University of Pittsburgh

School of Medicine
UPMC Vascular Medicine Institute

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: Phase 2 Open-Label Study of Safety and Efficacy Trial of CXA-10 in Pulmonary Arterial Hypertension

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Key Information

You are being asked to take part in the research study. Research studies include only people who choose to take part. The study team members will explain the study to you and will answer any questions that you may have. You should take your time to make your decision.

- The purpose of this study is to see if the investigation drug CXA-10 helps patients with pulmonary arterial hypertension (PAH).
  The study has 9 visits over the course of about 5 months.
- Study procedures include blood draws, lung function test, questionnaires, 6-minute walking test (6MWT), activity monitors, intravenous glucose tolerance tests (IVGTT), electrocardiograms (ECG), right heart catheterizations (RHC) and echocardiogram tests.
- You will be asked to take a pill once daily for the duration of the study.

Risks and side effects related to the study include those which are common while taking CXA-10 - diarrhea, nausea and abdominal pain; those related to blood draw – bruising or swelling at the site; those related to right heart catheterization – bruising or swelling at the site; those related to confidentiality – small risk of information being disclosed. These risks will be reviewed

in much more detail below.

You may feel better as a result of taking part in this study. There is, however, no guarantee that you will benefit from taking part in this study. Taking part in this study may help doctors learn more about CXA-10 and PAH. It is hoped that this information will help in the treatment of future patients with conditions like yours.

If you decide not to participate in this research study, your other options are to continue to get regular care from your doctor and/or talk to your doctor about other medicines to treat PAH.

We invite you to take part in the CXA-10 research study. We want you to know that taking part in this research study is completely voluntary. Your doctor may be involved as an investigator in this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor. Please take your time to make your decision about taking part.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by US law. This website will not include information that can identify you. At most, the website includes the summary of results. You can search this website any time.

One or more of the investigators conducting this research has a financial interest as an inventor/developer of the drug being evaluated/developed in this study. Furthermore, one or more of the investigators conducting this research has a financial interest in a company with intellectual property rights (property that result in patents, copyrights, and trademarks) the drug being evaluated/developed in this study. The University of Pittsburgh also has a financial interest in this company, has received charitable gifts from the company, and has sold and/or licensed intellectual property, including intellectual property being evaluated/developed in this study, to the company. This means that the results of this study could lead to personal profit for the individual investigator(s) or the University of Pittsburgh. Any questions you might have about this will be answered fully by the Human Subject Protection Advocate of the University of Pittsburgh at (866) 212-2668 or the Principal Investigator, Dr. Marc Simon (412) 802-3131, who has no financial conflict of interest with this research.

Why is this research being done?

You are being asked to take part in this study because you have been diagnosed with Pulmonary Arterial Hypertension. PAH is a medical disease that affects your heart and lungs. Having PAH means that you have high blood pressure in your blood vessels that travel from your heart to your lungs. This happens because there is narrowing of the blood vessels which makes it is harder for your blood to pass through them. This causes your heart to overwork and can lead to a weakening of the heart.

This study involves the use of an investigational drug called CXA-10. At low levels, CXA-10 is normally found in the human body. This naturally-occurring substance helps to decrease inflammation (the human body's response to injury that results in swelling, redness, and heat) in the body. Inflammation is a body's healing response to injury, but sometimes inflammation plays as an important factor in certain diseases such as PAH. Researchers believe that CXA-10 plays a vital role in reducing inflammation, improving blood pressure in the blood vessels that travel from the heart to the lungs, and improves how the heart functions.

Complexa, Inc. is the pharmaceutical company sponsoring CXA-10 and preparing the capsules.

CXA-10 is not FDA-approved for use in patients with PAH. However, the FDA does permit it to be used in experimental research studies like this, under strict regulations.

Who is being asked to take part in this research study?
A total of 30 participants ages 18-80 who have been diagnosed with PAH are expected to be enrolled in this study.

What am I expected to do in this research study?
This study will last about 5 months. During this time, you will need to visit the study clinic on schedule (outlined below), take the study medication, get tests, and tell the study doctor or study staff about any changes in your health or the way you feel. You may have up to 9 visits to the outpatient clinic and will have multiple telephone calls from the study staff throughout your participation in the study treatment.

What procedures will be performed for research purposes?
You will visit the study clinic on scheduled dates, receive tests, and tell the study doctor or study staff about any changes in your health or the way you feel. The research study tests and procedures listed below are not part of your routine care. We will give you 300 mg of CXA-10 once daily in the morning with food at home for 12 weeks. You will be asked to thoroughly record your exact date and time of your CXA-10 dosing and report any symptoms. There will be 9 visits over about 5 months. During this 5 month period, we will be asking you to undergo 2 RHC at visit 2 (week 0) and at visit 7 (week 12). The study personnel will contact you to review your medications and perform a safely evaluation approximately 2 weeks after certain visits. You will receive reminder calls or emails for appointments.

The study visits will take place at the UPMC Heart and Vascular Institute (including the outpatient cardiology clinic and cardiac catheterization lab), the Comprehensive Lung Center at Falk Clinic, the Clinical Translational Research Center (CTRC) located on the 6th floor of UPMC Montefiore, and the Endocrinology and Metabolism Research Center (EMRC), which is located on the 8th floor of UPMC Montefiore and Pulmonary Physiology Laboratory on the 12th floor of the Kaufmann Medical Building.

SCREENING PROCEDURES:
Procedures to determine if you are eligible to take part in a research study are called screening procedures. Your study coordinator will work with you to schedule your screening procedures for Visit 1. This Visit 1 will take place within 4 weeks prior to taking the study drug.

<u>Visit 1- Screening</u>
This visit will take place in the UPMC Montefiore, Presbyterian Hospital and/or the Kaufmann Medical Building. The screening visit assessment will take place on (2) separate days if a screening right heart catheterization (RHC) is needed. You will need to fast a minimum of 8 hours (plain water is ok) prior to each visit. For this research study, the screening procedures include:

1. We will review the study with you again and review the study consent form, which you will need to sign with a study doctor to be a part of the study.
2. Review your medical history, demographics and medications.
3. Physical examination including measurement of your height, weight, vital signs, and the stage of your heart failure - this is also known as the World Health Organization (WHO) functional class assessment (based on symptoms related to heart failure). A clip will also be placed on your finger to measure the oxygen in your blood.

4. We will draw a blood sample from a vein in one of your arms or hand to conduct routine laboratory tests to help evaluate your overall health such as fasting glucose, comprehensive metabolic panel (blood test that measures your glucose levels, electrolyte and fluid balance, liver function, and kidney function), fasting lipid profile (tests that measure fats in your blood) , CBC/Diff test (a test to make sure that you do not have few red blood cells, uric acid (a test to measure uric acid in the blood to test for gout), and a hemoglobin A1c (a test to measure your average blood sugar level in the last 2-3 months), NT-proBNP (marker for heart failure). We will collect blood to test your PT/INR. This test is to measure how long your blood takes to clot.
5. We will collect and test a small volume of your urine to check for infection.
6. A urine pregnancy test is required if you are a woman of child-bearing potential.
7. You will be asked to do an ECG test. Electrocardiogram measures your heart's electrical activity. This procedure is done by putting small sticky pads on your chest, ankles, and wrists while you lay down flat. It is important for you to relax while lying down for a few minutes before taking the reading because this allows the ECG to be more reliable.
8. You will complete a lung function test. This test (spirometer that is a small machine with an attached mouthpiece) measures how well your lungs are working. If you completed a lung function test no more than 12 months prior to this screening visit, then we may use those results.
9. You will complete a 6-minute walking test (6MWT). You will walk as quickly as possible for 6 minutes on a standard course. We will measure the distance and speed while you walk, and we will also ask you to rate (with a number) how hard you are working while you are walking.
10. We will collect your saliva, tongue scrapings, and stool samples (you will have a kit to take home for stool collections).
11. On a separate day, the RHC will be performed if you have not had a RHC in the last 2 months of enrollment based on your medical records. In order for a RHC from 2 months ago to be eligible, you must be on stable doses of your medications and should have not started an exercise program right before your RHC 2 months ago or started one within 2 months prior to the screening visit. This RHC visit will take place in UPMC Presbyterian Hospital, 3rd FL Catheterization Laboratory, and may take up to 4 hours to complete. You will need to fast a minimum of 8 hours prior to this visit. You will be allowed to take necessary medication with sips of water as directed by the study doctor performing the procedure. You may be asked to hold anticoagulation therapy, oral hypoglycemics, and diuretics along with potassium, based on review of your case, as this is standard clinical care prior to RHC. We will provide you with specific instructions depending on the medications you are taking. The following procedures will be done at this visit:

    a. An IV will be placed into your vein. This IV will be used to give you medications for the right heart catheterization procedure and to draw blood if we need to do so. You may also receive medications to make you less nervous, such as midazolam and/or fentanyl intravenously.

    b. If you are a woman of child-bearing potential, a second urine pregnancy test will be performed.

    c. A clip will be placed on your finger to measure the oxygen in your blood, and a blood pressure machine will measure your blood pressure at regular intervals.

    d. You will have an echocardiogram in a UPMC lab usually prior to the RHC. If there

is a scheduling issue, the echocardiogram can be performed at another visit prior to beginning the 12-week daily dosing of CXA-10. An echocardiogram is the same as an ultrasound of the heart. Most people who have heart failure are familiar with this test. During an echocardiogram, a health care professional will press a probe with gel on it against the left area of your chest. The professional can then view images of your beating heart. This test can give measurements of how strongly your heart can pump.

e. Right heart catheterization (RHC) involves placing a thin, flexible tube into a vein in your arm, neck, or groin and guiding the tube into your main lung artery, where it can be used to measure your blood flow and lung artery pressures. X-ray may be used to track the tube. RHC is performed under local anesthesia, usually lidocaine, which will eliminate any associated pain. Using a TV screen and x-rays, the doctor threads the catheter along the vein, through the heart, and into the blood vessels going to your lungs. As the catheter is advanced toward the pulmonary artery, a number of blood pressure and blood flow measurements are taken in different places in the heart and lungs. Indirect measurements of pressures on the left side of the heart are made, as well, by inflating a tiny balloon at the tip of the catheter once the catheter reaches the pulmonary artery. This pressure measurement is called the pulmonary capillary wedge pressure (PCWP).

   Hemodynamic measurements (measuring blood flow in your body) will be taken during the RHC. If the RHC shows that you are ineligible for the study, you will not receive the study medication, CXA-10, and will have no further procedures or testing. If you are one of the first 10 subjects enrolled in the study and are eligible, you will be given a single dose of CXA-10 after the baseline hemodynamic measurements have been captured to assess an acute dose of CXA-10. We will then take another series of hemodynamic measurements after the dose of CXA-10. Food will be given to you prior to dosing. You will not begin the daily dosing until all eligibility criteria have been met and after all baseline procedures have been completed.

f. Blood samples will be collected to study how much of the drug goes into your bloodstream and how long it stays there before and after you receive the CXA-10. Additional blood samples will be collected to perform a biomarker and cytokine measurements (measurements that provided information about presence or progress of a disease) at the same time points (if not collected during initial screening visit). Approximately 1 ¾ tablespoons of blood may be collected throughout the entire procedure.

g. You will be monitored closely and given something to eat after the procedure is over. You will not be discharged until all medications have worn off and your breathing and heart rate are normal. The study doctor will see you before you leave the hospital. You should avoid strenuous activity for the rest of the day and call the study doctor **if you notice any symptoms you did not have before the test.**

12. We will monitor you for any adverse events.
13. You will be given an activity monitor to wear after all of the eligibility requirements have been met. This device measures your body movement, activity, and sleep over the entire 24 hour period each day it is worn. You will be asked to wear the monitor on your non-dominant wrist for at least 7 consecutive days at home prior to receiving the first dose of the study drug on Visit 2. You will wear it all hours of the day except when you

bathe. We will give you directions on how to wear it. You will be asked to return the monitor at the next visit.

The total amount of blood is approximately 5 tablespoons.

Visit 2 (Week 0-Baseline testing)

This visit will take place at UPMC Montefiore. You will be asked to fast a minimum of 12 hours prior to completing the tests listed below.

1. Brief physical exam with WHO Functional Class assessment and body weight measurement, vital signs (blood pressure, heart rate, respiratory rate, temperature, pulse oximetry) and review your medications
2. You will have an ECG performed.
3. We will draw your blood samples for tests (e.g., fasting glucose, comprehensive metabolic panel, fasting lipid profile, CBC/Diff, and uric acid), PT/INR, NT-proBNP
4. Blood samples will be collected to perform a biomarker and cytokine measurements
5. Collect and test a small volume of your urine for a urinalysis
6. A urine pregnancy test is required if you are a woman of child-bearing potential.
7. Intravenous glucose tolerance test (IVGTT) is given to measure your sensitivity to insulin and your insulin's secretion. We will give you glucose through an IV, then after we will give you insulin to control the glucose. If you are taking oral hypoglycemic, we may ask you to hold those medications during this test, but you can take those medications the same day following the completion of this test. This test will take 3 hours.
8. We will have you complete the health related quality of life questionnaire-Pulmonary Arterial Hypertension-Symptoms and the Impact (PAH-SYMPACT) questionnaire. This questionnaire is used to assess your pulmonary arterial symptoms and the impact on your life.
9. Return activity monitor
10. Monitor for any adverse events

The total amount of blood is approximately 20 tablespoons.

Visit 3 (Week 0 – First dose)

This visit will take place at UPMC Montefiore. Subjects do not need to fast for this visit and this visit will last up to 4 hours.

1. You will complete the 6-minute walking test (6MWT) with Borg Dyspnea (how short of breath you are) questionnaire.
2. We will draw your blood sample for the Population PK sampling (test is used to see how well the human body handles the study drug, CXA-10). We will draw your blood again for the PK sampling 2-4 hours after taking the study drug.
3. Blood samples will be collected to perform a biomarker and cytokine measurements which be collected at the same times as the PK sampling.
4. Dispense study drug. You will be instructed to take the first dose of study medication at the clinic after a breakfast/morning snack (i.e. such as a granola bar)
5. We will review your medications
6. Monitor for any adverse events.

Visit 3a (Week 1)

1. If you are on warfarin, you will be asked to return to the clinic for a blood draw one week after taking CXA-10, to check your PT/INR. You will not need to fast at this visit.

Visit 4 (Week 4) and Visit 5 (Week 8)-Study Drug

You will be asked to fast (no food and drinks, only water) for a minimum of 8 hours overnight prior to this visit. You should not take your study medication in the morning, prior to arriving for your visit. You will be asked to take 300 mg of CXA-10, by the study doctor or study coordinator after completing assessments and tests during the morning. This visit will take place in UPMC Montefiore and will last up to about 4 hours.

Procedures done before you take the study drug:

1. Brief physical exam with WHO Functional Class assessment and body weight measurement, vital signs (blood pressure, heart rate, respiratory rate, temperature, pulse oximetry) and review your medications
2. You will be asked to complete an ECG test.
3. We will draw your blood samples for tests (e.g., fasting glucose, comprehensive metabolic panel, fasting lipid profile, complete blood count, and platelet and differential, uric acid and NT-proBNP).
4. We will draw your blood sample for the Population PK sampling and blood samples will be collected to perform a biomarker and cytokine measurements.
5. Collect and test a small volume of your urine.
6. A urine pregnancy test is required if you are a woman of child-bearing potential.
7. You will complete the 6-minute walking test (6MWT) with Borg Dyspnea questionnaire
8. You be asked to complete the health related quality of life-PAH-SYMPACT.

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Procedures done after you take the study drug:

1. You will be given a breakfast/snack with the 300 mg dose of CXA-10, during the morning.
2. We will draw a blood sample for Population PK sampling 2-4 hours after taking the study drug and blood samples will be collected to perform a biomarker and cytokine measurements.
3. Monitor for any adverse events.
4. Dispense study drugs
5. At Visit 5, we will provide you an accelerometer and instruct you to wear this for at least 7 consecutive days prior to the next visit (Week 12).

The total amount of blood is approximately 4 tablespoons for visits 3 and 3a. The total of blood is approximately 5 tablespoons for visit 4 and the total of blood is approximately 5tablespoons for visit 5.

Visits 6-8(Week 12)-End of Treatment

The visits listed above are repeated at the end of the study and will take about 3 days to complete. The tests are listed below and are done the same way as described above in Visits 1, 2 and 3.

Visit 6 (Week 12)-End of Treatment

You will be asked to come to UPMC Montefiore for this visit. Subjects will be asked to fast a minimum of 12 hours to perform the assessments listed below. The visit will last approximately 6 hours.

1. Brief physical exam with WHO Functional Class assessment and body weight measurement, vital signs (blood pressure, heart rate, respiratory rate, temperature, pulse oximetry) and review your medications
2. You will be asked to complete an ECG test.

3. We will draw your blood samples for tests (e.g., fasting glucose, comprehensive metabolic panel, fasting lipid profile, complete blood count, and platelet and differential, uric acid, PT/INR, hemoglobin A1c (this test is performed if subject has abnormal HbA1c) NT-proBNP).
4. Blood samples will be collected to perform a biomarker and cytokine measurements
5 Oral and stool samples will be collected.
6. You will have a IVGTT.
7. A PAH-SYMPACT questionnaire will be performed.
8. You will return the accelerometer for data download.
9. Review your medications.
10. Monitor for adverse events.

The total amount of blood is approximately 20 tablespoons.

Visit 7 (Week 12)-End of Treatment

You will report to the clinic on the morning of Week 12 after a minimum 8-hour overnight fast. You should not take their study medication that morning, prior to arriving at the clinic for your pre-dose assessment.

Procedures done before you take the study drug:

1. Brief physical exam An echocardiogram will be performed.
2. You will have a RHC.
3. Hemodynamic measurements (measuring blood flow in your body) will be taken during the RHC. You will be given a single dose of CXA-10 that you will take with food after the baseline hemodynamic measurements have been captured to assess an acute dose of CXA-10. We will then take another series of hemodynamic measurements after the dose of CXA-10. You will take food prior to dosing.
4. We will draw your blood sample for the Population PK sampling
5. Blood samples will be collected to perform a biomarker and cytokine measurements which these samples are collected at the same time as Population PK sampling.

Procedures done after you take the study drug:

1. We will draw your blood sample for the Population PK sampling
2. Blood samples will be collected to perform a biomarker and cytokine measurements which these samples are collected at the same time as Population PK sampling.
3. Review your medications
4. Monitor for adverse events

The total amount of blood is approximately 3.5 tablespoons.

Visit 8 (Week 12-End of Treatment)

You will be asked to come to UPMC Montefiore for this visit and this visit will last up to 6 hours. You will not need to fast for this visit.

Procedures done before you take the study drug:

1. You will complete the 6-minute walking test (6MWT) with Borg Dyspnea questionnaire
2. We will draw your blood sample for the Population PK sampling.

3. Blood samples will be collected to perform a biomarker and cytokine measurements which these samples are collected at the same time as Population PK sampling.
4. You will be given a breakfast/snack with the 300mg dose of CXA-10, during the morning.

Procedures done after you take the study drug:

1. We will draw your blood sample for the Population PK sampling.
2. Blood samples will be collected to perform a biomarker and cytokine measurements
3. We will review your medications
4. Monitor for adverse events.
5. Dispense 1st month supply of CXA-10 (optional).

The total amount of blood is approximately 3.5 tablespoons.

Open Label Period

Upon completion of the end of treatment visits, you will be given the option to receive a 6-month supply of CXA-10. If you decide to receive the CXA-10, we will follow up with you in the clinic at month 1, 2, 4 and 6 to monitor your vital signs, blood work, six-minute walk test, and questionnaires. Months 3 and 5 will be a phone call to perform a safety evaluation and to see if there are any changes in medications. The total amount of blood drawn at each visit is about 5 tablespoons.

Visit 3b (Week 2), Visit 4a (Week 6), Visit 5a (Week 10)-Telephone Calls

A member from the study team will contact you by phone to perform a safety evaluation and ask if there were any changes in medications that you are currently taking approximately 2 weeks after Visit 2, Visit 3 and Visit 4. You will be reminded to bring any remaining medication to your next clinic visit.

Visit 9 (Week 16)-Follow-up Visit

This visit will take place approximately 4 weeks after the end of treatment. You will fast (no food and drink, except water) overnight for 8 hours prior to coming to this visit. This visit will last about 1 hour.

1. Brief physical exam with WHO Functional Class assessment and body weight measurement, vital signs (blood pressure, heart rate, respiratory rate, temperature, pulse oximetry) and review your medications
2. We will draw your blood samples for tests (e.g., fasting glucose, comprehensive metabolic panel, fasting lipid profile, complete blood count, and platelet and differential, uric acid and NT-proBNP).
3. Blood samples will be collected to perform a biomarker and cytokine measurements
4. Collect and test a small volume of your urine.
5. A urine pregnancy test is required if you are a woman of child-bearing potential.
6. You will complete the 6-minute walking test (6MWT) with Borg Dyspnea questionnaire
7. Monitor for adverse events.
8. Dispense 2nd month supply of CXA-10 (optional).

The total amount of blood is approximately 3.5 tablespoons.

What side effects or risks can I expect from being in this research study?

As with any experimental procedure, there may be adverse events or side effects that are

currently unknown and certain of these unknown risks could be permanent, severe, or even life threatening.

Risks of CXA-10
There are risks associated with the study drug, CXA-10. The most common side effects on an empty stomach were: diarrhea, nausea, abdominal pain, and vomiting. Other less common side effects were: abdominal discomfort, dizziness, tiredness, lightheadedness, and a metallic taste in the mouth. The rare side effects were: heart burn, fainting, indigestion, headache, and rectal discomfort. The side effects were mild to moderate. When CXA-10 is taken with food, some subjects experienced: diarrhea and nausea.

Risks of blood draw/intravenous line:
A risk of drawing blood is anemia, which is a lower hemoglobin level. A common symptom of anemia is fatigue (feeling tired or weak). The amount of blood to be drawn over the course of this investigation could be a maximum of about 52 tablespoons among the blood draws, cardiac catheterizations and IVGTTs. This is about 4 cups which is a little more than what is taken at a blood donation. We encourage you not to give blood just before enrolling or during the time you are in the study, to minimize the risks of blood tests a RN, MD, technician or phlebotomist will draw your blood. Common risks of blood sampling by venipuncture or intravenous line placement include temporary pain, bruising which may last for several days, redness, swelling and phlebitis. Infrequent risks include feeling lightheaded or faint when blood is drawn. This is usually due to nervousness (not due to the amount of blood taken), and it is not usually serious. Infrequent risks for the intravenous line include infiltration (a leakage of anything that has been given through the vein (such as the saline, dextrose, insulin) into the arm tissue that surrounds the vein and holds the IV). Rare risks include infection and bleeding.

Allergic Reaction Risks
As with taking any drug, there is a risk of allergic reaction including serious reaction that may be life-threatening and cause death. Some allergic reactions risks: rash, wheezing and difficulty breathing, dizziness and fainting, swelling around the mouth and throat or eyes, a fast pulse, and sweating.

Reproductive Risks
It is not known if the study drug can affect an unborn baby. Therefore, you should not become pregnant and you should perform the appropriate methods to prevent pregnancy. You should not father a baby while on this study and you should perform the appropriate methods to prevent pregnancy. If you are physically able to father a baby, you must use an effective method of birth control while in this study. If you become aware that you or your sexual partner is pregnant during the course of your participation in this research study, you must contact, as soon as possible, the study doctor listed on the first page of this form.

Risks of 6MWT
The 6-Minute Walk Test, can cause muscle soreness or fatigue (occurs in 10-25% of people). Other changes include shortness of breath, abnormal blood pressure, or fainting (occurs in 10-25% of people). Heart attack, stroke, or sudden death are rare (occur in <1% of people). Rarely, exercise may cause moderate to extreme pain which could be due to muscle sprains, muscle strains, broken bones, or chest pain.

Electrocardiogram (ECG) Risks
There is no known risk associated with this procedure. You may develop a mild skin rash from

the ECG leads.

Echocardiography Risks
There is no known risks associated with this procedure. Gel will be applied during the test which may cause coldness and/or irritation.

Risks of Activity monitor/Accelerometer Use
Common risks associated with wearing the accelerometer are redness, irritation, and chaffing.

Right Heart Catheterizations (RHC) Risks
The common risks of RHC are pain at the needle entry site and slight risk of bleeding around the site, bruising at site, lightheadedness or dizziness during the needle stick.

The uncommon risks are puncturing the lung which would require a chest tube insertion and/or having irregular heartbeats which usually stop when the long tube is removed from the heart.

The very rare complications include cardiac arrhythmias (irregular heartbeats), cardiac tamponade (blood or fluids build up in the space between the heart muscle and other outer covering sac of the heart which causes pressure on the heart), low blood pressure, infection, or embolism (blockage of material inside a blood vessel) caused by blood clots at the tip of the catheter.

There is no expected additional risk from the additional time of the procedure for measuring the hemodynamics (measuring blood flow in your body) 30 minutes after giving you the study drug.

Risks of Medications used during Catheterization
The medications used for sedation are used for a short period of time during the right heart catheterization. These medications should wear off within several hours. The side effects are listed below for each drug.

- 1% Lidocaine: Will be used to numb the area prior to the insertion of the cardiac catheter into either the arm, neck or groin vein. A common side effect is slight burning at the site which dissipates quickly.
- Fentanyl: Common side effects include temporary light-headedness, dizziness, and nausea, vomiting or sweating.
- Midazolam: Common side effect includes drowsiness. Infrequent side effects are nausea, vomiting. Breathing problems are rare. Allergic reactions (e.g., hives, itching, etc.) to lidocaine, fentanyl, or midazolam are rare.

Risks of Lung Function Test (spirometry)
Spirometry can infrequently make the chest tight or short of breath. Albuterol will be available if this occurs. Rarely, you may have coughing or lightheadedness with this test. If Albuterol is needed, you will get up to 4 puffs of albuterol. Albuterol may make you feel slightly jittery or nervous, but the feelings are temporary.

Risks of IVGTT
Common risks include: phlebitis (inflammation of a vein), transient hyperglycemia (high blood sugar not requiring treatment). The risk of receiving insulin during the study is that it could cause a low blood sugar reaction (termed “hypoglycemia”). Hypoglycemia, which is rare (occurs in <1% of people), may cause symptoms such as shakiness, nervousness, sweating, hunger, dizziness, and a fast heart rate. If severe, hypoglycemia can cause coma, seizure, or even

death, all of which are rare (occurs in <1% of people). It is very unlikely that severe hypoglycemia will occur during the insulin infusion because the blood sugar will be monitored every few minutes by trained nursing staff. As an additional safety measure, you will be kept awake during the insulin infusion. This will allow the study team to be certain that you are not experiencing any kind of unusual or unexpected reaction to the insulin infusion.

Risks of X-ray used during the Catheterization
An x-ray may be done during the right heart catheterization. An X-ray performed for the purpose of this research study involves exposure to radiation. There is no minimum amount of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure received from participation in this study is considered to be low.

Risks of Stool Collection
There is no risks from stool collections.

Risks of oral sample collections (saliva and tongue scrapings)
There is no risks from oral sample collections. The tongue scrapings might cause gagging or mild local irritation or very small bleeding that will resolve on its own.

Risk of Breach of Confidentiality
Although we are taking many steps to protect your information, there is always a chance that your information or identity could be disclosed. We will continue to review and improve the ways we keep your information private. To protect your information, paper-based records will be kept in a secure location and only be accessible to personnel involved in the study. Paper charts will contain subject identifiers but will be in locked cabinets within a locked office on a unit that has restricted access.

Are there benefits to taking part in this research study?
There may or may not be direct benefits for you participating in this study. However, there may be a potential future benefit to society as a whole, from the information obtained from the conduct of this study through the advancement of knowledge.

May I withdraw, at a future date, my consent for participation in this research study?
You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study). Any identifiable research or medical information recorded from your participation in this research study prior to the date that you formally withdraw your participation may continue to be used and disclosed by the investigators for the purposes described above.

Your data and biological samples will be stored indefinitely unless you request for the samples to be destroyed. Your samples will not be labeled with direct identifiers. Your identity on these samples and records will be indicated by a random case number, rather than by your name, social security number or any other label that could identify you.

To formally withdraw your consent for participation in this research study, you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.
If you are withdrawn from this study, you will be asked to report to visit 6.

If I agree to take part in this research study, can I be removed from the study without my consent?
You may be removed from the study by the investigators in the event that the investigators feel that the study drug adversely influence your health; if you don't comply with study requirements; if a pregnancy test proves positive; or other situation at Dr. Simon's discretion.

Any identifiable research or medical information recorded for, or resulting from your participation in this research study prior to the date that you were withdrawn from participation may continue to be used and disclosed by the investigators for the purposes described.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
You will be promptly notified if any new information develops during the conduct of this research study that may cause you to change your mind about continuing to participate.

The study team will discuss any research results that would affect your health care with you; for example if any of your labs are abnormal.

Will this research study involve the use or disclosure of my identifiable medical record information?
As part of this screening process, we will review your identifiable medical records to see if you are eligible for this study. We will protect your privacy and the confidentiality of your records, as described in this document, but cannot guarantee the confidentiality of your research records, including information placed in your medical records, once your personal information is disclosed to others outside UPMC or the University.

Will my information be kept private?
Any information about you obtained from or for this research study will be kept as confidential (private) as possible. All records related to your involvement in this research study will be kept in a locked file cabinet or in a password protected computer database accessible only to study personnel. Your identity on these records will be indicated by a unique study number, rather than your name, and the information linking this study number with you identity will be kept separate from the research records. You or your family will not be identified in any publication of the research study.

Who will have access to identifiable information related to my participation in this research study?
In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

- Authorized representatives of the Office of Research Protections may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

- Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

- Authorized representatives of this research study (National Institute of Health (NIH) will review and/or obtain identifiable information; which may include the subject's identifiable medical information related to participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for preparing required scientific analyses of the research data. Authorized representatives of the study sponsors may also be present during the subject's participation in certain research procedures. While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical information, the UPMC and the University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor.

- Authorized representatives of the Food and Drug Administration and the study sponsor (the National Heart, Lung, and Blood Institute, a part of the National Institutes of Health), who may need to review the records for accuracy and completeness. Representatives of the study sponsor may also be present during your participation in the research study. While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical record information, UPMC and the University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor.

- In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings; if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The researchers may share your de-identified data with the maker of the drug, Complexa, Inc. We may also share de-identified data with other researchers in the future.

Though none is planned at present, your samples, (blood, saliva, stool, tongue scrapings) may undergo genetic analysis in the future. This may include whole genome sequencing, which is identifying your entire, unique genetic code from your biological parents. Please ask the study team any questions you have about this.

Will I have to pay anything to be part of this study?
Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed for the purpose of this research study, i.e. study drugs and the tests performed on your body and your blood collected for the study. All laboratory, physician, and hospital costs not related to the research are considered to be "routine clinical services" that you would have received even if you were not participating in the research study. All costs of the study are covered by the National Institute of Health (NIH). If you receive a bill or believe that your health insurance has been billed for something that is part of the research study, immediately notify a member of the research team or UPMC Patient Billing Services.

Will I be paid if I take part in this research study?
You will be paid up to the total of $930 if you complete this study. Here is a breakdown of payments:

- $20 for Visit 1
- $150 for Visit 2
- $100 for Visit 3
- $10 for Visit 3a
- $50 for Visit 4
- $50 for Visit 5
- $200 for Visit 6
- $200 for Visit 7
- $100 for Visit 8
- $50 for Visit 9

You will receive payment following the completion of all study visits. In order to be compensated for your participation in this study, you will have to provide your Social Security Number. If you receive more than $600 in a calendar year, it will be reported to the IRS as income.

You will also be provided a ticket for outpatient parking costs at all visits. In the event that you do not complete the study due to study related adverse events, you will be reimbursed for the individual study visits that were completed to date per the above reimbursement schedule. Travel accommodations and travel reimbursement may be provided in certain circumstances.

What happens if I am injured because I took part in this study?
If you believe that you are injured as a result of the research procedures being performed, please contact immediately the Principal Investigator or one of the co-investigators listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. It is possible that UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated. There is no plan for monetary compensation. You do not, however, waive any legal rights by signing this form. University of Pittsburgh researchers and their associates who provide services at UPMC recognize the importance of your voluntary participation in their research studies. These individuals and their staffs will make reasonable

efforts to minimize, control, and treat any injuries that may arise as a result of this research.

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.

VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns, or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that have occurred during my participation.

By signing this form, I consent to participate in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

CERTIFICATION of INFORMED CONSENT
I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise.

I further certify that no research component of this protocol was begun until after this consent form was signed.

Printed Name of Physician Obtaining Consent	Role in Research Study
Signature of Person Obtaining Consent	Date