Evaluation of Ivacaftor in Patients Using Ataluren for Nonsense Mutations

Study Protocol, Statistical Analysis Plan & Consent Form

NCT03256799

February 1, 2019

Steven M. Rowe, M.D., Principal Investigator
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Birmingham, AL 35294

PROTOCOL

Title:	An Open Label, Study to Investigate the Role of Ivacaftor for the Treatment of Cystic Fibrosis in Combination with Ataluren (PTC124) in Cystic Fibrosis Patients using Ataluren for Nonsense Mutations
Lead Investigators	Steven M. Rowe, MD MSPH 1819 University Blvd MCLM 768 Birmingham, AL 35249-0005 Telephone: 205-934-9640 Email: smrowe@uab.edu
Clinical Phase	NA

Study Plan

General Description: Cystic Fibrosis is a life threatening genetic disorder resulting from mutations found in the CF gene known as the cystic fibrosis transmembrane conductance regulator of CFTR. This defect prevents correct chloride absorption in and out of the cells. The purpose of this study is to explore the combination of ataluren and ivacaftor as a treatment for patients with a specific cystic fibrosis mutation. In about 10% of patients with CF, the defect in the gene is known as a stop mutation. This mutation truncates the CFTR protein production by introducing a premature stop in the messenger RNA (mRNA), this type of mutation is known as a stop mutation. Ataluren is a novel, oral drug that promotes this gene to work effectively and readthrough that premature "stop sign". It is hypothesized that ivacaftor may increase the efficacy of ataluren by activating a specific protein that may not be functioning properly.

Primary Objective:

1. Evaluate the change in lung function as measured by spirometry

Inclusion Criteria:

1. Evidence of signed and dated informed consent/assent document(s) indicating that the subject (and/or his parent/legal guardian) has been informed of all pertinent aspects of the trial.
2. Age ≥19 years
3. Body weight ≥16 kg
4. Diagnosis of cystic fibrosis and documentation of the presence of a nonsense mutations of the CFTR gene, as determined by historical genotyping
5. Ability to perform a valid, reproducible spirometry with demonstration of a forced expiratory volume in 1second (FEV_1) ≥30% of predicted for age, gender, and height.
6. If the subject is sexually active, willingness to abstain from sexual intercourse or employ a barrier or medical method of contraception during the study drug administration
7. Willingness and ability to comply with all study procedures and assessments.
8. Currently receiving ataluren for nonsense mutations through other clinical trial access.

Exclusion Criteria

1. Any change (initiation, change in type of drug, dose modification, schedule modification, interruption, discontinuation, or re-initiation) in a chronic treatment/prophylaxis regimen for CF or for CF-related conditions within 2 weeks prior to screening.
2. Evidence of pulmonary exacerbation or acute upper or lower respiratory tract infection (including viral illnesses) within 2 weeks prior to screening.
3. Ongoing immunosuppressive therapy (other than corticosteroids up to 10mg/d equivalent of prednisone)
4. Ongoing warfarin, phenytoin, or tolbutamide therapy.
5. History of solid organ or hematological transplantation.
6. A history of positive hepatitis B surface antigen test, hepatitis C antibody test, or human immunodeficiency
7. Major complications of lung disease (including massive hemoptysis, pneumothorax, or pleural effusion) within 4 weeks prior to screening.
8. Pregnancy or breast-feeding.

9. Current smoker or a smoking history of ≥10 pack-years (number of cigarette packs/day × number of years smoked).
10. Prior or ongoing medical condition (eg, renal failure, alcoholism, drug abuse, psychiatric condition), medical history, physical findings, ECG findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results.

Investigational Drug: Ivacaftor, 150 mg PO every 12 hrs (or matching placebo)

Schedule of Study Visits:

Visit 1 This visit will take approximately 4 hours. We will discuss the study with the participant and answer any questions. We will ask the participant to show agreement by signing the consent document on the appropriate lines. After signing the consent form the following procedures will be performed. During this visit about 6-8 tablespoons of blood will be collected.

- Medical History
- Vital Signs including O2 Saturation
- Concomitant Medication review
- Physical Exam
- Questionnaire
- Clinical Data Collection Including:
  - Safety Laboratory Assessments
  - Urinalysis
  - Serum Pregnancy Test for Females
  - Blood for characteristics of lung disease
  - Spirometry
  - Sweat Chloride Collection
  - NPD
  - EKG

Visit 2 (beginning a 2 week period in which the participant will take Ivacaftor. The Ivacaftor has previously been prescribed by the participants doctor and the participant will bring this drug with them , we will not be dispensing it): this visit will take approximately 3 hours. The following procedures will be performed.

- Concomitant Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam

- Vital Signs including O2 Saturation
- Questionnaire
- Clinical Data Collection Including:

Urine Pregnancy Test for Females
Spirometry
Sweat Chloride Collection
NPD
Safety Laboratory Assessments if clinically indicated per protocol
Urinalysis if clinically indicated per protocol
Blood for characteristics of lung disease
EKG

Visit 3(+/- 5 days, beginning a 2 week period of suspending ivacaftor) this visit will take approximately 2 hours. The following procedures will be performed. During this visit about 3-4 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire
- Clinical Data Collection Including:

Urine Pregnancy Test for Females
Spirometry
Blood for Safety Laboratory Assessments
Urinalysis
Blood for characteristics of lung disease
Sweat Chloride collection
EKG

Visit 4 (+/- 5 days beginning a 2 week of taking Ivacaftor) this visit will take approximately 2 hours. The following procedures will be performed.

- Concomitant Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire

Clinical Data Collection Including:

Urine Pregnancy Test for Females
Spirometry
Blood for Safety Laboratory Assessments
Urinalysis
Blood for characteristics of lung disease
Sweat Chloride collection
EKG

Visit 5 (+/- 5 days beginning a 2 week off period of suspending Ivacaftor): this visit will take approximately 2 hours. The following procedures will be performed. During this visit about 3-4 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire
- Clinical Data Collection Including:

  Urine Pregnancy Test for Females
  Spirometry
  Blood for Safety Laboratory Assessments
  Urinalysis
  Blood for Biomarker characteristics of lung disease
  Sweat Chloride collection
  EKG

Visit 6 Day 0 (+/- 5 days. Ivacaftor will be taken every day from this point forward): this visit will take approximately 3 hours. The following procedures will be performed.

- Concomitant Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire

Clinical Data Collection Including:

Urine Pregnancy Test for Females
Spirometry
Blood for Safety Laboratory Assessments
Urinalysis

Blood for Biomarker characteristics of lung disease
Sweat Chloride collection
NPD
EKG

Visit 7 (Day 30 +/- 5 days): this visit will take approximately 2 hours. The following procedures will be performed. During this visit about 6-8 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire
- Clinical Data Collection Including:

Urine Pregnancy Test for Females
Spirometry
Sweat Chloride
Blood for Safety Laboratory Assessments
Urinalysis
Blood for characterization of Lung Disease
NPD
EKG

Visit 8 (Day 90 +/- 5 days): this visit will take approximately 2 hours. The following procedures will be performed. During this visit about 6-8 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire
- Clinical Data Collection Including:

Urine Pregnancy Test for Females
Spirometry
Sweat Chloride
Blood for Safety Laboratory Assessments
Urinalysis
Blood for characterization of Lung Disease
EKG

Explanation of Study Procedures

Questionnaires:

The CFQ-R is a questionnaire that collects information about CF-related symptoms and quality of life. It is estimated that it will take about 15 minutes to complete the questionnaire. The participant will need to complete this questionnaire at each indicated visit.

Medical History:

Information about previous medical records and health will be obtained. This information will include previous health problems, tests, and treatments. The participant will be asked about your medical history before starting study treatment.

Physical Exam:

This exam will include the following: blood pressure, height, weight, heart rate, temperature, respiration rate, general appearance, general impression of your chest, heart, head, eyes, ears, nose, throat, neck, abdomen, extremities, skin, neurological and any other notes made by the health care provider.

Blood Draw:

About 6-8 tablespoons of blood will be taken from the participant for safety parameters, and lung biomarkers . An average of 2-3 tubes of blood will be collected for safety labs. The safety labs indicated in each visit (CBC/Diff and a GRENAL/LFT chemistry panel) include sodium, potassium, chloride, CO2, BUN, Glucose, Crdatinine, Albumin, ALk Phos, AST, Total Bili, Alt, Calcium, Total Protein, HDL, triglycerides, CK, CPK, phosphorus and Uric Acid.

Electrocardiogram (ECG)

ECGs will be performed to check the electrical activity of the heart. This test is painless and takes about 10 minutes.

Pregnancy Test:

Females who are pregnant or nursing a child cannot be in this study. If there is a physical possibility of being or getting pregnant, a serum pregnancy test followed by urine pregnancy tests will be given.

Spirometry:

This is a test that measures how well the participant can breathe. The participant will wear a nose clip and breathe out forcefully into a machine called a spirometer. This machine measures how much air the participant will blow out and how fast it comes out.

Nasal Potential Difference Test:
The Nasal Potential Difference test will require placement of a small needle under the skin of the arm a few inches above the wrist. A very thin piece of tubing will be placed into the nose about one inch. Amiloride, which can block salt uptake, will be infused into the nose through the thin tubing, as well as isoproterenol, albuterol and/or adenosine, and ATP (the body's natural energy source) which cause a greater difference in measurements between cystic fibrosis patients and normal subjects. Measurements using this same thin piece of tubing will be taken on the skin's surface of the arm and hand. The NPD solutions are prepared by Dr. Rowe's trained laboratory staff, in which they prepare the solutions according to the provided SOP. Li Ping Tang in Dr. Rowe's labatory will make the NPD solutions following the NPD SOP as published by the Therapeutics Development Network. Ms. Tang will be supervised by Dr. Rowe.

Sweat Chloride Test:
In the sweat test, a place on the arm is stimulated with electrodes to produce sweat. The sweat is caught in a collector disc placed on the skin. We will measure chemicals, such as salt, in the sweat. To collect the sweat, 2 probes will be attached to the skin in the arm for 5 minutes. A gel-like medicine called pilocarpine is put on the probes and causes the sweat glands to produce more sweat. The probes stay on for about 4 minutes, then are removed and replaced by a disc to collect sweat for about 30 minutes. The entire procedure will then be repeated on the other arm.

The schedule of visits is detailed below describing all visits to the clinic and the time needed to complete each visit. An average of 2-3 tubes of blood will be collected for safety labs. The participant will take the medicine for two weeks followed by a two week off period of not taking the drug. This will continue 56 days. After the 56 days the participant will take the twice a day by mouth for a 6 month period or 180 days followed by a follow up visit.

Biostatistics: The within-subject change in FEV1 will be the primary efficacy outcome measure. Based on the design, the primary analysis will be a descriptive analysis of within-subject changes in outcome measures from week 1 to 24 of CFTR function, with each of 3 replicates analyzed as within subject repeated measures. These data also will be used to test the null hypothesis of no change using the non-parametric Wilcoxon signed-rank test (due to small numbers). Change with washout (if conducted; this can be omitted for safety considerations) also will be informative. AE reporting will be conducted via listing tables and classified according to causality, per protocol. All statistical tests will be two-sided and will use α=0.05.

Consent Form

TITLE OF RESEARCH:	An Open Label, Study to Investigate the Role of Ivacaftor for the Treatment of Cystic Fibrosis in Combination with Ataluren (PTC124) in Cystic Fibrosis Patients Using Ataluren for Nonsense Mutations
UAB IRB PROTOCOL:	**F161208009**
INVESTIGATOR:	Steven M. Rowe, MD, MPH
SPONSOR:	UAB Department of Medicine Cystic Fibrosis Research Center

Purpose of the Research

You have been invited to take part in this research study because you have cystic fibrosis (CF) and have been prescribed Ivacaftor, a drug approved by the US Food and Drug Administration (FDA) in combination with receiving open label Atularen through and independent open label clinical trial at another center.

CF is a disease caused by a mutation (error) in the gene for a protein present on the cell surface (called CFTR "cystic fibrosis transmembrane conductance regulator"). In some people with CF, a specific mutation in the CFTR gene, called a "nonsense" mutation, causes the production of the CFTR protein to stop too early. As a result, the protein is too short to work properly.

This research study will test a proprietary new drug of PTC Therapeutics, Inc. ("PTC") called ataluren (also sometimes called PTC124), which is an experimental drug that is not yet available for sale and has not received approval from the FDA for use in CF in combination with commercially available Ivacaftor. Ataluren is an oral drug that targets the nonsense mutation. Studies in adults and children with CF caused by a nonsense mutation show that ataluren treatment may help the CFTR protein to work properly. These studies have shown that ataluren is usually well tolerated.

This is a pilot study since it is the first time the drug has been tested in combination with commercially available Ivacaftor. We are testing this combination to define side effects, learn how the combination is used in the body, and learn how it helps CF.

Explanation of Procedures

You will enter into the study will take the drug, Ivacaftor along with Atularen in which you are receiving through participating in an open label clinical trail at another center. You will asked to

come to the clinic for study visits 8 times across a 3-4 month period. One person will be enrolled in at UAB

Visit 1 (28 Day Screening Period): this visit will take approximately 4 hours. We will discuss the study with you and answer any questions. We will ask you to show agreement by signing the consent document on the appropriate lines. After signing the consent form the following procedures will be performed. During this visit about 6-8 table spoons of blood will be collected from a vein in your arm.

- Medical History including your past lung health, previous diagnosis, etc
- Vital Signs including O2 Saturation
- Prescribed Medication Review
- Physical Exam, the study doctor will listen to your heart, lungs, etc
- Questionnaire
- Clinical Data Collection Including:
  - Blood and urine for Safety Laboratory Assessments
  - Serum Pregnancy Test for Females
  - Blood for characteristics of lung disease
  - Spirometry
  - Sweat Chloride Collection
  - NPD
  - EKG

Visit 2 (Day 1): this visit will take approximately 3 hours. The following procedures will be performed.

- Prescribed Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire
- Clinical Data Collection Including:
  - Blood and urine Safety Laboratory Assessments if clinically indicated per protocol
  - Serum Pregnancy Test for Females
  - Blood for characteristics of lung disease
  - Spirometry
  - Sweat Chloride Collection
  - NPD
  - EKG

Visit 3 (+/-5 days) this visit will take approximately 2 hours. The following procedures will be performed. During this visit about 3-4 tablespoons of blood will be drawn.

- Prescribed Medication Collection

- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire
- Clinical Data Collection Including:
  - Urine Pregnancy Test for Females
  - Spirometry
  - Blood and urine for Safety Laboratory Assessments
  - Blood for characteristics of lung disease
  - Sweat Chloride collection
  - EKG

Visit 4 (+/- 5 days): this visit will take approximately 2 hours. The following procedures will be performed.

- Prescribed Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire
- Clinical Data Collection Including:
  - Urine Pregnancy Test for Females
  - Spirometry
  - Blood and urine for Safety Laboratory Assessments
  - Blood for characteristics of lung disease
  - Sweat Chloride collection
  - EKG

Visit 5 (+/- 5 days): this visit will take approximately 2 hours. The following procedures will be performed. During this visit about 3-4 tablespoons of blood will be drawn.

- Prescribed Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire
- Clinical Data Collection Including:
  - Urine Pregnancy Test for Females
  - Spirometry
  - Blood and urine for Safety Laboratory Assessments

Blood for Biomarker characteristics of lung disease
Sweat Chloride collection
EKG

Visit 6 Day 0 (+/- 5 days): this visit will take approximately 3 hours. The following procedures will be performed.

- Concomitant Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire
- Clinical Data Collection Including:
  Urine Pregnancy Test for Females
  Spirometry
  Blood and urine for Safety Laboratory Assessments
  Blood for Biomarker characteristics of lung disease
  Sweat Chloride collection
  NPD
  EKG

Visit 7 (Day 30 +/- 5 days): this visit will take approximately 2 hours. The following procedures will be performed. During this visit about 6-8 tablespoons of blood will be drawn.

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- Interval Medical History
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  Blood for characterization of Lung Disease
  NPD
  EKG

Visit 8 (Day 90 +/- 5 days): this visit will take approximately 2 hours. The following procedures will be performed. During this visit about 6-8 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Interval Medical History
- Physical Exam
- Vital Signs including O2 Saturation
- Questionnaire
- Clinical Data Collection Including:
  - Urine Pregnancy Test for Females
  - Spirometry
  - Sweat Chloride
  - Blood and urine for Safety Laboratory Assessments
  - Blood for characterization of Lung Disease
  - EKG

Questionnaires:
You will be asked questions about the history of your health and cystic fibrosis.

Physical Exam:
This exam will include the following: blood pressure, height, weight, heart rate, temperature, respiration rate, general appearance, general impression of your chest, heart, head, eyes, ears, nose, throat, neck, abdomen, extremities, skin, neurological and any other notes made by the health care provider.

Blood Draw:
About 6-8 tablespoons of blood will be taken from your arm for a Cystic Fibrosis genetics test, safety parameters, and pharmacokinetics analysis at each visit. A small IV will be placed in your arm on the days that require additional pharmacokinetics so that you will only be stuck with a needle one time.

Pregnancy Test:
Females who are pregnant or nursing a child cannot be in this study. If there is a physical possibility of being or getting pregnant, a serum pregnancy test followed by urine pregnancy tests will be given.

Spirometry:
This is a test that measures how well you breathe. You will wear a nose clip and breathe out forcefully into a machine called a spirometer. This machine measures how much air you blow out and how fast it comes out.

Sweat Chloride Test:
In the sweat test, a place on your arm is stimulated with electrodes to produce sweat. The sweat is caught in a collector disc placed on the skin. We will measure chemicals, such as salt, in your sweat. To collect the sweat, 2 probes will be attached to the skin in your arm for 5 minutes. A gel-like medicine called pilocarpine is put on the probes and causes the sweat glands to produce more sweat. The probes stay on for about 4 minutes, then are removed and replaced by a disc to

collect sweat for about 30 minutes. The entire procedure will then be repeated on the other arm.

NPD:
The Nasal Potential Difference test will require placement of a small needle under the skin of the arm a few inches above the wrist. A very thin piece of tubing, through which salt water and low chloride solution will be pumped, will be placed through the nostril and back into the nose about one inch. Amiloride, which can block salt uptake, will be infused into the nose through the thin tubing, as well as isoproterenol, albuterol and/or adenosine, and ATP (your body's natural energy source) which cause a greater difference in measurements between cystic fibrosis patients and normal subjects. Measurements using this same thin piece of tubing will be taken on the skin's surface of the arm and hand.

Electrocardiogram (ECG)

ECGs will be performed to check the electrical activity of your heart. This test is painless and takes about 10 minutes.

Risks and Discomforts

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Questionnaires:

There is a possible risk of loss of confidentiality in questionnaires is due to medical history not remaining private. This potential risk is guarded against by maintaining completed questionnaires in a locked filing system in a locked room at the Child Health Research Center and in password-protected computers located at the center.

Blood draw:
Drawing blood from your arm may cause pain, bruising, light-headedness, and, on rare occasions, infection.

Spirometry:
Some people may have some light-headedness or chest soreness from the hard blowing. The chest soreness usually goes away by itself. It can also be helped with non-prescription pain-relievers.

During this test, you will be given a drug called a bronchodilator (Albuterol) to open the airways. Side effects of Albuterol may include tremors (shakiness), chest tightness, dizziness, nervousness, cough, headaches, and sleeplessness. Serious allergic reactions that can be life threatening may occur.

Sweat Test:
The Macroduct System is a frequently used system in hospitals and clinics worldwide. This is considered to be a very safe painless procedure, but rare small burns have been reported at the site of the electrode even though the participant showed no discomfort during the test.

NPD:
Local irritation of the skin where the needle is placed and local infection at the site are possible but unlikely. Nasal irritation, tearing and sneezing may occur because of the tubing placement in the nose. Nose bleeding is possible, but very unlikely.

Infusion of amiloride, isoproterenol and ATP into the nose has risks that we are aware of or that have been reported from patients after 20 years of performing this test. However, isoproterenol is a drug known as a beta-agonist, which means it affects the muscles around the airway and could cause you to experience an increase in heart rate.

Information for Women of Childbearing Potential and/or Men Capable of Fathering a Child

The effects of ataluren on being able to have children have not been extensively studied, but in the research animals treated to date, no evidence of abnormalities in the testes or ovaries was observed. It is important that you abstain from sexual intercourse or use appropriate birth control measures while taking ataluren and 60 days after the last dose of ataluren. You should discuss appropriate birth control with your doctor. If this is relevant to you, you will need to discuss the form of birth control used and this will be recorded in your chart. If you become pregnant while taking ataluren, consult your doctor immediately

Benefits

You may not benefit directly from taking part in this study. However, this study may help us better understand how to treat people with bronchiectasis and chronic bronchitis in the future.

Alternatives

One alternative is to not participate in this study. There are other drugs that may be used to treat bronchiectasis and chronic bronchitis. Your study doctor will review your medication list and if there is a medication available for your condition that you may benefit from, your study doctor will discuss this with you. If you have bronchiectasis or chronic bronchitis, this study will not give you medical care for your condition. If you have flare up, get medical care from your regular doctor.

Confidentiality

The information gathered during this study will be kept confidential to the extent permitted by law. However, the study doctors, the U.S. Food and Drug Administration (FDA) and UAB's Institutional Review Board (IRB) will be able to inspect your medical records and have access to confidential information that identifies you by name. Your records could also be reviewed by the Office for Human Research Protections (OHRP). For safety purposes we will report ~~and~~ any health related safety concerns that occur during the study to your CF doctor at Long Beach Memorial Hospital and/or your clinical trial study team at the Children's Hospital of Colorado.

Information relating to this study, including your name, medical record number, date of birth, and social security number maybe shared with the billing offices of UAB and UAB Health System affiliated entities so that claims may be appropriately submitted to the study sponsor or

to your insurance company for clinical services and procedures provided to you during the course of the study.

The results of this study may be published for scientific purposes. However, your identity will not be given out. Research records will be held in locked cabinets or secure storage rooms at the Child Health Research Unit when staff is not in attendance.

Monitors, auditors, the Institutional Review Board for Human Use, and regulatory authorities will be granted direct access to your original medical records for verification of trial procedures and/or data without violating confidentiality.

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

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution. However, you should return to see the study doctor for safety reasons so you can be taken off the study drug and referred for follow-up care.

You may be removed from the study without your consent if the doctor ends the study, if the study doctor decides it is not in the best interest of your health, or if you are not following the study rules.

Cost of Participation

All exams, and medical care related to this study will be provided to you at no cost during the study period. Travel cost to and from study visits will be reimbursed. The cost of the medication will not be provided by the study.

The costs of your standard medical care will be billed to you and/or your insurance company in the usual manner. If you are on Medicare Advantage (Medicare Managed care plan), you should contact someone at your plan before you start a clinical trial. They can provide more information about additional cost you could incur from participating in clinical trials.

Payment for Participation in Research

You will be paid as detailed below for each study visit that you complete. Payment will be made after each completed visit. Payments will be made by check and sent to you in the mail. If you do not finish the entire study, you will be paid at the time you decide to stop taking part in the study. If you complete the entire study, you will receive a total of $600.00

Visit 1	$120.00
Visit 2	$ 90.00
Visit 3	$60.00
Visit 4	$60.00
Visit 5	$60.00
Visit 6	$90.00
Visit 7	$60.00
Visit 8	$60.00

Additional reimbursement is outlined below (you must provide original receipts for all reimbursable expenses):

- You will be reimbursed for parking or transportation to the study site on the days of your visits, up to $40.00 per day. You will also be reimbursed for mileage and lodging. Mileage will be reimbursed to you at the Internal Revenue Service (IRS) rate. You will be responsible for your own airline ticket, but the cost will be reimbursed should you travel by plane.
- You may get reimbursed for reasonable meal costs.

You are responsible for paying any state, federal, social security or other taxes on the payments you receive. You will receive a form 1099 in January of the year following your participation in this study. This form is also sent tot the IRB to report any money paid to you. No taxes are kept from your check.

If you terminate the study early, you will receive an amount based on the visits that you have completed. If you miss any of the visits, you will not be compensated for those visits. How and when you will be paid will be explained to you by the study staff.

Payment for Research-Related Injuries

UAB has not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

You will be told by your doctor or the study staff if new information becomes available that might affect your choice to stay in the study.

Questions

If you have any questions, concerns, or complaints about the research or a research- related injury including available treatments, you may contact Dr. Steven Rowe. He will be glad to answer any of your questions. Dr. Rowe's phone number is 205-975-9776. He may also be reached after hours by paging them at 205-934-3411.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Legal Rights

You are not waiving any of your legal rights by signing this informed consent document.

Signatures

Your signature below indicates you agree to participate in this study. You will receive a copy of this signed consent form.

Signature of Participant	Date
Signature of Principal Investigator or person obtaining Consent	Date

University of Alabama at Birmingham
AUTHORIZATION FOR USE/DISCLOSURE OF PROTECTED HEALTH INFORMATION (PHI) FOR RESEARCH

Participant Name: _____
Research Protocol An Open Label, Study to Investigate the Role of Ivacaftor for the Treatment of Cystic Fibrosis in Combination with Atularen (PTC124) in Cystic fFbrosis Patients using Atularen for Nonsense Mutations.

UAB IRB Protocol Number: F161208009
Principal Investigator: Steven M. Rowe, MD
Sponsor: UAB Department of Medicine

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your protected health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your protected health information may be used for the research.

Why do the researchers want my protected health information? The researchers want to use your protected health information as part of the research protocol listed above and as described to you in the informed consent.

What protected health information do the researchers want to use? All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills, and any other information related to or collected for use in the research protocol, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes.

Who will disclose, use and/or receive my protected health information? All Individuals/entities listed in the informed consent documents, including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees and agents, including any CRO; and any outside regulatory agencies, such as the Food and Drug Administration, providing oversight or performing other legal and/or regulatory functions for which access to participant information is required.

How will my protected health information be protected once it is given to others? Your protected health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel this Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the research protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the protected health information that was provided before you cancelled your authorization.

Can I see my protected health information? You have a right to request to see your protected health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date: _____

or participant's legally authorized representative: _____ Date: _____

Printed Name of participant's representative: _____Relationship to the participant: