



**UNIVERSITY OF CALIFORNIA, SAN DIEGO
CONSENT TO ACT AS A RESEARCH SUBJECT**

SARA: STUDY OF ACID REFLUX AND ASTHMA

Steve Wasserman, M.D. and his associates are conducting a research study to determine if adding a study drug for gastroesophageal reflux to inhaled steroid therapy in asthmatics reduces the number of asthma flare-ups. Gastroesophageal reflux means that more stomach acid than usual is getting up into the esophagus (swallowing tube). This condition is usually called GE reflux or GERD. GE reflux may worsen asthma symptoms, but it is not clear how important this effect might be. The sponsors of this study are the American Lung Association (ALA), National Heart, Lung, and Blood Institute (NHLBI) and the National Institutes of Health (NIH).

You are being invited to join this study because you are being treated for asthma and you have been having some problems controlling your asthma symptoms. There will be 400 subjects in 19 other sites enrolled in this study. At this site, we plan on enrolling up to 25 subjects.

However, it is important for you to know that participation in this research study is not meant to replace usual care for your asthma. You must see your regular asthma doctor for treatment of your asthma. You must also tell your regular asthma doctor that you are in this research study. We will send a letter to your regular asthma doctor to tell him or her that you are in this research study. We will notify your doctor if you cannot be in this study due to poor asthma control. During the study, if you have poor asthma control and need additional medical care, we may contact your doctor.

The study group that you are assigned to take will be determined randomly (like the flip of a coin). You will have an equal chance of receiving active or inactive medicine. The study drug is Nexium®, an FDA approved drug for GERD. Nexium® inhibits the acid production in your stomach. The dose you will be receiving of 40 mg twice a day is twice the current FDA guidelines at 40 mg once daily. Neither you nor the study doctor or study staff will know to which group you are assigned, but this information can be obtained if medically necessary. You will be instructed when and how to take the study drug. You will be asked to bring your pill bottles to each clinic visit so that we can count the pills.

You will continue on your current asthma medications. You must still be having asthma symptoms even though you are being treated with inhaled steroids (like albuterol). During the study you will receive an extra study drug to take for 24 weeks.

You are not eligible for this study if you have heartburn that requires treatment twice a week or more often; are currently taking a drug for reflux like omeprazole (Prilosec®) or esomeprazole (Nexium®) or cimetidine (Tagamet®) or ranitidine (Zantac®) or have had surgery for reflux. Other reasons you may not be able to join include poor lung function, having another chronic illness, or current use of various medications (like theophylline or antifungal medications, iron, coumadin, insulin, digitalis or other research drugs) within the past 30 days. You cannot join this study if you cannot give the information needed for the study or if you have smoked within the past 6 months.

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After you complete the study, you will be told which study drug you received.

Procedures

If you agree to join this study, the following things will happen:

Screening Visit 1 (this visit will occur two months to two weeks before the Randomization Visit and last approximately 4 to 6 hours)

- Explanation of study by study coordinator
- Obtain informed consent
- Complete baseline eligibility forms
- Distribute baseline diary and peak flow meter
- Asthma action plan (a summary of the procedures for home care in the event of asthma symptoms or a drop in peak flow)
- Schedule brief physical exam (may be same visit and last approximately 20 minutes)
- Perform pulmonary function test (PFT) (a measure of how your lungs work)
- Asthma, GERD, QOL questionnaires (answer questions about your asthma symptoms and on your stomach symptoms)
- Conduct a urine pregnancy test for all women of childbearing potential
- Receive peak flow meter (measure your breathing status at home)
- Receive a diary to write down your peak flow and symptoms every day
- Methacholine challenge test (MCT) a test which measures how sensitive your airways are to irritation
- Schedule pH probe study (the test for GE reflux) (separate visit approximately 24 hours wearing monitor). (A further description of this procedure can be found on page 3 of this informed consent.)
Timing of the probe test will depend on the lab's schedule and when you are available.

Randomization Visit 2 (this visit will last approximately 2 hours and will take place after the pH probe test). You will be assigned to one of two groups at this visit. As mention above, this will be determined by randomly.

1. Esomeprazole (NexiumTM) 40 mg twice a day
2. Placebo (an inactive substance) twice a day

Esomeprazole is approved for the treatment of GE reflux in adults.

You may take antacid medications (such as Tums® or Maalox®) as needed.

- Review consent, study expectations.
- Review diaries
- Review asthma action plan
- Interval asthma/health history
- Conduct urine pregnancy test
- Review eligibility
- Randomization
- Review asthma, GERD, QOL questionnaires
- Perform PFT



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- Distribute study drug
- Review study visit schedule

You will receive one of the following medications by chance.

- Esomeprazole (Nexium®) 40 mg twice daily by mouth before your breakfast and evening meal
- Inactive similar-appearing placebo twice daily by mouth before your breakfast and evening meal.

There is a 50% chance you will receive active drug. Neither you nor the study team will know which drug you will be taking.

Visit 3 (this is a telephone call which will occur between Visits 2 and 4 and last approximately 15 minutes)

- Review the necessity of doing the daily diary completion and peak flow monitoring
- Review any health issues that have occurred since starting the study
- Confirm first follow-up visit date

Visits 4 through 8 (these visits will occur every 4 weeks after Visit 3 and last approximately one to two hours)

- Return, review asthma diaries
- Review asthma, GERD, QOL questionnaires
- Review any health related issues
- Review asthma/health history

Visit 9 (this visit will occur 4 weeks after Visit 8 and will last approximately one to two hours)

- Perform MCT
- Perform PFT



Tests and Diary

pH Probe Test

This is a test of how much stomach acid gets up into the esophagus. It is done by the Gastroenterology (GI) Laboratory under the supervision of a gastroenterologist. A thin plastic tube is placed through the nose and down into the esophagus. Pressure measurements done through the tube make sure it is in the right place. The tube has a sensor for acid at the end. The tube and sensor are connected to a recorder that you can wear around your waist. You will wear the tube for 24 hours, and then return to the lab to have it removed and turn in the recorder. This test will be done once between Visits 1 and 2.

Methacholine Challenge

This is a breathing test. The test measures how much, if any, the airways narrow when you breathe in. This is called airway responsiveness. For safety reasons, we will not do the methacholine test if you are having asthma symptoms or if your lung function is less than 70% of normal before starting the test. Each methacholine challenge test may take 30 to 60 minutes. The test consists of an initial test of

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lung function followed by repeated tests after breathing in up to 6 mists of different solutions. After each mist is breathed in, your lung function will be measured.

The initial test of lung function takes 2 to 5 minutes. If your lung function is not high enough, the test will stop. If your lung function is high enough, the test will continue with you breathing in the first mist.

The first mist used in the test contains no methacholine, only saline (salt water) and a preservative (phenol) that helps to keep the solution sterile. The second mist contains a very small dose of methacholine, and each solution that follows contains a larger dose of methacholine in the mist. Each of these mists also contains saline and preservative.

After taking 5 breaths of the first mist, you will do another breathing test to see if there has been any effect. The breathing test takes about 2 to 5 minutes. Once your ability to blow out forcefully decreases by 20% or other symptoms develop we will stop the test. If your lung function does not change much you will breathe in the next mist, and the breathing test will be repeated. This process will continue until you have a significant change in lung function or after the sixth mist is given.

When the test is stopped, you will be given a bronchodilator (albuterol) to open the airways. Breathing is measured after the bronchodilator is used to be sure that all effects of the methacholine are over. You will not be allowed to leave the clinic until breathing has returned to normal or nearly normal level.

This test will be done twice during the study at Visits 1 and 9. Women of childbearing potential will have a urine pregnancy test before each methacholine challenge test.

Pulmonary Function Test (PFT) or Spirometry

Spirometry is a test that will measure how well you are able to breathe. You will wear a nose clip and breathe out forcefully into a machine that measures how much air you blow out and how fast it comes out. You will do this before and after inhaling a bronchodilator medication to see if the medication improves your test results. The bronchodilator is albuterol. Albuterol can help open up the breathing tubes in the lung in people with asthma. This test will be done eight times during the study at Visits 1, 2, 4, 5, 6, 7, 8, and 9.

Peak Flow Meter

We will give you a peak flow meter. The meters are used to test the lungs. To use it, you need to take a deep breath and make a strong blow into the tube. At Screening Visit 1 we will show you how to use the peak flow meter and how to read and record the results. If you cannot use the peak flow meter, you cannot join the study. You will need to use the peak flow meter every morning during the study.



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Pregnancy Test

For all women of childbearing ability, a pregnancy test is required at the Screening Visit 1 and the Randomization Visit 2. At each following clinic visit, women of childbearing ability who are not using a good method of birth control (no sexual intercourse, combination barrier and spermicide, or hormonal) may be monitored. Women involved in methacholine challenge testing will also be asked to take a pregnancy test before the breathing test is given. The pregnancy test may require a sample of urine.

Asthma Diary

We will ask you to measure and record your peak flow every morning, and to record asthma symptoms or other symptoms you might experience in a diary. You will also record whether you took the study drug each day. We will ask you to bring in the completed asthma diaries when you come for each visit. The purpose of this diary is to see how well your asthma symptoms are being controlled. You will keep a daily asthma diary after the Screening Visit 1 and during the entire 6 months of the study.

Questionnaires

Medical History: You will be asked a series of questions about the history of your health and asthma at the Screening Visit 1.

Asthma Control Questionnaires: You will be asked to complete a series of multiple-choice questions about your asthma symptoms and your daily activities. This will be used to measure your asthma control. You will complete these questionnaires at all the visits.

Quality of Life Questionnaires: You will be asked to complete a series of multiple-choice questions about your daily activities and health. This will be used to measure the quality of your life as it relates to your asthma. You will complete these questionnaires at all the visits.

Gastrointestinal Questionnaire: You will be asked to complete a series of multiple choice questions about symptoms from your stomach and esophagus. This will be used to measure symptoms from these areas.

Pregnancy: If you are a female and capable of child-bearing, a sample of urine will be collected before the study is begun in order to be as sure as possible that you are not pregnant. Your participation requires that you use a birth control method, such as abstinence, diaphragm, condom or intrauterine device to prevent pregnancy during the study, as the study drug being tested may cause harm to an unborn child. If you miss a period or think you might be pregnant, you will notify the doctor. You may have to withdraw from the study. A pregnancy test will be performed at the clinic as part of the Screening Visit 1 and Randomization Visit 2 and may be performed at the clinic as part of the other study Visits 4 through 9.

Participation in this study may involve some added risks or discomforts. These include:

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Esomeprazole

You will be taking one capsule twice daily of this study drug or an identical appearing inactive medication. The dose of the study drug that you will be taking is higher than the dose that is usually recommended for a starting dose because we want to have a greater than 90% chance that we will block all of the acid produced by your stomach. It is possible that this higher dose of study drug will cause more side effects than usual. If you do experience side effects that might be due to the study drug that are more than mild, the study drug will be discontinued for 2 weeks and then restarted. If the side effects recur you will be taken off study drug for the rest of the study period.

Side effects with this study drug are not very common. The most common side effects of esomeprazole are headache, dry mouth, nausea, bloating, diarrhea, constipation, and flatulence (intestinal gas). These symptoms usually go away if the study drug is stopped.

Other events that have happened in people taking esomeprazole include rashes, hepatitis, decreased blood cells, chest pain, awareness of rapid or pounding heartbeat, mental status changes, which may include slow reaction time, difficulty following conversations, low sugar or sodium in the blood, which may cause faintness or dizziness, weight gain, swelling, breast enlargement in men, blood cells or protein in the urine, painful night-time erections, inflammation of the kidney, visual disturbances such as blurriness, nose bleed, cough, hair loss, muscle or joint pain, back pain, and ringing in the ears.

Procedures

pH Probe Test

Inserting the tube for this test may be uncomfortable. You will be given numbing solution for your nose and throat to ease the discomfort of inserting the thin tube. The nasal spray is 2% zylcaine solution and for your throat 20% benzocaine solution. Sometimes there is brief nosebleed, gagging or cough. Some subjects may have mild discomfort in chest or over the stomach from the probe. There is a rare chance of an allergic reaction to the numbing solution, perforation causing bleeding of the GI tract or aspiration (fluid from the stomach going down into the lungs) from the procedure. These may be life threatening. Precautions are taken including detailed allergy history, the test being performed by a licensed gastroenterologist and team members skilled in the procedure. Subjects must carry the device for a 24-hour period, which may cause some inconvenience or embarrassment.

Methacholine Challenge

Methacholine challenge should not be done in anyone with current asthma symptoms (such as, asthma causing shortness of breath or chest discomfort or wheezing on the day of the test) or low lung function. The methacholine challenge will not be done unless you meet lung function requirements; a breathing test is done before the challenge starts to measure and check your lung function on the day of the test.

Methacholine challenge should not be done in anyone with known allergy to methacholine. There may be other reasons you cannot take this test. The study doctor will discuss this with you. There are other medical conditions that are affected by methacholine. If you have such a condition, your study doctor must approve of you taking the test.

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This test is not likely to cause serious symptoms. Some people have coughing or a tight sensation in their chest from breathing the methacholine, but it is usually mild. About 1 in 4 subjects having this test notices some cough or shortness of breath and about 1 in 10 notices some wheezing. However, reaction to methacholine can include severe bronchoconstriction (such as, a severe asthma attack) and loss in breathing function.

If you become pregnant during the study, you must agree to let the clinic know about your condition and any problems you have while you are pregnant. If you suspect that you have become pregnant while participating in the study, you must contact the study doctor immediately.

The safety of methacholine during pregnancy and nursing is not known.

You as the study participant may only take the study drug. Keep out of reach of children.



Spirometry

There is little risk from spirometry. Some people may have some chest soreness from the hard blowing or light-headedness. The chest soreness usually goes away by itself, but can be relieved with non-prescription pain-relievers. The most common side effects associated with albuterol are tremors, chest tightness, dizziness, nervousness, cough, headaches, and sleeplessness. Serious allergic reactions that can be life-threatening may occur. These reactions may by severe drop in blood pressure or constriction of your breathing tubes.

Peak Flow Measurement with Peak Flow Meter

Asthma patients commonly use peak flow meter readings to see how their lungs are doing. There is little risk from use of a peak flow meter. Some people may have some chest soreness from the hard blowing or light-headedness if they use it standing up. The chest soreness usually goes away by itself, but can be relieved with non-prescription pain-relievers. If you get lightheaded, you should perform the peak flow measurements while sitting down.

The study procedures and drugs may involve risks that are currently unforeseeable. However, if any new risks become known in the future you will be informed of them.

There may or may not be any direct benefit to you from these procedures. The investigator, however, may learn more about asthma and acid reflux or GERD. Subjects who receive active study drug (esomeprazole) might experience a decrease in asthma symptoms. There are no guaranteed health benefits to you for joining this study. You may feel better knowing that this study may be helpful to other people with asthma.

We will give you a peak flow meter to use during the study. This device will help you keep closer track of your health. You can keep it after the study is over.

Payment

You will be compensated up to \$450.00 for participating in this research. If the study is discontinued through no fault of yours or if you withdraw from the study, you will be compensated for those visits that you have completed. The reimbursement distribution is as follows:

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Visit 1 = \$50.00
Visit 2 = \$50.00
Visit 3 = \$50.00

Visit 4 = \$50.00
Visit 5 = \$50.00
Visit 6 = \$50.00

Visit 7 = \$50.00
Visit 8 = \$50.00
Visit 9 = \$50.00

If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. Neither the University nor the Astra-Zeneca (the maker of Nexium®), ALA, and the NIH will provide any other form of compensation if you are injured. You may call the UCSD Human Research Protections Program (HRPP) Office at (858) 455-5050 for more information about this, to inquire about your rights as a research subject, or to report research-related problems.

Dr. Steve Wasserman and/or _____ has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Dr. Wasserman or the study team at (619) 294-6251 or toll free at (888) 827-3247 or his research staff during regular business hours at (619) 294-6238.

Alternative Treatments

There are currently no FDA-approved treatments available for GER-related asthma. Your doctor or Dr. Wasserman can discuss what other non-FDA approved treatment or other treatments that are available for asthma could be offered to you, as an alternative to participation in this study. Your physician will monitor these and all medications closely. You do not have to participate in this study to receive treatment for your condition. The quality of your health care will not be affected if you decide to withdraw from the study or have been asked to withdraw from the study by your doctor or the Sponsor.

Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care you will receive at this institution or any benefits to which you are entitled.

Research records will be kept confidential to the extent allowed by law. However, Dr. Wasserman and/or one of his staff, the sponsor of this study, the FDA, Astra-Zeneca, and the UCSD Institutional Review Board (IRB) have the right to review the research records of this study. The results of this study may be submitted to governmental agencies in other counties where the study drug may be considered for approval and may be published in scientific journals or be presented at medical meetings; however, no individual participant will be identified by name.

You will be told if any important new information is found during the course of this study that may affect your wanting to continue

All costs of study procedures will be provided at no cost to you.

Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care you will receive at this institution. You may be withdrawn from the study for the following reasons: (1) Failure to follow Dr. Wasserman and/or his associates

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instructions; (2) A serious adverse reaction which may require evaluation; (3) If Dr. Wasserman believes that it is in your best medical interest; (4) Study termination; (5) Pregnancy.

You are encouraged to contact Dr. Wasserman or one of his medical staff if you decide not to continue participation in this study. If you decide that you no longer wish to continue in this study, you will be required to: (1) Return ALL study drugs; and (2) Complete ALL final visit procedures (i.e. laboratory tests and physical examinations Dr. Wasserman considers necessary).

Consent to Participate:

You have read the above information and have had an opportunity to ask questions.

You have read, reviewed, and received a copy of this consent document and the “Experimental Subject’s Bill of Rights” to keep.

You agree to participate in this study.

Participant’s Name (please print)

Participant’s signature

Date

Witness’ Name (please print)

Witness’ signature

Date

