CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Steroids in Eosinophil Negative Asthma (SIENA)
Study Investigator: Christine A Sorkness, PharmD, 608-263-2285
Co-Investigator: Robert F Lemanske, Jr., MD, 608-263-6184
Study Coordinators email address: AsthmaNet@medicine.wisc.edu

In this consent form, “you” always refers to the participant. If you are a legally authorized representative of a minor (such as the parent), please remember that “you” refers to the child.

INVITATION
You are invited to take part in this research study because you are at least 12 years old and are healthy other than having asthma. A study coordinator will talk with you about other entry requirements. Participation in this research study is voluntary. If you decide not to participate, any relationship you have with the study site and its doctors (including your health care providers) will not be affected in any way.

As many as 1,152 people may need to be screened so that about 384 people will participate across the nation. Up to 45 people can be enrolled at the University of Wisconsin-Madison.

WHAT IS THE PURPOSE OF THIS STUDY?
Most people with asthma have inflammation in their airway. Asthma controller medications, like inhaled corticosteroids, are meant to reduce this inflammation. Reducing airway inflammation should make one’s breathing easier. However, many people with asthma don’t breathe easier when they take an inhaled corticosteroid.

We know that there are many cells that can cause airway inflammation. However, inhaled corticosteroids mostly target only one cell called the eosinophil.

The purpose of this study is to find out if people should take an asthma controller medication based on the type of inflammatory cells present in their airway.

WHO IS FUNDING THIS STUDY?
The study is funded by the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI). UW-Madison is one of the research centers. The network’s purpose is to develop and carry out research on asthma and the best treatments for it.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?
AsthmaNet Registration. Before you enroll in an AsthmaNet study, you must first be entered into the AsthmaNet Registry. This Registry has been set up to collect basic background information that will probably not change over time. This information is limited to: your initials, date of birth, gender, and race/ethnic identification. Your Registry information will be coded with a unique AsthmaNet identification number. Only study staff at UW-Madison will have access to the key that links this number to your name. No information that directly identifies you will be entered into the AsthmaNet database or sent to the Data Coordinating Center (Penn State University, Hershey, PA). Registry data help us track your participation in multiple AsthmaNet studies over time. Knowing that you were in more than one study is useful when we look at study results.
Your agreement to provide the information for the AsthmaNet Registry is voluntary. However, if you choose not to provide it, you cannot be screened for or enrolled in any AsthmaNet study. Once you consent to be entered into the Registry, your information cannot be removed and will be maintained in the study database into the future. You will only be asked to supply Registry information one time during your participation in AsthmaNet studies. Registration happens before or during your first study visit.

**Stopping asthma controller medication (Supervised Inhaled Corticosteroid (ICS) Washout).** This study will enroll participants who have not taken asthma controller medications in the prior 6 weeks. If you would like to join the study and currently take asthma controller medications and your asthma is well-controlled, study staff could supervise your medication washout with 3 study visits over 9 weeks. Your medication will be cut in half at week zero and stopped completely at week 3. You will have an action plan to follow if your asthma worsens. You will come in at week 9 to enter the study run-in.

We strongly recommend that you discuss any medication change with your health care provider.

**Study run-in.** The study run-in is 3 visits and two phone contacts over 4-6 weeks. Run-in visits take from 2 to 3 hours. You will be asked to give a sputum sample 2-3 times during the run-in to find out what inflammatory cells are present in your airway. You must have two good-quality sputum samples to continue in the study. A blood sample will be taken for each sputum sample you give. We will also look at your level of asthma control during this run-in period to make sure that your asthma is not too severe. In addition, you must either respond to the albuterol reversibility test or methacholine challenge to continue in the study. These procedures and tests are explained below.

**Main Study.** If you are eligible to continue in the study, you will have 6 study visits and 6 phone contacts over 36 weeks. Study visits take 1 to 3 hours. The phone contacts usually take less than 10 minutes to complete. If your asthma worsens during the study, you may be asked to come in for one or more extra safety visits and will receive additional phone contacts.

The following procedures will take place during the study. Please refer to the table on the last page to see which procedures take place at each visit.

**Spirometry:** You will wear a nose clip, take in a full inspiration and breathe hard into a machine called a spirometer. The machine measures how fast and how much air moves out of your lungs. You will be asked to blow into the spirometer several times. This test tells us how well your lungs are working and will be done at each visit.

**Sputum induction:** You will receive 4 puffs of albuterol to open your airways. You will be asked to breathe in a salty mist for up to 12 minutes. Every two minutes you will be asked to cough deeply and vigorously in order to bring up a sample of sputum (mucus from your airway). This screening procedure tells us which inflammatory cells are in your airway.

**Albuterol reversibility:** This test measures improvement in your breathing. You will perform spirometry, inhale 4 puffs of albuterol, and repeat spirometry 15 minutes later. If you show at least 12% improvement in spirometry, a methacholine challenge test will not take place.

**Methacholine challenge testing:** Methacholine is a drug that can cause narrowing of the airways. You will be asked to breathe in gradually increasing doses of methacholine. Spirometry
will be performed after each dose. The test will stop once your airways narrow by 20% or you have been given the last dose. You may have asthma symptoms during this test. You will receive albuterol to make these symptoms go away. This screening test will ONLY be done if you did not show improvement in spirometry during the albuterol reversibility test.

**Ipratropium reversibility:** You will perform spirometry, take 4 puffs of ipratropium (Atrovent® HFA) and repeat spirometry 30 minutes later. Ipratropium is an anticholinergic bronchodilator that is FDA approved for the treatment of chronic bronchitis, emphysema and chronic obstructive pulmonary disease (COPD). Although ipratropium is not FDA-approved for use in asthma or in children, it is widely used for asthma, and an NIH Task Force and US and International guidelines all recommend ipratropium in this dose for characterization of asthma. This is another test to measure improvement in spirometry but showing improvement with this test is not a screening requirement.

**Exhaled nitric oxide collection:** You will be asked to slowly blow into a mouthpiece attached to a machine that measures nitric oxide. The amount of nitric oxide in your breath may increase when the lungs are irritated or inflamed.

**Urine pregnancy testing:** If you are a female and can become pregnant you will have a urine pregnancy test up to 3 times during the study. You will know the pregnancy test results within minutes. You cannot join or continue in the study if the pregnancy test is positive. If you are able to get pregnant (that is, you are female who has begun menstruating and are not surgically sterile or post-menopausal), you must use birth control during the entire study. Acceptable birth control methods include: abstinence, birth control pills, diaphragm, intra-uterine device (IUD, IUS), Depo-Provera, NuvaRing, birth control patches, single or double barrier methods (condom plus foam/jelly) or surgical sterility.

If you are sexually active, there is a risk that pregnancy could still occur despite using birth control. You should notify the study doctor or staff as soon as possible of any birth control failure or if you become pregnant. If you become pregnant while in the study, the doctor may want to follow-up with you until the outcome of the pregnancy is known. The doctor may send information about the pregnancy to the drug manufacturer.

**Pregnancy testing in minors.** Urine pregnancy testing will be performed on every female who has begun menstruation (that is, has had at least one period). The first pregnancy test is done to find out if the participant is eligible for the study. If this first pregnancy test is positive, the results will only be reported to the minor, and she will not be able to join the study. Results from all other pregnancy tests done during the study may be reported to both the minor and her parents/guardian.

**Blood drawing (venipuncture):** You will have a needle stick to provide about 2 teaspoons (about one half ounce) of blood at each screening visit (2-3 times). Blood tests include periostin and complete blood count (eosinophils). Both of these tests are related to inflammation. If you provide 2 good-quality sputum samples, you will give blood twice. If you need to give a third sputum sample, you will be asked to give a third blood sample. The first sample you give will also include markers of allergy.

There is an optional blood collection for genetic testing purposes. Additional blood may be collected if you agree to the optional genetic testing. Please refer to the separate section on genetic testing below.
**Medical history:** You will be asked about your current and past health. You will also be asked about prescription and over-the-counter medications, vitamins and nutritional/herbal supplements that you use.

You may be asked to stop taking some medications while you are in the study. You should discuss medication changes with your primary care provider first. Stopping medications might involve some risk(s) or side effect(s) to you.

**Physical examination:** Whether the physical examination is just a blood pressure and listening to your lungs and heart or more will depend on the study visit. A thorough examination will be done at the first visit to make sure that it is safe for you to participate and at the last visit. This may include listening to your lungs and heart, looking into your ears, nose and throat, and measuring your height, weight, blood pressure and heart rate. At certain visits we will also measure the size of your waist, neck, and hips. If you are under 21 years of age, you will have your height measured at all visits.

**Questionnaires:** You will be asked to complete many types of questionnaires. Most will tell us how you feel about your asthma, your asthma medications, and how asthma affects your life. You will also be asked about your nasal symptoms, home environment and socioeconomic status (household income, number of people supported by the household income, and educational level). Lastly, when you leave the study you will be asked to complete an optional anonymous questionnaire that measures your level of satisfaction with being in the study.

**Peak flows/e-diary entries and medication use:** You will use a small electronic device (tool) for peak flow measurements and to record your asthma symptoms at home twice every day. It is called a Spirotel®. Study staff will teach you how to use the Spirotel®.

Study staff will also review your peak flows and symptom scores collected with your electronic Spirotel®. The purpose is to check on your asthma symptoms and asthma control since your last visit. The coordinator will also check your medication use. These steps are to ensure that you are doing as asked with the at-home study procedures. These are described in detail below.

**Telephone contact:** A study coordinator will call you to check on your asthma symptoms, asthma control, general health and medication usage between visits.

**Study Medications.**

**During the run-in,** you will be asked to take an inhaler, two puffs each morning. This inhaler is either a long-acting muscarinic antagonist or a placebo.

If you pass the run-in (gave good sputum samples, took run-in inhaler as asked), you will be given two inhalers. One inhaler is either an inhaled corticosteroid or placebo. The other inhaler is either a long-acting muscarinic antagonist or placebo. Inhalers are described in detail below.

**Mometasone (Asmanex®):** The inhaled corticosteroid is mometasone, 110 mcg per puff. Mometasone is approved by the FDA for the treatment of asthma. It has been prescribed to millions of people. It can be given to children as young as 4 years of age. You will be asked to take 2 puffs every morning and evening.

**Tiotropium:** The long-acting muscarinic antagonist (LMA) medication is tiotropium Respimat®, 2.5 mcg per puff. You will be asked to take 2 puffs (total daily dose = 5 mcg) once a day. Tiotropium is from a class of drugs that relieve and prevent airway constriction. Tiotropium
Respimat® is not currently approved for use in the US. It is, however, approved in many other countries for treatment of chronic obstructive pulmonary disease (COPD). A different form of tiotropium is approved in the US for the treatment of COPD.

The study drug, tiotropium, is delivered by the Respimat® in the form of an inhalation solution. Tiotropium Respimat® is an investigational bronchodilator drug (one which helps to open airways as described above). The same active ingredient, tiotropium, is available in a dry powder inhalation form marketed as Spiriva® HandiHaler®. Spiriva® HandiHaler® is approved by the US FDA and many other countries for the treatment of COPD (emphysema and bronchitis). The safety and effectiveness of Spiriva® HandiHaler® in children have not been established. The Respimat® is a different type of inhaler than the HandiHaler®.

Placebo inhalers: The placebo inhalers will look like the mometasone and tiotropium described above, but will not contain active medication. They will have similar ingredients but no mometasone and no tiotropium in the respective placebo inhalers.

Study treatments: You will have 12 weeks on each of the three possible study treatments. The order of these treatments will be decided randomly, like flipping a coin. You and the study staff will not know which treatment you are getting. The treatments include:

- active mometasone plus placebo tiotropium
- placebo mometasone plus active tiotropium
- placebo mometasone plus placebo tiotropium

Rescue medication: An FDA-approved short-acting ‘rescue’ bronchodilator medication called albuterol will be given to you. It will help open your airways and reduce asthma symptoms. You can use it as needed during the study to treat asthma symptoms. You will be given an action plan that explains the proper use of this medication.

Prednisone ‘Rescue’ Pills (for emergency use only): You will be given a supply of prednisone to keep at home. This prednisone can only be used if you are having a bad asthma attack AND study staff or a treating physician tells you to begin taking it. You will be given a home rescue plan that helps you know if you should call for prednisone instructions.

High-dose inhaled corticosteroid ‘Rescue’ (for emergency use only): If your asthma worsens during the study, study doctors might decide to give you a high-dose of mometasone (220 mcg per puff). You might be asked to take 2 puffs twice a day for 10 days. If you need high-dose mometasone “rescue” treatment twice during the run-in, for your safety, you will be asked to leave the study.

Home procedures
Completing all of the home procedures should take about 10 minutes a day. Try to do the procedures about the same time each day. It is VERY important that you ask questions about how to measure your peak flow, how to use your electronic diary, and how to take the study drugs. Please ask questions until these procedures are CLEAR to you. If you don’t do the home procedures, you might be asked to leave the study. Please bring ALL study supplies and inhalers with you to ALL study visits, including empty inhalers and your Spirotel®.

Peak flow monitoring: You will be asked to check your peak flow in the morning and evening every day of the study. This involves taking in a full breath and blowing hard and fast into an electronic peak flow meter. The electronic peak flow meter is combined with an e-diary.
(electronic diary) in the Spirotel® device. Peak flow and e-diary data will be stored in the device until your next study visit when it will be transferred to a study database and reviewed with you. The study will give you a Spirotel® device to use, but it must be returned at your last visit.

**E-diary:** Before you use the Spirotel® device to take your peak flow in the morning and in the evening, it will ask you a series of questions about your asthma symptoms and rescue medication use. You will be expected to answer these questions twice a day, and to bring the Spirotel® to study visits.

**Study drug (mometasone/placebo):** You will be asked to take 2 puffs each morning and 2 puffs each evening.

**Study drug (tiotropium/placebo):** You will be asked to take 2 puffs each morning.

**WHERE WILL THE STUDY VISITS TAKE PLACE?**
All study visits and procedures will take place at the University of Wisconsin-Madison.

**CAN I STOP BEING IN THE STUDY?**
Yes, you can decide to stop at any time. It is important to tell the study doctor if you are thinking about stopping so that your doctor can evaluate any risks from stopping your study medications. They may wish to discuss alternative follow-up care and testing.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped by the sponsor.

**WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?**
Everyone taking part in the study will be watched carefully for any side effects. Side effects may be mild or very serious. You should talk to your study doctor about any side effects you experience while taking part in this study. Please call immediately if you experience severe side effects or if you need medical advice (Dr. Lemanske at 608-263-6184).

The medications and procedures involved in this study may have risks that are not possible to predict. Below is a list of the risks we know about for each medication and procedure. If you have any of these problems, you should tell the investigator or study staff.

**Study procedure risks:**
**Spirometry:** Breathing fast and hard into a spirometer or peak flow meter can cause coughing, lightheadedness, or chest tightness. This should go away shortly after the test is done.

**Sputum Induction:** Breathing in salty mist may cause an unpleasant salty taste. Coughing hard to produce sputum can cause a sore throat or bother your asthma. The 12-minute test will be stopped sooner if your lung function gets worse.

**Albuterol reversibility:** Taking the 4 puffs of albuterol required for this test can make your heart race or make you feel jittery. It can also cause an increase in blood pressure, nausea or headache. These symptoms usually go away in less than an hour.

**Methacholine challenge testing:** This test could cause coughing, chest tightness, shortness of breath and wheezing. You will receive albuterol at the end of this test to reverse any symptoms. In the unlikely event that your symptoms are severe, albuterol will be given and the challenge will be stopped. A study doctor will be available to treat you immediately, if this occurs.
**Ipratropium reversibility:** Taking the 4 puffs of ipratropium (Atrovent® HFA) required for this test can cause headache, dry mouth, nausea, bronchitis, and shortness of breath. These side effects were reported in patients with COPD who took ipratropium for 12-weeks. Since you will only take ipratropium once, the likelihood of these side effects is much less. The safety of ipratropium in children is not known.

**Pregnancy Test:** There are no risks associated with pregnancy test. There may be unknown risks to the fetus/unborn child if you become pregnant while in this study. Although birth control is required, you should notify your study doctor or study personnel immediately if you become pregnant during the study. You must stop the study if you become pregnant.

It might make parents/legal guardians uncomfortable that the first pregnancy test results will only be reported to the study participant, even if the test is positive.

**Blood drawing:** Drawing blood may cause pain, bleeding or bruising. In a few people it may cause lightheadedness and fainting or rarely, result in an infection at the insertion site. EMLA cream may be put on the skin before the blood draw to reduce the pain of the needle stick. Side effects from this cream (mainly skin rash) are rare, but may occur.

**Questionnaires:** The questionnaires are not tests. There are no right or wrong answers. Any questions that are uncomfortable to answer may be skipped.

**Non-physical risks:** There is risk of loss of confidentiality through unintentional disclosure of protected health information. This risk is very minimal.

**Risks related to study medication:** There is a chance that you could be allergic to any of the medications given in this study. If your breathing suddenly worsens, your face, throat, lips or tongue swells, you get hives, itching or rash, stop taking the study medication and seek immediate medical help.

**Changing asthma medication.** If you participated in the Supervised Inhaled Corticosteroid Washout before the run-in, you will have stopped taking an asthma treatment to join this study. It is possible that this could worsen your asthma. If your asthma does begin to get worse, you will have a home rescue plan and rescue medications to use.

**Mometasone (Asmanex®, 110 mcg/puff, 2 puffs, twice a day):** The most common side effects from inhaled corticosteroids are throat irritation, hoarseness and infection of the mouth or throat. To avoid these side effects, you will be asked to rinse your mouth with water and spit the water out each time you use the inhaler. Some people get a headache from taking mometasone. High doses of mometasone taken for a long period of time may also cause thinning of the skin and changes to your immune system, bones or eyes. These side effects are not expected because you will only be taking a medium dose for a short time.

People with severe milk allergies have a very rare risk of going into shock. Please let the study coordinator know if you are allergic to milk.

A concern for young children taking mometasone is the possibility of slowed growth. Catch-up growth after stopping mometasone has not been fully studied. The height of young people (12-21 years old) in the study will be carefully measured at each study visit.
Tiotropium Respimat® (2.5 mcg/puff, two puffs each morning): While tiotropium Respimat® has not yet been approved for use in the US, it has been tested in 3282 patients with COPD and 1634 adults and teens with asthma. The most common side effects are stuffy nose, sore throat, cough, dry mouth, sinusitis and bronchitis. Tiotropium should not be taken by people with narrow angle glaucoma (high pressure in the eyes), prostatic hypertrophy (enlarged prostate), bladder-neck obstruction (difficulty in urination), or renal insufficiency (kidney disease).

A few reports suggested that tiotropium Respimat® might increase the risk of stroke, heart attack, and death in patients with COPD when compared with the FDA-approved tiotropium HandiHaler®. To clarify this question and to exclude a relation between treatment with tiotropium Respimat® and an increased rate of deaths, a large long-term study of 17,135 patients with COPD was conducted. Analysis of the data from the trial concluded that tiotropium Respimat® had a safety profile similar to tiotropium HandiHaler® in patients with COPD, and was not associated with an increased risk of death.

Placebo: Placebo is an inactive medication that is unlikely to cause any side effects. Both inhalers will be placebo for one of the treatment options. That means that you will not receive active (study) treatment for twelve weeks. It is possible that your asthma will get worse when you are taking only placebo. You will have albuterol to use as needed and will have an action plan to follow.

Prednisone: You will only take this medication in an emergency if your asthma worsens. The most common side effect is heartburn. The risk is less if the medication is taken with food. Other side effects include increased appetite (munchies), nervousness, restlessness, or trouble sleeping. More side effects are reported with high doses and long term use. We don’t expect you to have those side effects because you will not take a high dose and will only take the medication for a short time (5 days), if at all.

A very uncommon side effect has been reported with prednisone in which the hip bone weakens. While this effect tends to be related to longer prednisone use, it has been reported after short courses. The occurrence of this side effect with short term use is very rare.

High-dose rescue mometasone (Asmanex®, 220 mcg/puff, 2 puffs, twice a day): You will only take this medication if your asthma worsens. Similar to the lower dose mometasone used as a study medication, the most common side effects from high dose mometasone are change in voice, headache and infection of the mouth or throat (thrush).

Bronchodilator: Albuterol might cause tremors, nervousness, dizziness, difficulty sleeping, headache, rapid or irregular heartbeats, drying and irritation of your mouth, sore throat, upset stomach, and coughing. If such symptoms occur, they usually go away within a short time and do not require treatment.

Ipratropium (Atrovent® HFA): This drug is only used once in this study for reversibility testing. Possible risks are already listed under ipratropium reversibility testing, above.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
There is no guarantee of direct benefit to you from participating in this study. However, there is a potential benefit of reduced asthma symptoms while taking study medication. This study may help doctors learn more about the treatment of patients with asthma.
ARE THERE ALTERNATIVES TO JOINING THIS STUDY?
Taking part in this research study is voluntary. You may choose to:

- Not join the study and not take any asthma treatment
- Get asthma treatment from your health care provider without being in a study
- Join a different research study

Please talk to your doctor about your choices before deciding if you will take part in this study.

HOW WILL MY PRIVACY BE PROTECTED?
We will do our best to make sure that the personal information is kept confidential. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Your records regarding this study may be subject to review by the FDA. Please see the Research Authorization form for details about who will be able to review your study records.

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. Data collected from you during the study will be coded with a unique study identification number. Only the UW-Madison research team has access to the link connecting information like your name and address to the study identification number. This link is kept in a secure area within a locked room. Computers that store coded information are password protected, encrypted and kept in locked rooms. A UW Hospital medical record will be created because of your participation in this study. Your consent form and some of your research test results may be included in your UW Hospital medical record. Therefore, your other doctors may become aware of your participation in this study. Hospital regulations require that all health care providers treat information in medical records confidentially.

To further protect your privacy, AsthmaNet has applied for a Certificate of Confidentiality from the FDA. With this Certificate the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally-funded projects or for information that must be disclosed in order to meet the requirements of the FDA.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project in cases of suspected child abuse or intent to hurt self or others.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
You will not be charged for any of the study activities or medications.
WILL I BE PAID FOR TAKING PART IN THIS STUDY?
It is important to know that payment for participation in a study is taxable income. Participants of the Supervised Inhaled Corticosteroid Washout will be paid up to $140. You (the minor) can be paid up to $995 for completing the entire study. You (the minor) might get paid less if you forget to bring your peak flow meter and/or study medications to a visit. If your asthma worsens during the study, and you have extra safety visits--you will be paid for those visits too. You will only be reimbursed for the visits you have completed (see tables, below).

Payment schedule for Supervised ICS Washout

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Payment schedule for Study:

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WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
In the event that you are physically injured as a result of participating in this research, emergency care will be available. You will be responsible for the charges for the emergency care. There is no commitment to provide any compensation for research-related injury. You should realize that you have not released this institution from liability for negligence. Please contact the study investigator Dr. Sorkness at 608-263-2285 if you are injured or for more information.

IF I JOIN THE STUDY, CAN I CHANGE MY MIND?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

If you choose to leave the study, please talk with your study doctor. He or she can help you stop in the safest way possible. We will ask you to come in for an early final visit. We may perform procedures such as questionnaires and spirometry at your final visit. We will also collect all study supplies, including the Spirotel® peak flow meter.
WILL I BE TOLD ABOUT NEW INFORMATION?
While you are in this study, we may learn about new information that may affect your willingness to continue to participate. If this happens, we will tell you about this new information in a timely manner and you can choose to continue or stop your participation in the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?
You can talk to your study doctor about any questions, concerns, or complaints you have about this study. You can reach Dr. Sorkness at 608-263-2285.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, contact the UWHC Patient Relations Representative 608-263-8009.

ClinicalTrials.gov is a website that provides information about clinical trials. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

GENETIC BLOOD DRAW AND TESTING SECTION (OPTIONAL)

WHAT IS THE PURPOSE OF GENETIC TESTING?
You are being invited to participate in an optional part of this study which involves giving a blood sample for genetic testing (DNA analysis). Deoxyribonucleic acid (abbreviated DNA) is the genetic material contained in all cells of your body, including blood cells. DNA stores information in the form of a code. It is the material that determines, among other things, your physical characteristics such as your height and the color of your eyes. Genetic testing can be used to find out if you are more likely to develop a particular disease or to determine how you might respond to different medications. Another purpose of genetic testing is to identify genes and/or variations in genes. Genes are parts of DNA that have complete messages for building the proteins that make our bodies work.

For this study we will perform DNA tests for the molecules related to your response to asthma medications such as albuterol, long-acting muscarinic antagonists and inhaled steroids. We will try to find out if your DNA results are associated with your response (or lack of response) to different medications, and whether your results are related to information we collect about you in the study. We will also look for genes and/or variations in genes related to asthma, allergies, and related diseases. Identifying genes and their variations may help develop a new treatment for people with asthma who have certain genes. We will also perform a test for proteins present in the plasma leftover from your blood sample. Other tests on the plasma may be performed at a later time, but they have not yet been defined. Any future tests will need to be approved by the AsthmaNet Steering Committee.

If you do not agree to give a blood sample for genetic testing, you can still participate in this study.

WHAT DOES PARTICIPATION INVOLVE?
If you agree to genetic testing, we will use a needle to collect 30 ml (about 2 tablespoons) of blood from a vein in your arm. DNA will be removed from your blood sample and stored in a lab. Plasma (the liquid part of your blood in which blood cells are suspended) leftover from the DNA removal process also will be stored for future research in the areas of asthma, allergies and related diseases.
HOW WILL MY BLOOD BE HANDLED?
Your blood sample collected for genetic testing will be labeled with a code number, your initials, and blood draw date and transferred to the Tucson Genetics of Asthma Lab in Tucson, Arizona for DNA removal and storage, and storage of the leftover plasma. The Data Coordinating Center in Hershey, Pennsylvania will provide the Tucson lab a new genetics code number (unrelated to the original), along with your gender and birth year (not complete date of birth). The genetics code number will not contain any information about you or your clinical site. After the DNA removal process is complete, the genetics lab will have access only to the new genetics code number, your gender, and your year of birth to identify your samples. The Tucson lab will not store your initials with your samples and will not be able to see your initials in the study database following processing of your sample.

The clinical site where you are seen for study visits will not have access to the genetics code number linked to your samples. Therefore, it would be very difficult for staff at the clinical site or at the Tucson lab to identify the person belonging to any given DNA/plasma sample.

In the future, with the permission of the AsthmaNet Steering Committee, your DNA and/or plasma samples may be transferred to other laboratories for analysis. In each case, only the genetics code number, gender, and birth year will be transferred with your samples.

HOW WILL THE GENETICS INFORMATION BE HANDLED?
The coded results (that do not identify you) of the genetic testing will be sent to our central Data Coordinating Center in Hershey, Pennsylvania. The Hershey site will keep the links among all the code numbers and will be able to join the clinical data from the study, such as results of your breathing tests, with genetics data in order to perform analyses. The Hershey site does not have access to your name, address, social security number or other personal identifying information.

The coded analysis results will only be released to other scientists working on this study. It is almost impossible for the genetics results to be associated with you personally, unless your clinical site gives additional identifying information to the Data Coordinating Center (which it will not do) or unless the Data Coordinating Center gives additional information to your clinical site (which it may do under specific conditions which require approval as outlined in the next paragraph).

In the future, we may want to perform studies where it would be necessary to get in touch with you based on your genetic information. Only your specific clinical site will have enough information to do this, with your approval. Your specific clinical site will only be provided enough information to contact you based on your genetic information if both the AsthmaNet Steering Committee approves and the local clinical site’s Human Subjects’ Protection Board agrees that doing such testing and contacting you are appropriate. If you agree to future contact, you will always be able to opt out of (not participate in) the future study.

WHO WILL SEE THE RESULTS OF THE GENETICS TESTING?
Coded (not identifiable to you) genetic information will be seen by the study investigators at your site and in the AsthmaNet and by other NIH/NHLBI research centers/investigators with whom the AsthmaNet agrees to share such information.

Currently, individual genetic results will not be known and you will not be notified of your results. Therefore, your genetic results will not become part of your medical record. However, the investigators at your center, with the Human Subjects’ Protection Board approval, might carry out a study in which they do genetic analysis specific to you in order to contact you about a study based on your genes related to asthma, allergies or related diseases, or on your response
to medications used to treat those conditions. At that point, if approved by the AsthmaNet Steering Committee and the Human Subjects’ Protection Board, only the investigators at your site would be made aware of any results linked to you and would contact you to find out if you are interested in providing more information or participating in a study. You can tell us whether or not you would like to be contacted for this purpose at the end of this section.

**HOW LONG WILL MY SAMPLES AND INFORMATION (DATA) BE STORED AND USED FOR RESEARCH?**

Your DNA and plasma samples will be stored for as long as they are useful to the AsthmaNet researchers. There is no limit on the length of time your information will be stored for research.

**WILL THE GENETIC SAMPLES HAVE COMMERCIAL VALUE?**

This genetic testing or other follow-up studies may lead to the development of a test that might tell in advance if a person will respond to certain asthma treatments, but you or your heirs will not be able to share in the profits made by the company that sells it.

**WHAT IF I CHANGE MY MIND?**

Your agreement to provide a blood sample for DNA analysis and plasma storage is voluntary. You may refuse to provide a blood sample without any loss of rights or privileges to which you are otherwise entitled. If you do not wish to provide a sample for DNA analysis, you still can participate in this study.

As explained above, it will be very difficult to link your blood sample to you. It will be very challenging to withdraw your sample after it has been sent for genetic analysis, but we will make a good faith effort to ensure that all stored genetic material is destroyed. Please think very carefully about your decision to provide a blood sample for DNA analysis.

If you wish to withdraw your permission for your DNA and/or your plasma to be used for this research study, please contact Drs. Sorkness or Lemanske by calling the phone number on the front page of this consent form.

**RISKS AND DISCOMFORTS RELATED TO GENETIC TESTING:**

**Blood Draw.** If possible, the genetic blood sample will be taken when other blood samples are needed for the study so that you will not have to undergo an extra needle stick. Blood drawing may cause a small amount of pain. In addition, a temporary bruise or "black and blue mark" may develop. Rarely, people faint after blood drawing. Very rarely, the vein in which the needle has been inserted may become inflamed (red and swollen) or infected, but this can be treated.

**Confidentiality/Disclosure.** Information about your participation in a genetics study may influence insurance and/or employers regarding your health status. If a result is accidentally disclosed and you are considered a high insurance risk as a result, this could lead to loss of health insurance, difficulty obtaining insurance, or an increase in premiums. If your employer becomes aware of the result, this could lead to the loss of your job or make it harder to get a new one. To help prevent disclosure, information about your participation and the results of the research will not be placed in your medical records. In addition, your blood sample will be coded and the key to the code kept in a separate locked physical or password-protected electronic file at your clinical site. Once the sample is processed at the genetics lab in Tucson, Arizona, a new unrelated code number will be used and no key linking your identity (name, address, etc.) to the DNA and plasma samples will exist. Not sharing information about your participation in this study with others will lower these risks. Although every effort will be made to keep your participation confidential, the investigators cannot guarantee absolute confidentiality. Even
though we will remove identifying information and do not intend to tell you or anyone else the results of the genetic testing on your sample, there is a very small chance that this information could accidentally become known to you, your doctor, or others.

To further reduce your risks, there is a new Federal law, called the Genetic Information Nondiscrimination Act (GINA). This law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, this law does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Other Risks. There might be other risks associated with genetic testing that we do not know about yet.

As we learn more about asthma-related genetic testing, we may contact you to provide or request more information.

Do you agree to genetic testing and the sharing of your (your child’s) coded genetic samples with AsthmaNet and NIH/NHLBI research centers/investigators for the purposes of identifying genes and/or variations in genes related to asthma, allergies, and related diseases (to be performed only with the agreement of the AsthmaNet Steering Committee)?

(Please initial) YES___________ NO___________

Do you agree to allow your clinical site to identify and get in touch with you in the future based on the results of genetic testing (to be performed only with the agreement of the AsthmaNet Steering Committee and the local Human Subjects’ Protection Board)?

(Please initial) YES___________ NO___________

Your authorization to participate in the genetics blood draw and testing as part of the SIENA study was provided in the previous section through your initials on the appropriate lines for the two stated questions. Below is authorization for the main study, SIENA.

REQUEST FOR PERMISSION TO CONTACT YOU ABOUT FUTURE STUDIES:

1. May we contact you for future studies conducted by the University of Wisconsin or AsthmaNet?
   If yes, we may need to look at your/your child’s Protected Health Information (PHI) to check for study eligibility.

   ___ Yes      ___ No

2. May other University of Wisconsin physicians conducting asthma research contact you?
   If yes, your PHI may be shared with those physicians.

   ___ Yes      ___ No
If you agree to being contacted, the investigators will explain the future studies to you, and you can decide whether to take part. You may still refuse to join those future studies. Also, you can ask us at any time to take your name off of our contact list.

**CONSENT TO PARTICIPATE IN THE SIENA RESEARCH STUDY:**

You have been given copies of this consent form to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIAPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

I have read the information in this consent form and reviewed any questions. I voluntarily agree to participate (or have my child participate) in this study. I have received a copy of this consent form.

PRINT NAME OF PARTICIPANT:

________________________________________

Date Participant's signature (ages 18 and up)

________________________________________

Date Person Obtaining Consent
LEGAL GUARDIAN/PARENT AUTHORIZATION:

We are the parents/legal guardians of the child named below. We have had a chance to discuss this study protocol and to ask questions. Our questions have been answered to our satisfaction. We have received a copy of this consent form.

By signing this form I have not given up any legal rights that my child would otherwise have as a research participant.

Subject Name (please print) Age

Parent/legal guardian Name (please print) Phone number

Parent/legal guardian Signature Date

Parent/legal guardian Name (please print) Phone number

Parent/legal guardian Signature Date

Signature of person obtaining consent Date

ASSENT FOR CHILDREN AGES 15-17:

I have had a chance to discuss this study protocol and to ask questions. My questions have been answered to my satisfaction. I have received a copy of this consent form.

By signing this form I have not given up any legal rights that I would otherwise have as a research participant.

Subject Name (please print)

Subject Signature Date
### Study Procedure Table.

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1. V3 albuterol reversal, V3 sputum induction, V3 blood sampling and V3 exhaled nitric oxide ONLY if needed to obtain two good sputum samples.

2. Methacholine challenge test 1-2 days after visit 1 ONLY if you did not show reversal to albuterol at visit 1. You must either reverse to albuterol or respond to the methacholine challenge to qualify for the study.

3. The genetics blood sample is optional.

4. The waist, hip and neck measurements are only done on participants 18 years or older.