UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: *Steroids in Eosinophil Negative Asthma (SIENA)*

This is a medical research study. Your study doctor(s) Stephen Lazarus, MD and Michael D. Cabana, MD, MPH from the UCSF Departments of Medicine and General Pediatrics or one of their research associates will explain this study to you.

Medical research studies include only people who choose to take part. Take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you are at least 12 years old and are healthy other than having asthma. If you are a parent or legal guardian, you are being asked to read this consent form and consider giving permission for your child to take part in this research. In this consent form, "you" refers to the child.

Why is this study being done?

Most people with asthma have inflammation in their airway. Asthma controller medications, like inhaled corticosteroids, are meant to reduce inflammation in the airway. 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 several types of 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 cells present in their airway. We will examine the response to inhaled corticosteroid, which is the standard treatment, and tiotropium, an inhaled medication that has been FDA-approved for COPD (Chronic Obstructive Pulmonary Disease, a smoking related disease that is similar to asthma) but not for asthma, in participants with different types of airway inflammation. The FDA is aware of this and has provided us permission to use tiotropium in this study.

Who pays for this study?

This study is funded by the National Institutes of Health's National Heart, Lung and Blood Institute (NHLBI) through the "AsthmaNet" network of centers. The Network's purpose is to develop and carry out research on asthma and the best treatments for it. Nine AsthmaNet research centers across the United States are taking part in this study. UCSF is one of them.

How many people will take part in this study?

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 UCSF.

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 and entered into the AsthmaNet database (Data Coordinating Center, Penn State University, Hershey, PA). Data collected from your participation in the SIENA study might be combined or used with data from other studies for analyses performed by AsthmaNet investigators and their collaborators. Registry data help us track your participation in multiple AsthmaNet studies over time. For some analyses, it is important to know if you were in more than one study.

Your agreement to provide the information for the AsthmaNet Registry is voluntary. However, if you choose not to provide this information, you cannot be enrolled in this 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 Washout). This study will enroll participants who have not taken asthma controller medications for 3 weeks before entering the study. 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 5 weeks. Your medication will be cut in half at week zero and stopped completely at week 2. You will have an action plan to follow if your asthma worsens. You will come in at week 5 to enter the study run-in. If you are taking very low dose asthma controller medication, taking controller medication less than 5 days a week, or are taking a leukotriene modifier, study staff could supervise your medication washout with 2 study visits over 3 weeks. Your medication will be stopped completely at week zero, and you will come in at week 3 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 are from 2 to 3 hours long. You will be asked to give a sputum sample 2-3 times during the run-in to find out what 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.

Study Procedures.
If you are eligible to continue in the study, you will have 6 study visits and 6 phone contacts over 36 weeks. Study visits are from 1 to 3 hours long. 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 under the heading “Study Chart” to see which procedures take place at each visit.

Spirometry: You will wear a nose clip, take a big breath in and then blow out all your air hard and fast into a machine called a spirometer. The machine measures how much air you blow out and how fast it comes out. 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 before this procedure 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 cells are in your airway.

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

Methacholine challenge testing: Methacholine is a drug that can cause narrowing of the airways of the lung. You will be asked to breathe in gradually increasing doses of methacholine. Spirometry will be performed after each dose of methacholine. The test will stop once your airways narrow by 20% or you have been given the last dose. You may have mild 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 is thought to 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 and are not surgically sterile or post-menopausal), you must use birth control during the entire study. Acceptable birth control methods include: abstinence (not having sex), 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 (a possible marker of who responses to steroids) and complete blood count (eosinophils) with each sputum induction. 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. Please refer to the separate consent section about 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 questionnaires 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 (your 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 get a small electronic device (tool) to check your breathing and record your asthma symptoms at home twice a day, every day. It is called a Spirotel®. The Spirotel® checks your “peak flow” which is how fast you can blow air out of your lungs. 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.

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 (a drug that works to open the airways by a mechanism that is different from albuterol) or a placebo (an inactive inhaler).

If you pass the run-in, you will be given two inhalers. One inhaler is either an inhaled steroid or placebo. The other inhaler is either a long-acting muscarinic antagonist or placebo. Inhalers are described in detail below.

Mometasone (Asmanex®): The inhaled steroid is mometasone, 110 mcg per puff. Mometasone is approved by the US Food and Drug Administration (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 must take 2 puffs every morning and evening.

Tiotropium (Spiriva®): The Long-acting muscarinic antagonist (LMA) medication is tiotropium Respimat, 2.5 mcg per puff. You will 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 is available in two types of delivery devices. The device used in this study delivers tiotropium as a soft-mist, and is marketed as Spiriva® Respimat®. Spiriva® Respimat® was FDA-approved for treatment of chronic obstructive pulmonary disease (COPD) in the US in September, 2014. Tiotropium is also available as a dry powder inhaler marketed as Spiriva® HandiHaler®. Spiriva® Handihaler® has been FDA-approved for the treatment of COPD (emphysema and bronchitis) in the US since 2004.

Tiotropium is an investigational bronchodilator drug (one which helps to open airways as described above) for the treatment of asthma. The safety and effectiveness of Spiriva® in pediatric patients have not been established.

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: Each person 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 like albuterol will be given to you. It will help open the 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 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 'Rescue' (for emergency use only): If your asthma worsens during the study, study doctors might decide to give you a high-dose inhaled steroid called mometasone (220 mcg per puff). You might be asked to take 2 puffs twice a day for 10 days. If you need high-dose "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 understand 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 then 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. The study will give you a Spirotel® device to use, but it must be returned at your last visit. 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.

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 e-diary 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.

Study Location
All study visits and procedures will take place at UCSF Clinical Airway Research Center or the UCSF Pediatric Clinical Research Center.

Study Chart

The chart below shows what will happen at each visit.

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Week	**0**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**
Informed consent	X								
Full medical history	X								
Long physical exam	X								X
Body measurements (ht, wt, waist, hip, neck)	X								X
Sputum collection	X	X	X[1]						
Blood sampling	X	X	X[1]						

Spirometry	X	X	X	X	X	X	X	X	X
Albuterol reversal	X		X[1]						
Methacholine challenge	X[2]								
Ipratropium reversal		X							
Exhaled nitric oxide	X	X	X[1]						
Urine pregnancy test	X								X
Genetics blood sample[3]		X							
Short physical exam		X	X	X	X	X	X	X	
Questionnaires	X	X	X	X	X	X	X	X	X
Exacerbation packet distribution			X						
Review e-diaries		X	X	X	X	X	X	X	X
Review medication use		X	X	X	X	X	X	X	X
Satisfaction questionnaire									X

[1] Albuterol reversal, sputum induction, blood sampling and exhaled nitric oxide performed prior to Visit 3 (at Visit 2A) 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.

How long will I be in the study?

If you qualify and are eligible for the study, you will have 9-12 study visits and up to 6 phone contacts over 42-51 weeks. Study visits are from 1 to 3 hours long. 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.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop so that your study 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?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects.

We anticipate that some participants in this study will have exacerbations, because this is a naturally occurring event in asthma. When exacerbations occur, the study team will prescribe additional medications and have you come in for an additional visit to be evaluated. If you have an exacerbation during the run-in period you will be withdrawn from the study. If you have an exacerbation during the double-blind randomized period, you will move to the next treatment period and begin taking the study medication or placebo for that period after finishing treatment for the exacerbation. If you experience an exacerbation in the last treatment period, you will be withdrawn from the study after follow-up phone contacts are completed.

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. You should talk to your study doctor about any side effects you experience while taking part in the study.

Spirometry - breathing fast and hard into a spirometry machine or peak flow meter can cause side effects which should go away shortly after the test is finished.

Likely

- Coughing
- Lightheadedness
- Chest tightness

Sputum Induction: Breathing in salty mist and coughing hard to produce sputum may cause side effects. The 12-minute test will be stopped sooner if your lung function gets worse.

Likely

- Salty mouth taste
- Sore throat

Less likely

- Asthma symptoms

Albuterol reversibility: Taking the 4 puffs of albuterol may cause the below side effects. These symptoms usually go away in less than an hour.

Less likely

- Fast heart rate
- Jittery feeling
- Increase in blood pressure
- Nausea
- Headache

Methacholine challenge testing: This test could cause the below side effects. 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 immediately and the challenge will be stopped.

Likely

- Coughing
- Chest tightness
- Shortness of breath
- Wheezing

Ipratropium reversibility: Taking the 4 puffs of ipratropium (Atrovent® HFA) required for this test can cause the adverse effects listed below. 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.

Less likely:
- Headache
- Dry mouth
- Nausea

Rare but serious:
- Bronchitis
- Shortness of breath

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:

Likely:
- Pain
- Bleeding or bruising

Less likely:
- Lightheadedness and fainting

Rare but serious:
- Infection

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 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, we have built into the study procedures to "rescue" you before your asthma gets bad.

Mometasone (Asmanex®, 110 mcg/puff, 2 puffs, twice a day): To avoid likely side effects, you will be asked to rinse your mouth with water and spit the water out each time you use the inhaler.

Likely:
- Throat irritation
- Hoarseness
- Infection of the mouth or throat

Less likely:
- Headache

Rare but serious:
- Thinning of the skin (only seen with higher doses taken for a long period of time and not expected because they will only be taking a medium dose for a short time)
- Changes in the immune system, bones or eyes (only seen with higher doses taken for a long period of time and not expected because they 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.
- CHILDREN ONLY: 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 growth of adolescents (12-18) in the study will be carefully measured at each study visit.

Tiotropium Respimat (Spiriva®, 2.5 mcg/puff, two puffs each morning): Tiotropium Respimat® has been tested in 3282 patients with COPD and 1634 adult and adolescent patients with asthma.

Less Likely:
- Pharyngitis
- Cough
- Dry mouth
- Sinusitis

Tiotropium should not be taken by patients 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 the possibility 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 formulation available for treatment. 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. Although patients taking placebo may report respiratory infections, headache, nasopharyngitis, and asthma, it is not likely that these were caused by the placebo. Both inhalers will be placebo for one of the treatment options. When you are on placebo, you will not receive active (study)

treatment for twelve weeks. It is likely that your asthma will get worse when you are taking 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. 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.

Likely:

- Heartburn - The risk is less if the medication is taken with food
- Increased appetite
- Nervousness
- Restlessness
- Trouble sleeping

Rare but serious:

- Weakening or break down of hip bone

While this side 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 Mometasone (Asmanex®, 220 mcg/puff, 2 puffs, twice a day): You will only take this medication if your asthma worsens.

Likely:

- Throat irritation
- Hoarseness
- Infection of the mouth or throat
- Headache

Bronchodilator: If side effects occur, they usually go away within a short time and do not require treatment.

Likely:

- Tremors
- Nervousness
- Dizziness
- Difficulty sleeping
- Headache
- Rapid or irregular heartbeats
- Drying and irritation of your mouth
- Sore throat
- Upset stomach
- Coughing

Ipratropium (Atrovent® HFA)**:** This drug is only used once in this study for reversibility testing at visit 2. Possible risks are already listed under ipratropium reversibility testing, above.

Unknown Risks: The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

There will be no direct benefit to you from participating in this study. However, this study will help doctors learn more about the treatment of future patients with asthma.

What other choices do I have if I do not take part in this study?

Taking part in this research study is voluntary. Your other choices to joining the study may include:

- Not joining the study and not taking any asthma treatment;
- Getting asthma treatment from your health care provider without being in a study;
- Joining a different research study.

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

How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Study tests that are performed by research labs, and information gathered directly from you by the researchers will be part of your research records. Hospital regulations require that all health care providers treat information in medical records confidentially.
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.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Appropriate officials of UCSF
- Study sponsor and/or its agents: AsthmaNet (other facilities and investigators involved with this study), NIH/NHLBI
- The Food and Drug Administration (FDA)
- Boehringer-Ingelheim (manufacturer of tiotropium)
- Other labs contracting with AsthmaNet for analysis of blood, urine or other biological specimens (e.g., local labs) In addition:
- AsthmaNet Data Coordinating Center, Penn State University College of Medicine, Hershey PA
- AsthmaNet Data and Safety Monitoring Board (DSMB)

- MedGraphics, St. Paul, MN (spirometry data; also will house data from spirotel e-diary/PEF meter)
- Medical International Research Inc. (MIR), Waukesha, WI and Rome, Italy (makers of spirotel e-diary/PEF meter device)
- Respitech Medical, Inc., Lancaster, PA (servicing of spirotel devices)
- Aerocrine Inc, Morrisville, NC (maker of NIOX MINO for FeNO testing)
- Spirometry overreader, Madison, WI (Rick Kelley, who serves as our grader)
- ADx Labs, National Jewish Health, Denver CO (ImmunoCAP analysis)
- Tucson Genetics of Asthma Lab, University of Arizona, Tucson, AZ (genetics lab; storing DNA and plasma)
- Genentech, South San Francisco, CA and Covance CLS, Indianapolis, IN (periostin analysis)
- Fahy Laboratory, University of California, San Francisco, CA (sputum lab)
- Other people or organizations assisting with AsthmaNet research efforts (this may include drug manufacturers, packagers/distributors, and/or their designees)

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers can use the Certificate to legally refuse 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.

Exceptions: A Certificate of Confidentiality does not prevent researchers from voluntarily disclosing information about you, without your consent. For example, we will voluntarily disclose information about incidents such as child abuse, and intent to hurt yourself or others. In addition, 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. Finally, the Certificate may not be used to withhold information from the Federal government needed for auditing or evaluating Federally funded projects or information needed by the FDA.

What are the costs of taking part in this study?

You will not be charged for any of the study activities.

Will I be paid for taking part in this study?

You will be paid a total of $1,082-$1,267 if you complete the study. You will be paid $35 for the first hour and $25 (prorated) for each additional hour that you are at UCSF for a study visit. You will be paid $15 per week for completing the at-home procedures (twice-daily peak flow monitoring, electronic diary completion, taking study drugs as directed). If your asthma worsens during the study, and you have to come in for one or more extra safety visits, you will be paid for that visit too. If you do not complete the study, you will be reimbursed for the visits you have completed (see table, below). It is important to know that payment for participation in a study is taxable income. Payments will be given in the form of a check mailed 4-6 weeks after your study visit:

Payment schedule for Supervised Washout

Visit	Approximate Time	Amount
0A	2 hours	$60
0B	1 hour	$35
Diary Completion	4-6 weeks	$60-90
TOTAL	3 hours	$155-185

Payment schedule for Study:

Visit	Approximate Time	Amount
1	3 hours	$85
2	2 hours	$60
3	2 hours	$60
4	1 hours	$35
5	1 ½ hours	$47.50
6	1 hours	$35
7	1 ½ hours	$47.50
8	1 hours	$35
9	1 ½ hours	$47.50
Subtotal for Visits		$452.50
Diary Completion	42 weeks	$630
TOTAL	14 ½	$1,082.50

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Stephen Lazarus, MD (415-476-2091) or Micheal Cabana, MD, MPH, (415-514-2660) if you feel that you have been injured because of taking part in this study.

> **Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California or the study sponsor AsthmaNet, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415-476-1814.

What are my rights if I take part in this study?

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. They 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.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor Stephen Lazarus, MD (415-476-2091) Michael Cabana, MD, MPH (415-514-2660).

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, please call the Office of the Committee on Human Research at 415-476-1814

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 asked 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 upon receiving your written request. 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. Steven Lazarus, MD or Michael D. Cabana in writing.

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 (DNA) 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**_____

Do you agree to the storage and sharing of leftover plasma from your (or your child's) genetics blood sample with AsthmaNet and NIH/NHLBI research centers/investigators for use in future research in the areas of asthma, allergies and related diseases?

(Please initial) **YES**_____ **NO**_____

Your authorization to participate in the genetics blood draw and testing 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 UCSF 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 UCSF 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.

PARTICIPATION 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

_____ _____

Date Person Obtaining Consent

The person being considered for this study is unable to consent for himself/herself because he/she is a minor. By signing below, you are giving your permission for your child to be included in this study.

PRINT NAME OF Parent or Legal Guardian:

_____

_____ _____

Date Parent or Legal Guardian Signature

PRINT NAME OF Parent or Legal Guardian:

_____

_____ _____

Date Parent or Legal Guardian Signature