PTC Study to Evaluate Ataluren in Combination with Ivacaftor

Study Protocol & Statistical Analysis Plan

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Steven M. Rowe, M.D., Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

PROTOCOL

Title:	An Open-Label N of 1 Study to Evaluate the Safety and Efficacy of Long-Term Treatment with Ivacaftor in Combination with Ataluren (PTC124®) in Subjects with Nonsense Mutation Cystic Fibrosis
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

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
2. ~~Evaluate change in health related quality of life as assessed by the cystic fibrosis questionnaire revised.~~

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 ≥6 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% and ≤90% 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 being administered ivacaftor, either alone (Kalydeco) or in combination with lumacaftor (Orkambi)

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. Ongoing participation in any other therapeutic clinical trial.
3. Evidence of pulmonary exacerbation or acute upper or lower respiratory tract infection (including viral illnesses) within 2 weeks prior to screening.
4. Ongoing inhaled tobramycin therapy.
5. Ongoing immunosuppressive therapy (other than corticosteroids up to 10mg/d equivalent of prednisone)
6. Ongoing warfarin, phenytoin, or tolbutamide therapy.
7. History of solid organ or hematological transplantation.
8. A history of positive hepatitis B surface antigen test, hepatitis C antibody test, or human immunodeficiency
9. Major complications of lung disease (including massive hemoptysis, pneumothorax, or pleural effusion) within 4 weeks prior to screening.
10. Pregnancy or breast-feeding.
11. Current smoker or a smoking history of ≥10 pack-years (number of cigarette packs/day × number of years smoked).
12. 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

Schedule of Study Visits:

Visit 1 (4 Week 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 tablespoons of blood will be collected.

- Medical History
- Vital Signs including O2 Saturation
- Concomitant Medication review
- Physical Exam including height and weight
- Questionnaire
- Clinical Data Collection Including:
  - Safety Laboratory Assessments
  - Serum Pregnancy Test for Females
  - Urinalysis
  - EKG
  - Spirometry
  - Sweat Chloride Collection

Visit 2 (Baseline): this visit will take approximately 4 hours. The following procedures will be performed. During this visit about 8 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Physical Exam including height and weight
- Vital Signs including O2 Saturation
- Questionnaires
- Clinical Data Collection Including:
  - Safety Laboratory Assessments
  - Blood for lung biomarkers
  - Serum Pregnancy Test for Females
  - Urinalysis
  - Spirometry
  - Sweat Chloride Collection
  - Nasal potential Difference Measurement
- Ataluren Administration and dispensing

Week 4 (Safety Assessment): this visit will take approximately 4 hours. The following procedures will be performed. During this visit about 6 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Physical Exam including height and weight
- Vital Signs including O2 Saturation
- Clinical Data Collection Including:
  - Safety Laboratory Assessments
  - Serum Pregnancy Test for Females
  - Urinalysis
  - Spirometry

Sweat Chloride Collection
Nasal potential Difference Measurement
Queastionaires

Week 12 (+/- 7 days): this visit will take approximately 4 hours. The following procedures will be performed. During this visit about 6 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Physical Exam including height and weight
- Vital Signs including O2 Saturation
- Questionnaires
- Clinical Data Collection Including:
  - Safety Laboratory Assessments
  - Blood for lung biomarkers
  - Serum Pregnancy Test for Females
  - Urinalysis
  - Spirometry
  - Sweat Chloride Collection
  - Nasal potential Difference Measurement
- Ataluren Administration and Dispensing

Week 24 (+/- 7 days): this visit will take approximately 4 hours. The following procedures will be performed. During this visit about 6 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Physical Exam including height and weight
- Vital Signs including O2 Saturation
- Questionnaires
- Clinical Data Collection Including:
  - Safety Laboratory Assessments
  - Blood for lung biomarkers
  - Serum Pregnancy Test for Females
  - Urinalysis
  - Spirometry
  - Sweat Chloride Collection
  - Nasal potential Difference Measurement
- Ataluren Administration and Dispensing

Week 36 and Week 48 (+/- 7 days): this visit will take approximately 4 hours. The following procedures will be performed. During each visit about 8 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Physical Exam including height and weight
- Vital Signs including O2 Saturation
- Questionnaires

- Clinical Data Collection Including:
    - Safety Laboratory Assessments
    - Blood for lung biomarkers
    - Serum Pregnancy Test for Females
    - Urinalysis
    - ECG
    - Spirometry
- Drug Administration and Dispensing

Explanation of Study Procedures

Visit 1 (4 Week 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 tablespoons of blood will be collected.

- Medical History
- Vital Signs including O2 Saturation
- Concomitant Medication review
- Physical Exam including height and weight
- Questionnaire
- Clinical Data Collection Including:
    - Safety Laboratory Assessments
    - Serum Pregnancy Test for Females
    - Urinalysis
    - EKG
    - Spirometry
    - Sweat Chloride Collection

Visit 2 (Baseline): this visit will take approximately 4 hours. The following procedures will be performed. During this visit about 8 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Physical Exam including height and weight
- Vital Signs including O2 Saturation
- Questionnaires
- Clinical Data Collection Including:
    - Safety Laboratory Assessments
    - Blood for lung biomarkers
    - Serum Pregnancy Test for Females
    - Urinalysis
    - Spirometry
    - Sweat Chloride Collection
    - Nasal potential Difference Measurement
- Ataluren Administration and dispensing

Week 4 (Safety Assessment): this visit will take approximately 4 hours. The following procedures will be performed. During this visit about 6 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Physical Exam including height and weight
- Vital Signs including O2 Saturation
- Clinical Data Collection Including:
  - Safety Laboratory Assessments
  - Serum Pregnancy Test for Females
  - Urinalysis
  - Spirometry
  - Sweat Chloride Collection
  - Nasal potential Difference Measurement
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Week 12 (+/- 7 days): this visit will take approximately 4 hours. The following procedures will be performed. During this visit about 6 tablespoons of blood will be drawn.

- Concomitant Medication Collection
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- Physical Exam including height and weight
- Vital Signs including O2 Saturation
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  - Sweat Chloride Collection
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- Ataluren Administration and Dispensing

Week 24 (+/- 7 days): this visit will take approximately 4 hours. The following procedures will be performed. During this visit about 6 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Physical Exam including height and weight
- Vital Signs including O2 Saturation
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- Clinical Data Collection Including:
  - Safety Laboratory Assessments
  - Blood for lung biomarkers
  - Serum Pregnancy Test for Females
  - Urinalysis

Spirometry
Sweat Chloride Collection
Nasal potential Difference Measurement

- Ataluren Administration and Dispensing

Week 36 and Week 48 (+/- 7 days): this visit will take approximately 4 hours. The following procedures will be performed. During each visit about 8 tablespoons of blood will be drawn.

- Concomitant Medication Collection
- Adverse Event Assessment
- Physical Exam including height and weight
- Vital Signs including O2 Saturation
- Questionnaires
- Clinical Data Collection Including:
  - Safety Laboratory Assessments
  - Blood for lung biomarkers
  - Serum Pregnancy Test for Females
  - Urinalysis
  - ECG
  - Spirometry
- Drug Administration and Dispensing

You will be evaluated at Week 48 visits to see if this treatment is working for you and if you need to continue receiving it.

4- Week post treatment follow up (+/- 7 days):

- Physical Exam including height and weight
- Adverse Event Assessment

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. You will need to complete this questionnaire at each indicated visit.

Medical History:

Information about your previous medical records and health will be obtained. This information will include previous health problems, tests, and treatments. You 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 your arm to monitor your body's response to the study drug, and lung biomarkers.

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.

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, 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.

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.

Biostatistics: The within-subject change in FEV_1 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 $\alpha=0.05$.