or choose to withdraw from the study, your access to health care, your employment and/or your academic status will not be affected.

Please take time to read the following information carefully. You may ask the study staff any questions you may have before, during and after the study. Please feel free to discuss this study with your family, friends and/or primary care physician before making a decision about participating.

Funding:

The University of Saskatchewan (USask) Department of Medicine has provided funding to conduct this clinical trial. The Investigators have no financial interest in the outcome of this study. The Investigators

are not being paid beyond their regular salary to conduct this clinical trial. The study drug will be obtained from the manufacturer (Boehringer Ingelheim Canada).

Purpose of the Study:

Tiotropium (Spiriva Respimat®) is a medication used to treat respiratory conditions. Technically, tiotropium is referred to as a long acting muscarinic antagonist or "LAMA". The term long acting suggests the drug is used once a day. Muscarinic refers to a type of receptor on airway smooth muscle involved in causing bronchoconstriction or a tightening of the airway which makes breathing more difficult. Antagonist means it blocks or inhibits the effect. Therefore, tiotropium blocks muscarinic receptors on airway smooth muscle and prevents bronchoconstriction. Tiotropium was recently approved by Health Canada for use as add-on therapy in poorly controlled asthmatics. Although tiotropium is approved for use as an add-on therapy in poorly controlled asthma, the use of tiotropium is not approved for use in mild allergic asthma. The use of tiotropium in this study is therefore investigational or experimental. Health Canada has approved the use of tiotropium in this study.

Recent research suggests tiotropium may also have anti-inflammatory effects. The potential anti-inflammatory effect of tiotropium is relevant to individuals with allergic asthma since allergen exposure not only causes acute bronchoconstriction (i.e. asthma symptoms) but also leads to airway inflammation. The purpose of this study is to investigate the protective effects of tiotropium on the response to allergen exposure in individuals with mild allergic asthma.

Study Design Overview:

This study is designed as a single-center, double-blind, randomized, placebo-controlled, cross-over study. There are two treatments, tiotropium and matching placebo. Single-center means only researchers from the U of S Asthma Research Lab are conducting the study. Double-blind means neither you nor the Investigators will know which treatment you are receiving when but this information is available in an emergency situation. Randomized means you will receive the treatments in random order. Placebo-controlled means one of the two treatments will be an inactive treatment (i.e. no active drug ingredient). Cross-over means you will receive both treatments but not at the same time. The Investigators plan to collect data from 15 individuals with mild allergic asthma.

Eligibility Criteria:

You are eligible to participate in this study if you are in general good health with no other medical conditions or lifestyle activities that would potentially alter the outcome of study procedures. You must be at least 18 years of age but not older than 65. You must have been diagnosed with asthma at least 3 months ago. Your asthma must be stable or well-controlled. Your baseline lung function, measured as the amount of air that you can forcefully exhale in the first second of exhalation (FEV_1), must be $\geq$870% of what is predicted for a person of your age, height, and sex. You must have a positive skin prick test to one of the study allergens and you must demonstrate airway responsiveness to methacholine (i.e. respond with a decrease in lung function of at least 20% following inhalation of methacholine).

You may not participate in this study if you require medications other than occasional salbutamol (e.g. Ventolin®) to control your asthma or anti-histamines to treat allergy symptoms. Salbutamol use may not exceed 4 times per week and anti-histamine use will need to be withheld prior to study visits. The duration to withhold the medication will depend on the anti-histamine used and this will be discussed with you.

You will be required to withhold salbutamol for six hours prior to any lab visit. However, should you need to use salbutamol or an anti-histamine within the required washout timeframe, you should take the medication and then contact study personnel to reschedule your visit, which may mean repeating previous visits.

You will not be eligible to participate if any of the following apply:

- you are pregnant or breast-feeding
- you have another lung condition or medical condition that would put you at risk if you participate
- you are a current smoker of nicotine products (e.g. cigarettes) or you have a significant smoking history (e.g. pack a day for 10 years)
- you use cannabis or other inhaled recreational products (e.g. e-cigarettes or other vaping products) on a daily basis; occasional use will require a 24 hour withhold
- you have experienced a worsening of your asthma within 4 weeks of starting this study that required a change in how you treat your asthma (e.g. use of inhaled corticosteroids)
- you have been exposed to a trigger that worsens your asthma (e.g. cat) within the last 4 weeks
- you have experienced a respiratory infection within the last 4 weeks
- you have a diagnosis of narrow angle glaucoma
- you have a diagnosis of urinary retention
- you have a known hypersensitivity to tiotropium or components of tiotropium formulation (e.g. benzalkonium chloride)
- you have a history of anaphylaxis or angioedema
- you currently use any of the following medications:
    - inhaled corticosteroid including combination therapies
    - inhaled muscarinic antagonists – except study treatment (e.g. ipratropium bromide)
    - long-acting beta$_2$-agonists (LABA; e.g. formoterol)
    - leukotriene receptor antagonists (e.g. montelukast)
    - biologics (e.g. benralizumab)
    - allergen immunotherapy
    - mast cell stabilizers (e.g. nedocromil sodium)

Visits, Procedures and Time Commitment:

If you decide to take part in this study, you will be required to attend the research lab (Room 346 Ellis Hall) on four occasions over the course of approximately 4 weeks. The study visits and procedures are summarized in Table 1 on page 4 of this document. At Visit 1, which will require about 2.5 hours of your time, study staff will provide an overview of the study purpose and procedures and answer any questions you may have. If you choose to participate, you will be required to sign the consent form (i.e. this document). After consent is obtained, you will be required to undergo the following tests to determine your eligibility and to capture baseline measurements: fractional exhaled nitric oxide (FeNO), spirometry, methacholine challenge, sputum induction, skin prick testing and skin titration endpoint testing. If you are eligible, you will be randomly assigned treatment 1. If you do not meet spirometry or methacholine

challenge eligibility requirements at first attempt, one re-screen attempt will be allowed. You will be trained on the use of the inhaler and the first dose will be administered. You will self-administer daily doses (2 puffs once a day) for the next six days before returning to the lab for Visit 2.

At Visit 2, which will require about 6 hours of your time, study staff will ask you about daily dosing and a final dose will be administered. Thirty minutes after dosing, blood pressure, FeNO and baseline spirometry will be performed followed by allergen inhalation challenge and then sputum induction. After Visit 2, there will be a washout period of at least two weeks before you return to the lab for Visit 3 and the start of treatment 2. The term "washout period" means you will not be receiving any treatment during this time.

Visit 3 procedures are similar to Visit 1 procedures and will require about 2 hours of your time. Procedures at this visit include baseline measurements of FeNO, spirometry, methacholine challenge and sputum induction. Following collection of these data, blinded treatment 2 will be provided to you and the first dose will be administered. You will again self-administer daily doses for the next six days prior to returning to the lab for Visit 4.

Visit 4 procedures are identical to Visit 2 procedures and will again require about 6 hours of your time.

Table 1 – Visits, procedures and time commitment:

Visit 1	Treatment Period	Visit 2	Washout	Visit 3	Treatment Period	Visit 4
Consent FeNO Spirometry MCT Sputum SPT STE Titration Randomization First Dose Tx1	Self administer Treatment 1 for 6 days	Final Dose Tx1 Blood pressure FeNO (pre AC) Spirometry Allergen Challenge FeNO (5 hrs post AC) Sputum (5 hrs post AC)	Minimum 2 weeks	FeNO Spirometry MCT Sputum Crossover Treatment First Dose Tx2	Self administer Treatment 2 for 6 days	Final Dose Tx2 Blood pressure FeNO (pre AC) Spirometry Allergen Challenge FeNO (5 hrs post AC) Sputum (5 hrs post AC)
Approx. time 2.5 hours		Approx.. time 6 hours		Approx. time 2 hours		Approx. time 6 hours

FeNO = fractional exhaled nitric oxide**;** MCT=methacholine challenge; SPT = skin prick test; STE = skin test endpoint; AC = allergen challenge

Study Assessments

Fractional Exhaled Nitric Oxide

The level of nitric oxide in your exhaled breath is an indicator of airway inflammation. The test requires you to inhale and exhale fully into a handheld device via a filter mouthpiece. The handheld device is connected to a small machine that measures the amount of nitric oxide in your exhaled breath and displays the value on the screen of the machine. At least two tests will be performed each time FeNO is measured. FeNO will be measured at all visits, twice on allergen challenge visits.

Spirometry

Spirometry is a necessary component of bronchoprovocation testing. Spirometry will be performed according to current industry standards and used to assess your resting lung function for determining eligibility criteria and for monitoring the magnitude of airway narrowing induced during allergen and methacholine challenges. To perform spirometry, you will be required to breathe through a mouthpiece with your nose clipped. You will inhale as much air as you can and then exhale forcefully until your lungs are empty. The spirometer is connected to a computer and the computer software generates various lung function parameters. The parameters we are interested in are the forced expiratory volume during the first second of exhalation (FEV_1) and the forced vital capacity (FVC). More simply put, FEV_1 is the amount of air you are able to forcefully exhale in one second and the FVC is the total amount of air you are able to forcefully exhale after fully inhaling. Spirometry is performed at all visits, multiple times.

Skin Prick Testing

Skin prick testing will be used to determine what allergies you have and identify the allergen to be used in the allergen challenge. Drops of allergen extracts (including a positive and a negative control) will be placed on your forearm and introduced through the skin by pricking with a lancet. After 10-15 minutes, the skin reaction will then be evaluated based on size. The allergen chosen for your allergen challenges will depend on the largest skin reaction produced through skin prick testing as well as on your clinical history regarding exposure to that particular allergen. Skin prick testing will be performed once at Visit 1.

Skin Test Endpoint (STE) Titration

The STE Titration test is similar to skin prick testing but instead of applying several different allergen extracts, duplicate drops of increasing concentrations of the specific allergen chosen from the skin prick test will be applied to the forearm, pricked with a lancet, and assessed to determine the concentration that produces a particular sized skin reaction (i.e. reaction resembling a mosquito bite that is less than 2mm in diameter). Skin test endpoint testing is performed once at Visit 1.

Methacholine Challenge Testing (MCT)

MCT will be performed with the Aerogen Solo® vibrating mesh nebulizer per an established standardized procedure known as the volumetric method. Baseline spirometry will first be performed to obtain at least two reproducible measurements of your resting FEV_1. Next, you will wear nose clips and inhale aerosolized saline through a mouthpiece while breathing normally until the nebulizer is empty

(approximately 1.5-2.5 minutes). FEV_1 measurements will be recorded at 30 and 90 seconds post-inhalation, and the next inhalation will begin five minutes after the start of the previous inhalation. Each subsequent inhalation will entail doubling doses of methacholine, a compound that may cause your airways to narrow (i.e. make it harder to breathe). The procedure will continue until your FEV_1 has dropped at least 17% from the value obtained after inhaling saline. You will be required to undergo two methacholine challenge tests, one at Visit 1 and one at Visit 3.

Allergen Challenge Testing

The early asthmatic response (EAR) allergen challenge will be performed per standard method. Following baseline spirometry, you will inhale doubling doses of allergen like was done with methacholine. Two FEV_1 measurements, one minute apart, will be recorded ten minutes after you finish inhaling each dose. Twelve minutes will elapse between the start of one inhalation to the start of the next inhalation. The allergen challenge ends when your FEV_1 drops at least 20% from the highest measurement obtained during baseline spirometry. You will be required to remain in the lab for the next 5 hours and perform FEV_1 measurements at various time points. FeNO will be measured again at 5 hours post allergen inhalation just prior to the final spirometry measurement. You will then self-administer 200mcg salbutamol and undergo a ten minute wait period before the process of sputum induction commences. Following sputum induction, you will self-administer an additional 200mcg salbutamol and 500mcg fluticasone propionate (or equivalent). A final spirometry measurement will be obtained to ensure lung function has returned to a safe level prior to leaving the lab. You will undergo two allergen challenges, one at Visit 2 and one at Visit 4.

Sputum Induction

Airway secretions (i.e. mucous or sputum) collected from your lungs are valuable samples for use in assessing airway inflammation. To help you produce sputum, you will be asked to inhale 3 different concentrations (3%, 5% and 7%) of "salty" water known as hypertonic saline, each for 7 minutes. Inhaling hypertonic saline creates an environment in your airways that draws sputum from your lungs into the airways where it can be expectorated (i.e. coughed, hacked, huffed up). After each inhalation you will be asked to blow your nose and rinse your mouth with water before trying to produce a sample. After each inhalation you will also perform an FEV_1 measurement to ensure your lung function is stable. You will undergo the process of sputum induction once at each visit.

Optional Sub-study

Sputum samples will be used to produce a layer of cells from your airway on microscope slides. These slides are then used to count the number of inflammatory cells on the slides which provides information about airway inflammation (i.e. the type of cells in the airway) and how the inflammation changes with exposure to allergen and following treatment with tiotropium. These data are required for the current study.

Sputum samples can also be used to look at mediators or biomarkers involved in different cellular processes or pathways that are activated by allergen exposure or inhibited by treatment. Although this is not the purpose of the current study, we would like to store part of your sputum sample for future research on mechanisms of airway inflammation specific to allergic asthma and how tiotropium may affect these events. Your samples will not contain identifiable information. Your samples will be stored in a freezer in the Asthma Research Lab for a period not exceeding 15 years. Your samples will not be shared. Any

future research conducted on your samples will be reviewed and approved by the University of Saskatchewan Biomedical Research Ethics Board but your consent will not be sought.

If you change your mind about allowing your samples to be stored, contact the Investigators and let them know you would like your samples destroyed. Your samples will be removed from the freezer and destroyed. Any data already collected from the use of your samples will be retained, however no additional future research will be performed.

You will be able to indicate your willingness (or not) to store your sputum samples for future use by indicating yes or no on the signature page of this document.

Potential Risks and Discomforts:

Fractional exhaled nitric oxide

There are no known risks associated with FeNO testing in individuals with mild allergic asthma.

Spirometry

There are no known risks associated with performing spirometry in individuals with mild allergic asthma.

Skin prick testing and skin titration endpoint testing

Skin prick testing and skin titration endpoint testing may cause itching and swelling where the allergens were administered. This usually subsides quickly. If symptoms persist, an antihistamine, topical corticosteroid cream, and/or an ice pack may be used to treat the reaction. Severe reactions from skin prick testing are very rare but may cause anaphylaxis which can be fatal. Such severe reactions typically occur shortly after testing during which time study staff will be monitoring you and ready to treat such a reaction immediately.

Methacholine Challenge Testing

Adverse reactions associated with inhaling methacholine may include headache, throat irritation, light-headedness and itching. Additionally, chest tightness, cough or wheezing may occur. Adverse reactions are generally mild and quickly resolve without the use of treatment. Lung function is monitored throughout the test and bronchodilator (salbutamol/Ventolin®) is immediately available if necessary. Severe adverse reactions are extremely rare.

Allergen Challenge Testing

Allergen inhalation challenges are relatively safe when performed in centers with highly experienced personnel and with proper oversight. Allergen challenge testing may cause coughing, chest tightness, wheezing, and difficulty breathing. The testing method is designed to minimize the risk of causing a severe reaction but there is a risk of severe airway narrowing (i.e. anaphylaxis) developing. If such a situation occurs, you will be treated immediately. Symptoms induced by the allergen challenge usually resolve over time without treatment or may be reversed by use of a bronchodilator (e.g. Ventolin®) and/or inhaled corticosteroid (e.g. Pulmicort®). Both of these treatments will be provided to you prior to leaving the lab.

The use of allergen extracts for inhalation purposes is not approved by Health Canada, however, Health Canada has authorized the use of allergen extracts for inhalation purposes in this research study.

Sputum Induction

Inhalation of hypertonic saline may cause bronchoconstriction but this is not anticipated in individuals with mild allergic asthma. As a precaution, salbutamol (Ventolin®) is administered prior to undergoing sputum induction. In the event that severe bronchoconstriction occurs during the process of sputum induction, you will be treated with salbutamol (Ventolin®). In addition, FEV_1 monitoring is performed during the process to monitor and detect any bronchoconstriction.

Tiotropium treatment

In the proposed study population (i.e. mild allergic asthma) adverse events associated with taking tiotropium are not anticipated. In theory, based on how the drug works, dry mouth may develop. The product monograph for tiotroium indicates adverse events occurred in 1.4-3.3% of individuals following use of tiotropium. Events included oral thrush (infection at back of mouth), dry mouth, gastroesophageal reflux, sinusitis (inflamed sinuses), cough, dysphonia (difficulty speaking) and rash. Less common events (occurring in <1%) were also observed and include: atrial fibrillation (abnormal heart beat), supraventricular tachycardia (increased heart rate), blurred vision, gingivitis (swelling of gums), joint swelling, dizziness, epistaxis (nose bleed), laryngitis and dry skin. These studies were conducted in individuals with severe asthma who were using additional medications such as inhaled corticosteroids and long acting beta agonists. Use of these types of medications are associated with some of the reported adverse events (e.g. oral thrush) In addition, these individuals were treated with tiotropium for a much longer duration (12 weeks to one year).

Placebo treatment

There are no anticipated adverse events associated with receiving placebo treatment.

Responsibilities of the Participant:

As a study participant, you will be expected to:

a. Follow the directions of the study staff
b. Report all medications (prescribed, over-the-counter, herbal etc.) currently being used
c. Report any changes in your health or medications used during the study

The study investigator may remove you from the study early for non-compliance with the above responsibilities.

Your health and wellbeing are most important and so, if faced with a situation where you must use a medication that will (or may) interfere with the study, we ask that you take the medication and contact us to reschedule your appointment.

Benefits of Participating in this study:

If you choose to participate in this study, there will be no direct benefit to you. This study will provide information on whether or not tiotropium is useful for treating allergic asthma.

Voluntary Withdrawal:

Participation in this study is entirely voluntary and you have the right to withdraw from the study at any time without providing a reason. The decision to withdraw will not affect your future health care, employment or academic standing. Data collected from you before your withdrawal may still be analyzed. You will be promptly notified if any new information regarding any aspect of this study becomes available that may affect your willingness to continue your participation.

Study-Related Injury:

In the unlikely event of a medical emergency seek immediate medical attention and notify study staff as soon as possible. Necessary medical treatment will be made available to you at no cost. By signing this document, you do not waive any of your legal rights against the investigators or anyone else.

Honorarium:

If you choose to participate in this study, you will not be charged for the study drugs or any research-related procedures. You will not be paid for your participation; however, you will be provided with an honorarium in the amount of $600 in order to cover your time and out-of-pocket expenses. In the event all study visits are not completed, the honorarium will be prorated based on the study procedures/visits you were able to complete. The University of Saskatchewan will require your social insurance number (asked for on the signature page of this form) to provide the honorarium and a T4A will be sent to you at the appropriate time.

Confidentiality:

In Saskatchewan, the Health Information Protection Act (HIPA) defines how the privacy of your personal health information must be maintained so that your privacy will be respected. Your name will not be attached to any information or mentioned in any study report or made available to anyone except the study staff and personnel of the University of Saskatchewan responsible for issuing the honorarium. Study records will identify you by a study code such as TIOAC01. All study related information will be stored in a locked room (e.g. asthma lab or investigator office) but no guarantee of complete confidentiality can be made. For quality assurance and/or monitoring reasons, the University of Saskatchewan Biomedical Research Ethics Board and/or Health Canada representatives have the right to inspect research records in the presence of the principal investigator or designate and some records may contain identifying information. It is the intention of the Investigators to publish results of this research in scientific journals and to present the findings at related conferences, but your identity will not be revealed. Per Health Canada guidelines, your records will be stored for a period not less than 25 years. After storage, your records will be shredded in a confidential manner.

Public Registry Listing and Study Results:

A description of this clinical trial will be posted on http://www.clinicaltrials.gov, as required by Health Canada. This website will not include information that can identify you. You can search this website at any time.

Study results and your individual results will be available to you once all study data collection is complete. If you are interested in receiving a copy of the results, please check the appropriate box(es) on the last page of this document.

Questions or Concerns Regarding the Study:

If you have any questions or concerns or would like additional information about this study before or during participation, you may contact Dr. Davis at 306-844-1444 or Dr. Cockcroft at 306-844-1446.

If you have any concerns about your rights as a research participant and/or your experiences while participating in this study, contact the Chair of the University of Saskatchewan Research Ethics Board at 306-966-2975 (or 1-888-966-2975 for out of town calls). The Research Ethics Board is a group of individuals (scientists, physicians, ethicists, lawyers and members of the community) that provide an independent review of human research studies. This study has been reviewed and approved on ethical grounds by the University of Saskatchewan Research Ethics Board.

Consent:

Study title: Tiotropium efficacy against allergen induced early asthmatic responses.

- I have read the information in this consent form.
- I understand the purpose, procedure and possible risks of the study.
- I was given sufficient time to think about it.
- I have had the opportunity to ask questions and have received satisfactory answers.
- I am free to withdraw from this study at any time for any reason and the decision to stop taking part will not affect my future medical care, employment or academic status.
- I agree to follow the instructions of the study staff and will immediately tell the study staff if I feel I have had any unexpected or unusual symptoms.
- I give permission for the use and disclosure of my de-identified personal health information collected for the research purposes described in this form.
- I understand that by signing this document, I do not waive any of my legal rights.
- I will be given a signed and dated copy of this consent form.

I consent to the storage of my sputum sample for future research on airway inflammation and how tiotropium alters airway inflammation specific to allergic asthma. □ YES or □ NO

I am interested in receiving a summary of group study results: □ YES or □ NO

I am interested in receiving my own study results: □ YES or □ NO

I agree to participate in this study:

Printed Name of Participant	Date
Signature of Participant	SIN #
Printed Name of Person Obtaining Consent	Date
Signature of Person Obtaining Consent	