TITLE: A Study of Pleiotropic Pioglitazone Effects on the Alcoholic Lung (APPEAL Study)

NCT NUMBER: NCT03060772

INFORMED CONSENT FORM VERSION DATE: April 12, 2019

ATLANTA VA HEALTH CARE SYSTEM
Consent to be a Research Subject

TITLE: A Study of Pleiotropic Pioglitazone Effects on the Alcoholic Lung (APPEAL Study)

PRINCIPAL INVESTIGATOR: David Guidot, MD

SPONSOR'S NAME: National Institutes of Health (NIH)

INTRODUCTION/PURPOSE:
You are being asked to volunteer for a research study at the Atlanta VA Health Care System because you regularly drink alcohol which can cause abnormalities in the lung. The purpose of the study is to see if a medication called pioglitazone can reduce oxidative stress in the lung and change the function of the alveolar macrophage—a type of immune cell.

Pioglitazone is an FDA-approved medication used to treat *diabetes.* However, the doctors in this study believe it may also help boost lung immunity in people who drink alcohol. Pioglitazone is considered experimental in this research study.

The APPEAL study is a *randomized* study. This means half of the participants will be assigned to take the study drug, while half will not.

If you choose to take part in this study, you will be asked to:

- take the study medication every day (but only if you are assigned to get treatment),
- have a procedure called a bronchoscopy before and after taking the study drug,
- have an x-ray
- fill out questionnaires, and
- give lung fluid, urine, and blood samples.

Women who are pregnant or plan to become pregnant in the next 6 weeks cannot be in this study.

We hope to enroll about 24 patients in this study at the Atlanta VA Health Care System. This study will last 2–4 weeks and require 4 study visits. All visits will take place at the Atlanta VA Health Care System.

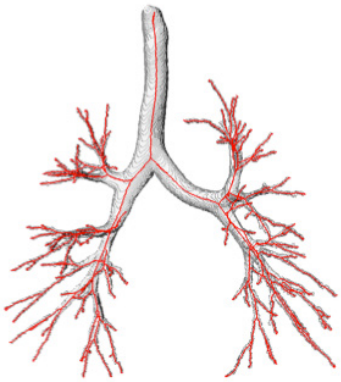
This form has been reviewed and approved by the Emory University Institutional Review Board (IRB). This board reviews research studies to protect the rights and well-being of the people taking part.

PROCEDURES:
Please read this consent form. Before you decide to take part, discuss any questions or concerns with the research team. If you agree to be in this study, you will need to sign this consent form and a HIPAA form before starting in the study. You will then go through these steps:

First Visit—Baseline:
This visit will take about 1.5 hours. At this visit you will be asked:

- About your medical history.
- To fill out questionnaires about your alcohol use.
- To have an x-ray of your chest (if you have not had one in the past year).

- To have your blood drawn to check your organ function (unless checked in the past month).
- To have a urine pregnancy test, if you are a woman who is able to have children.



Second Visit—Bronchoscopy Procedure #1:
Bronchoscopy with bronchoalveolar lavage and brushing is a common medical procedure. A bronchoscope will be passed through your mouth or nose into the lungs. Then, sterile salty water will be squirted into a section of the lung and collected. The doctors will use a tiny brush to gently rub against the wall of your airway to collect some cells. This will be done at the start of the study and then again 2–4 weeks later.

Before the procedure, you should not eat or drink for at least 6 hours. On the day of the procedure, you will have a brief physical exam and about 2–3 tablespoons of blood drawn from a vein in your arm. A urine specimen will also be collected.

Just prior to the bronchoscopy, lidocaine (liquid and/or vapor form) will be given to numb your throat. An intravenous (IV) catheter will be placed in your arm. Through the IV you will receive fluids and medicines (usually midazolam and fentanyl) to make you sleepy and to treat any discomfort.**

Next, the bronchoscope will be passed through your mouth or nose into your lung. There is a tiny camera with a light on the end of the bronchoscope to let us see inside of your lung. Salty sterile water will be gently squirted in and suctioned out. Your vital signs will be closely watched during the entire procedure.

The bronchoscopy should take about 10–15 minutes. Afterwards, you will be taken to the recovery room. There you will be watched until you are awake and it is safe for you to go home. All of this will take place in the pulmonary procedure suite on the 2nd floor of the hospital at the Atlanta VA Health Care System. The entire visit will take about 3–4 hours of time (from arrival to the end of the recovery period).

NOTE: For the bronchoscopy procedure(s) with conscious sedation medications, you are required to have a friend or family member accompany you to and from the hospital.**

I have read and understand the above statement. _____*(patient initials)*

***Upon request, patients may have the bronchoscopy without the use of sedatives or pain medication. If you choose this option, you are not required to have a friend or family member accompany you to and from the hospital.*

During this study, your blood and lung fluid samples will be used to measure levels of oxidative stress. The immune cells from your lung fluid will also be examined. Your urine samples will be used to measure alcohol metabolites and recreational drug use.

Treatment Assignment:
Right after your bronchoscopy, you will be randomly assigned to either **group 1** which will be taking the study drug (pioglitazone) or **group 2** which will not be taking the study drug. You will have a 1 in 2 chance of being put in either group. If you are put in group 1, you will begin your study pills the same day. You should take them every day as prescribed until your next bronchoscopy.

Third Visit—Brief Follow-Up:
About 1 week later there will be a brief follow up visit. We will review your alcohol intake and ask about any changes to your health. During this visit, we will collect your blood (2–3 tablespoons) and urine again. This visit will take 20–30 minutes of time and will occur at the Atlanta VA Health System.

Fourth Visit—Bronchoscopy Procedure #2:
Two to four weeks after your 1st bronchoscopy, you will have a 2nd one done. We want to repeat it to see if the fluid and cells in your lungs have changed. The second one will be just like the first. At this visit, we will again collect fluid from the lung, blood, and urine.

After your 2nd bronchoscopy, you will not return for any more study visits. However, we will follow up with you by phone 1–2 weeks later to see how you are doing.

During this study, you are encouraged to follow all recommendations of your VA providers and SATP counselors. Patients in this study are not required to drink alcohol.

RISKS:
Risks from chest x-ray:
Chest x-rays are routinely used for medical purposes. The chest x-ray in this study is not necessary for your regular medical care. It will only occur if you take part in this study.

The radiation dose you will get in this study is the same or less than what an average person in the US receives from the environment each year. The main risk linked with radiation is the chance of getting cancer later in life. We think that the risk from the radiation exposure you will get in this study is small compared to other daily risks.

The effects of radiation on an unborn child are not yet known. For that reason, pregnant women and those who may become pregnant should not take part in this study. If you are a woman of childbearing age, you will have a urine pregnancy test to make sure you are not pregnant.

Risks from blood draw and IV:
Common risks of blood draws and IVs are pain, swelling, and/or bruising where the needle enters your skin. Less common risks include infection, fainting, formation of a small blood clot, and bleeding from where the needle was inserted.

Risks from the questionnaires:
You may be uncomfortable answering some of the questions about your alcohol usage.

Risks from bronchoscopy with bronchoalveolar lavage (BAL) and brushing:
The bronchoscopy procedure can be uncomfortable. It may make you feel like you have to cough or cause minor irritation to your throat or lungs. This does not usually hurt the throat or lung. The bronchoscopy can also cause the level of oxygen in your blood to drop. To reduce this risk, we will monitor your oxygen level through the procedure. We will stop or provide immediate treatment if your

oxygen levels drop too low. There is a very small chance (less than 1%) that your lung could be seriously injured or collapse during BAL. In addition, there is a small risk for bleeding as a result of the bronchial brushing. In the rare event that a complication occurs, you will be given the appropriate medical treatment right away. The bronchoscopy will be performed or supervised by an experienced pulmonary physician. This procedure is being done for research purposes only in this study.

Risks of conscious sedation medications:
You will be given medications through your IV during the procedure that will relax you and decrease your level of consciousness. This will allow you to better tolerate the bronchoscopy. The medications that will be given are a benzodiazepine and an opiate (usually midazolam and fentanyl).

The risks of these medications may include slowed breathing, lowered blood pressure, and confusion. However, you will be closely observed while receiving these medications. If any adverse reactions should occur, you will be given the appropriate treatment right away.

If you have the bronchoscopy without sedative medications, these risks will not apply. The bronchoscopy procedure can safely be done without sedative medications, but will likely cause greater discomfort.

Risks of lidocaine used for local anesthesia:
Lidocaine is commonly used as a topical anesthetic during bronchoscopy, but in rare cases allergic reactions have been reported. In addition, lidocaine toxicity can occur. Although this complication is very rare, symptoms could include restlessness, dizziness, confusion, tremors, and altered mental status. If any adverse reaction to lidocaine should occur, you will be closely monitored and cared for by the study physicians.

Risks of pioglitazone treatment:
Thiazolidinediones (TZDs), including pioglitazone, can cause or worsen congestive heart failure (CHF) in some patients. Pioglitazone has also been associated with an increased risk for swelling, weight gain, and hypoglycemia (low blood sugar). Throughout the study, we will monitor for these potential side effects, but it is important that you are aware of them and notify your study doctor if you have any between your visits.

Tell your study doctor right away if you have chest pains, rapid weight gain (>5 pounds per week), fluid retention, swelling, or shortness of breath while in the study. Also, tell the study doctor if you have nausea, vomiting, stomach pain, tiredness, loss of appetite, dark urine, or yellowing of the skin.

Other negative effects reported more frequently than placebo include: upper respiratory tract infection (13%), headaches (9.1%), sinusitis (6.3%), muscle pains (5.4%), tooth disorders (5.3%), inflammation of the throat (5.1%), and in long term use in women, bone fractures (<1%).

Participants of Childbearing Potential
NOTE: Because pioglitazone can increase your chance of becoming pregnant, participants of childbearing potential must use two forms of birth control during this study. Abstinence is considered an acceptable form of birth control.

I agree to use two forms of birth control or practice abstinence. _____*(patient initials)*

Unknown risks:
This study involves taking a medication called pioglitazone. Although pioglitazone has been on the market since 1999, there may be risks that are not yet known. It is important that you track and report any new symptoms that you have after starting this drug.

BENEFITS: Taking part in this research study may or may not benefit you personally. If you are assigned to group 2 (no treatment), there will be no health benefit to you.

This study will help the researchers find out if pioglitazone is a promising treatment for people who regularly consume alcohol. From this study, we may learn new information that will help patients in the future.

ALTERNATIVES: There are no alternative treatments and/or procedures to those offered in this research study other than not to take part.

CONFIDENTIALITY: We will keep all information about you, including any research records we create, strictly confidential to the extent required by law.

For this study, each participant will be assigned a unique *study ID number.* We will use this *study ID number* to label all study specimens sent outside of the VA for processing. For this study, many of your samples will be processed here at the Atlanta VAMC. In addition, a research lab at Emory University in Atlanta will process some of the samples. No personal information such as your name, initials, date of birth, or social security number will be released outside of the VA.

All data collected electronically will be stored on a secure VA network. All data collected as a hard copy will be kept in a locked file cabinet in a locked office at the Atlanta VA Health Care System. Your name and other facts that might point to you will not appear when we present this study or publish its results.

People other than those conducting the study may look at your medical charts and study records:

- The Food and Drug Administration (FDA)
- National Institutes of Health (NIH)
- The Office for Human Research Protections
- The Government Accountability Office (GAO)
- The Office of Research Oversight (ORO)
- The Inspector General
- The Emory University Institutional Review Board and other offices in Emory University that help run and/or oversee studies
- The Emory Data Safety Monitoring Board
- The Atlanta VA Research Compliance Officer
- VA research staff within the VA Hospital or at Emory University (when data is stored at Emory)
- Any appropriate state or federal government agencies that make rules and policy about how research is done that are not listed above

If you are participating in a study where a test and/or procedure may be performed at Emory and you are not and have never been an Emory patient, you do not have an electronic medical record. Please note that an Emory medical record will be created if you have any services or procedures done by an Emory provider or facility for this study.

All research records and/or identifiers will be destroyed in accordance with the VA record retention schedule.

We have obtained a Certificate of Confidentiality from the Federal Government. This helps protect your privacy by allowing us to refuse to release your name or other information outside of the research study, even by a court order. By law, information can still be released if we find or suspect child abuse, elder abuse, an intent to harm yourself or others, or if you have an infectious disease that State or Federal law requires us to report. The Certificate does not prevent you or a member of your family from releasing data about yourself or your involvement in this study.

If you are a veteran who is a patient at the Atlanta VA Health Care System, a copy of your signed and dated consent and HIPAA forms may be placed in your medical record(s). If you are a non-veteran receiving clinical services (i.e., use of the laboratory, radiology, audiology, etc.) as part of this study, you will have an electronic medical record created for you. You will also be given a VA Notice of Privacy Practices (NOPP) and we will ask you to sign a form saying that you have received this notice.

If you are in an FDA sponsored clinical trial: A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

COMPENSATION: You will be compensated for your time and effort in this study as follows:

- First Visit—Baseline: $35
- Second Visit—Bronchoscopy Procedure #1: $200
- Third Visit—Brief Follow-Up: $35
- Fourth Visit—Bronchoscopy Procedure #2: $200

If you complete all 4 visits, the total amount you will receive is $470. Payments will be made using the Greenphire Clincard® which works like a debit card. When visits are completed, funds will be loaded on your card. You will be able to use the funds in approximately 1 business day.

Greenphire customer support will not have access to your name or contact information. Instead they will have your study ID number that will be provided to you by the study coordinator. You will be able to use this study ID number to check the balance on your Greenphire Clincard®.

You will receive emergency medical care if you are injured from being in this study. Under Federal Law, you will qualify for follow-up treatment if the injury was related to the research study. You may or may not get further compensation if you are injured in this study. This rule would not apply if you do not follow study procedures. If you believe you have been injured by this research, you should contact Dr. David Guidot at [redacted].

CONFLICT OF INTEREST: None

COSTS: There will be no costs to you for being in this study. You will not be required to pay for the study procedures or study medications that are part of this study.

Some veterans are required to pay co-payments for medical care and services provided by the VA. These co-payment requirements will continue to apply to medical care and services that are not part of this study.

CONTACT PERSONS: If you have any questions, concerns, or complaints about this study, you can call Dr. David Guidot at [redacted].

If you have been harmed from being in this study, call Dr. David Guidot [redacted].

If you want to speak to someone who is not a member of the study to discuss problems, ask questions, or voice concerns, you can call:

The Emory University Institutional Review Board at (404) 712-0720 or toll free at 1-877-503-9797

Or

The Research Compliance Officer at (404) 321-6111 ext. 6964 or the Clinical Studies Center Director at (404) 321-6111 ext. 206933.

If you have any questions about your rights as a participant in this research study, call the Emory University Institutional Review Board at (404) 712-0720 or toll free at 1-877-503-9797.

NEW FINDINGS: We may learn new things during the study that you may need to know. We can also learn about things that might make you want to stop participating in the study. If so, you will be notified about any new information.

VOLUNTARY PARTICIPATION AND WITHDRAWAL: Your participation is completely voluntary and you have the right to refuse to be in this study. You can stop at any time after giving your consent. This decision will not affect in any way your current or future medical care or any other benefits to which you are otherwise entitled. In addition, your participation in the study could be ended if a doctor, investigator, sponsor or committee overseeing the study recommends that stopping is in your best interest. If this happens, you will continue to receive standard care at your medical facility.

(Continued on the next page.)

We will give you a copy of this consent form to keep. If you are willing to volunteer for this research, please sign below.

RESEARCH PARTICIPANT'S SIGNATURE AND DATE:

_____
Research Participant's Name Printed

_____ _____ _____
Research Participant's Signature Date Time
(to be entered by participant)

_____
Name of Approved Individual Obtaining Consent

_____ _____ _____
Signature of Approved Individual Obtaining Consent Date Time
(to be entered by Approved Individual)

An Approved individual is one who has completed HRPP training and is officially approved to consent subjects for this specific study. The signature and date of this individual certifies that this is the most current approved consent document for this study.