Clinical Study Protocol

A Randomized, Double-blind, Phase 2, Placebo Controlled Study to Determine the Safety and Efficacy of Ivacaftor (VX-770) for the Treatment of Chronic Obstructive Pulmonary Disease (The Topic Trial)

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Principal Investigators: Steven M. Rowe, MD, MSPH

Mark T Dransfield, MD

PROTOCOL SYNOPSIS

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Lead Investigators: Steven M. Rowe, MD MSPH
1819 University Blvd
MCLM 768
Birmingham, AL 35249-0005
Telephone: 205-934-9640
Email: smrowe@uab.edu

Mark T Dransfield MD
422 THT
1900 University Blvd
Birmingham AL 35294-0005
Tel 205-934-5555
Email: mdrans99@uab.edu

Clinical Phase Phase 2

Study Synopsis

General Description: The study is a Phase 2 Study to establish the safety and efficacy of the CFTR potentiator ivacaftor in patients with chronic obstructive pulmonary disease (COPD), chronic bronchitis, and acquired CFTR dysfunction as detected by sweat chloride analysis. The design is a pilot, randomized (3:1, active:placebo), double-blind, placebo-controlled study to determine the safety and efficacy of ivacaftor (VX-770). Approximately 40 subjects with COPD will be randomized (Figure 1).

Primary Objective:

1. Evaluate the safety of ivacaftor treatment in patients with COPD and chronic bronchitis
2. Evaluate the pharmacokinetics of ivacaftor in patients with COPD and chronic bronchitis

Secondary Objectives:

1. Measure the pharmacodynamics of ivacaftor on CFTR activity (Sweat Chloride, MCC) in COPD patients with chronic bronchitis
2. Measure the effect of ivacaftor treatment on clinical outcomes (spirometry, patient symptoms, 6 minute walk test) in COPD patients with chronic bronchitis

Primary Endpoint:

1. Safety as determined by adverse events, clinical laboratory values (serum chemistry, hematology, coagulation studies), standard digital ECGs, vital signs, and physical examinations

2. Pharmacokinetic parameters of ivacaftor in COPD subjects (8 hr day 1 PK and PK peak and trough concentrations on days 28, and 84. A random PK will be collected on day 56)

Secondary Endpoints:

1. Change in respiratory and peripheral CFTR activity as detected by sweat chloride and MCC respectively
2. Indicators of respiratory function and COPD health (Change in FEV_1% as detected by spirometry, secondary spirometry values (FVC%, FEV_1/FVC), 6 minute walk test
3. Patient reported outcomes (San Diego Shortness of Breath Queastioniare [1], the Breathlessness, Cough, and Sputum Scale (BCSS)[2,3] the Cough and Sputum Assessment Questionnaire (CASA-Q)[4,5] and the COPD assessment test (CAT) the St. George Respiratory Questionnaire (SGRQ), and the EXACT-PRO).

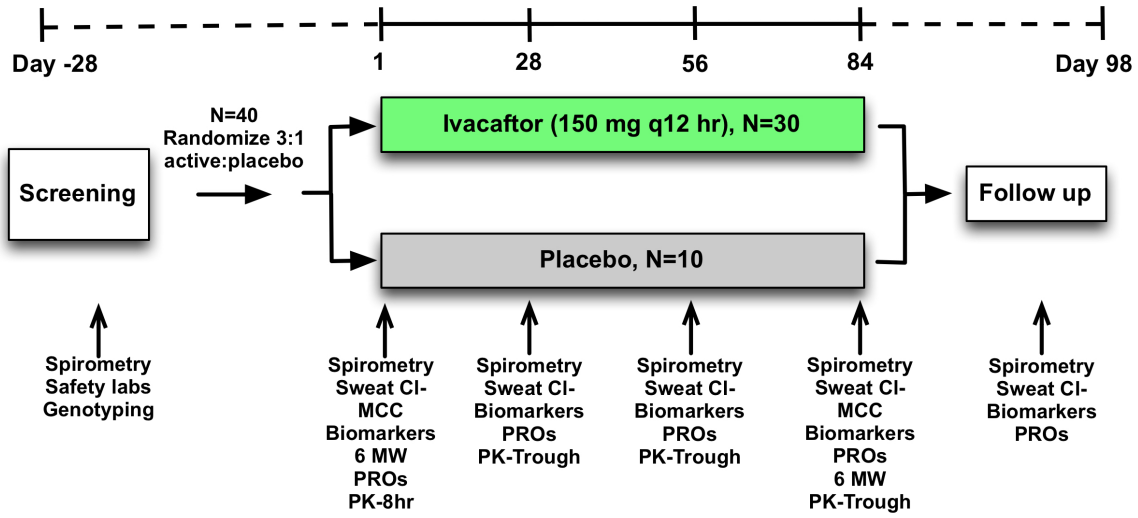

Fig. 1. Trial Schematic.

Study Population: The study is a Phase 2 Study to establish the safety and efficacy of the CFTR potentiator ivacaftor in patients with chronic obstructive pulmonary disease (COPD), chronic bronchitis, and acquired CFTR dysfunction as detected by sweat chloride analysis. The design is a pilot, randomized (3:1, active:placebo), double-blind, placebo-controlled study to determine the safety and efficacy of ivacaftor (VX-770) in approximately 40 subjects with COPD (Figure 1).

Inclusion Criteria:

- Male or Female age 40-80
- A Clinical diagnosis of COPD as defined by GOLD
- At Least a 10 pack year smoking history
- Exhibit symptoms of chronic bronchitis as defined by the Medical Research Council
- FEV1% predicted ≥ 35% and ≤70% Post Bronchodilator
- Clinically stable in the last 4 weeks with no evidence of COPD exacerbation
- Weight of 40 kg-120 kg
- Willingness to use at least one form of acceptable birth control including abstinence, condom with spermicide, or hormonal contraceptives from time of signing ICF through study follow up visit
- Willing to monitor blood glucose if known history of diabetes mellitus requiring insulin or medical therapy
- Element of CFTR Dysfunction, as defined by Sweat Chloride > 30 mEq/L)

Exclusion Criteria

- Current Diagnosis of Asthma
- Known Diagnosis of Cystic Fibrosis
- Daytime use of Oxygen Therapy
- Documented history of drug abuse within the last year
- Subjects should not have a pulmonary exacerbation or changes in therapy for pulmonary disease within 28 days before receiving the first dose of study drug.
- Cirrhosis or elevated liver transaminases > 3X ULN
- GFR < 50 estimated by Cockroft-Gault
- Any illness or abnormal lab finding that, in the opinion of the investigator might confound the results of the study or pose an additional risk in administering study drug to the subject.
- Pregnant or Breastfeeding
- Subjects taking moderate or strong inhibitors or inducers of CYP3A4, including certain herbal medications and grapefruit juice. (Excluded medications and foods including the drugs and foods listed in the IRB HSP application.)
- Uncontrolled Diabetes
- Recent (e.g 1year) arterial thrombotic events (peripheral arterial disease, thrombotic stroke)
- Clinically significant arrhythmias requiring anti-arrhythmic agent(s) or conduction abnormalities that in the opinion of the investigator that affect patient safety such as the abnormalities listed below (patients with stable coronary artery disease are eligible)
    - Angina symptoms
    - History of MI
    - Revascularization procedure in the last year prior to screening
    - Clinically significant congestive heart failure (known LVEF <= 45%, cor pulmonale, diastolic heart failure, etc)

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

Schedule of Study Visits: The first dose of ivacaftor will be administered at the Day 1 visit. Ivacaftor will be taken twice daily, with 12 hours between each dose from day 1 through the morning dose of day 84. Study visits will occur at Screening (-28 to -1 days), Day 1, Day 28 (± 7), Day 56 (± 7), Day 84 (± 7), and Follow-up (14 ± 7 days after the last dose of ivacaftor).

Outcome Measures:

Safety assessments: Assessments include tests used in clinical studies to monitor the safety of ivacaftor in CF, including adverse event reporting, clinical laboratory testing, physical exams, and spirometry. The PI will review all SAEs in real time and conduct appropriate reporting to the FDA and IRB, as required, within 24hrs at maximum. Interim safety analysis will include review of AEs and safety labs by the PI and will be conducted after completion of approximately 10, 20, and 30 subjects. Ocular exam will be performed at baseline unless known history of cataracts.

PK: PK/PD analyses between ivacaftor levels and CFTR activity in the sweat gland will reveal new insights into the degree that wild-type CFTR can be activated. Calculated PK parameters include: area-under-the-curve (AUC_{12}), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), oral clearance (CL/F), terminal apparent distribution volume (V_z/F), and elimination half-life ($t_{1/2}$). Subsequently, intensive data and sparse plasma concentrations will be combined to create a population PK model to assess covariates, such as age, weight, sex, smoking status, etc. as previously conducted by our group for NIH and industry sponsored studies.

MCC: Clearance of Tc^{99} sulfur colloid is a measure of MCC of the lungs, and is calculated by a standard protocol developed by the Cystic Fibrosis Therapeutics Development Network and in use at our center. The method provides a robust measure of MCC, and has been sensitive to the effects of inhaled pharmacologic agents in CF and COPD including improvements of an unprecedentedly large magnitude in CF patients with the G551D-CFTR mutation treated with ivacaftor measured in a multicenter study. The technique allows estimates of MCC in both the small and large airway compartments.

6 Minute Walk Test: this practical test is commonly used in the assessment of patients with COPD. The 6MWT will be used as a measure of functional status of patients and as a measurement of changes in functional capacity due to the intervention.

CFTR activity in the periphery: Sweat chloride abnormality is correlated with COPD severity and symptoms, and is a highly sensitive outcome measure for CFTR-directed therapeutics. We have shown sweat chloride is sensitive to the presence of cigarette smoking and COPD, and the test has been successfully used as an endpoint in multiple CF trials, including studies to detect the efficacy of ivacaftor therapy.

Spirometry: Spirometry is a standard outcome measure in COPD and a major indicator of efficacy and safety in COPD clinical trials. Post-bronchodilator spirometry will be performed by ATS criteria and percent predicted FEV_1, FVC, and FEF25-75 will be calculated based on Hankinson prediction equations.

Patient Reported Outcomes: Questionnaires designed to detect the burden of cough and sputum symptoms as well as overall health status will be used to monitor clinical outcome before and after study drug. This includes the San Diego Shortness of Breath Questionnaire, the Breathlessness, Cough, and Sputum Scale (BCSS), the Cough and Sputum Assessment

Questionnaire (CASA-Q), the COPD assessment test (CAT), the St. George Respiratory Questionnaire (SGRQ), and the EXACT-PRO (the latter which will be useful to track pulmonary exacerbations).

Biomarker collection: Serum and plasma will be stored with and without protease inhibitors to allow exploratory biomarker studies to be conducted upon conclusion of the study. We anticipate testing for free acrolein since we hypothesize elevated acrolein levels may be associated with CFTR dysfunction. Acrolein will be estimated using our LC/MS/MS protocol.

CFTR Genotyping: CFTR will be sequenced by commercially available procedures as performed by the John Hopkins University Genetics Laboratory. Analysis will be stratified by the presence and absence of CFTR mutations. Since we have a large pool of previously tested COPD patients, we will target our enrollment to those without known CFTR mutations.

Statistical plan: Safety analysis will be conducted by descriptive statistics. Pharmacodynamic analysis will be evaluated within group for the ivacaftor treatment group for changes between screening/day 1 and day 84, in comparison to between group changes in the placebo treatment group. The primary outcome measure is safety; the co-primary efficacy outcome measures are MCC (AUC_{60}) and change in FEV1 (% predicted). Power analysis for measurements of MCC, CFTR function measured by sweat chloride, and FEV1 (% predicted) are provided in below. Secondary outcome measures including change in other measures of spirometry, PROs, exacerbation frequency, and 6MWD will also be analyzed. The off drug effect will be measured by using data from the follow-up visit to assess the change from on drug to washout at the follow up visit.

Role of Vertex IIS:

- Vertex Pharmaceuticals will provide ivacaftor and matching placebo to randomize up to approximately 50 subjects to achieve approximately 40 completers (35 active patients and 15 placebo treated patients for 84 days, assuming 5 dropouts in the ivacaftor group and 5 dropouts in the placebo group). This will provide sufficient compound for lost samples, if they occur.
- To facilitate PK studies planned at UAB, we also request pure ivacaftor powder and stable isotope labeled internal standard for assay development and validation. We request 2-5 mg of each.

1.0 Rationale:

Like CF, COPD is characterized by small airway mucus obstruction that is associated with accelerated loss of lung function and mortality. Our preliminary data indicate that cigarette smoke exerts deleterious effects on airway epithelial function including the reduction of CFTR activity, enhanced mucus expression, and a pronounced reduction in mucociliary transport (MCT)[6] Preliminary data also indicate that approximately 50% of patients with COPD have reduced CFTR activity, as detected in the upper airways[6,7] lower airways[7] and sweat glands[8]. . Furthermore, CFTR dysfunction is independently associated with chronic bronchitis, can persist despite smoking cessation, and can be reversed by the CFTR potentiator ivacaftor (VX-770) in vitro by activating wild-type CFTR, resulting in a robust increase in MCT[6]. Combined with unprecedented clinical improvement via augmented mucociliary clearance in CF patients with a responsive CFTR mutation treated with ivacaftor[9,10], these data indicate that CFTR represents a viable therapeutic target to address mucus stasis in a large subset of COPD patients (potentially representing over 4 million patients in the U.S. alone)[11]. *This project will investigate the hypothesis that ivacaftor can augment CFTR activity in individuals with COPD who exhibit chronic bronchitis, resulting in meaningful improvements in epithelial function and respiratory health*. Our initial pilot study in patients with COPD and chronic bronchitis demonstrated that ivacaftor was safe, demonstrated stable pharmacokinetics, and exhibited a trend towards efficacy in measures of PROs and sweat chloride.[12] The current trial will test the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in a larger number of COPD patients with chronic bronchitis and for a longer treatment period, evaluating the potential of CFTR potentiator therapy to address acquired CFTR dysfunction in this population and set the stage for larger and longer-term trials in the future. Based on an IND already in place in the Rowe laboratory, an IRB familiar with the proposed study, an experienced clinical investigation team with expertise in all of the endpoints proposed, and a well characterized COPD population prioritized for the presence chronic bronchitis, CFTR dysfunction, and the absence of congenital CFTR mutations, we are poised to deliver the trial.

2.0 Known safety experience with ivacaftor

Up to now, more than 25 studies of ivacaftor have been completed or are ongoing in more than 400 healthy adult subjects and 680 adult and pediatric subjects with CF.

In completed studies in subjects with CF the most common adverse events reported in subjects receiving ivacaftor were Cough (34%) CF Pulmonary exacerbation (29%) Headache (17%) Upper respiratory tract infection (16%), Nasal congestion (16%), Oropharyngeal pain (mouth and throat pain) (15%), Pyrexia (fever) (11%), Productive cough (10%), Nausea (10%), Rash (10%), and Dizziness (5%).

A few subjects with CF receiving ivacaftor as well as placebo have shown signs of liver injury. In these cases, the liver injury was noticed as abnormalities in blood tests which were monitored as part of the study. The very high levels of these tests, called ALT and AST, led to stopping of Study Drug, although in some cases this was placebo. The levels of ALT and AST improved after Study Drug was stopped. Very severe cases of liver injury can become permanent or be life-threatening, although this has not been observed with ivacaftor. Overall, the data does not support an association between ivacaftor and ALT and AST elevations.

In programs that were designed to provide access to ivacaftor for subjects with CF and life-threatening severe lung disease, four deaths were reported. In a long term, open-label

extension study of ivacaftor in subjects with CF, two deaths were reported. The deaths were not considered related to ivacaftor.

The Study Drug may contain a very small amount of lactose, a sugar found in dairy products. The amount of lactose in a single pill is roughly the same as the amount in one teaspoon of milk. This amount of lactose is unlikely to cause symptoms in people who have lactose-intolerance.

3.0 Reproductive Risk related to ivacaftor:

The effects of ivacaftor on the reproductive system (sperm, eggs) or the unborn child are not known and may be hazardous. Birth defects, including physical deformities, mental retardation, and other problems, as well as premature birth are known risks of some drugs. For this reason, people taking ivacaftor should not become pregnant or father a child (or donate sperm). Women should not breastfeed a baby while in this study.

3.1 Possible Risks of Ivacaftor Based on Animal Studies:

In a study in which ivacaftor was given to newborn rats, cataracts (cloudiness of the lens of the eye) were seen. No cataracts were seen in studies of older animals (rats and dogs) dosed with ivacaftor for longer periods of time. No cataracts associated with ivacaftor use have been reported in humans in any ivacaftor studies to date. The significance of this finding to humans is not known. It is presently thought to only be a concern for very young individuals taking ivacaftor.

4.0 STUDY DESIGN

The study is a Phase 2 Study to establish the safety and efficacy of the CFTR potentiator ivacaftor in patients with chronic obstructive pulmonary disease (COPD), chronic bronchitis, and acquired CFTR dysfunction as detected by sweat chloride analysis. The design is a pilot, randomized (3:1, active:placebo), double-blind, placebo-controlled study to determine the safety and efficacy of ivacaftor (VX-770) in approximately 40 subjects with COPD.

Enrollment is planned at our single center, The University of Alabama at Birmingham. Patients will be randomized 3:1 to active drug (n=30) and placebo (10) to achieve the enrollment goal.

- A sufficient number of subjects will be screened to randomize up to 50 subjects to achieve 40 completed subjects to receive either ivacaftor 150 mg BID (n=30) or placebo (n=10) for 84 days.

- The schedule of assessments is shown in Table 1. The protocol design is shown in Figure 1.

- Ivacaftor and matching placebo will be orally administered as capsules according to the following guidelines:

    - Between study visit Day 1 and study visit Day 84, subjects will take 1 dose of study drug each day in the morning, beginning any time between 08:00 h (8:00 AM) and 12:00 h (12:00 PM). Whenever possible, subjects should take the study drug at the same time each day.

- On the study visit days when PK samples are collected (study visit Days 1, 28, 56, and 84), the study drug is to be taken by the subject while he/she is at the study site

- For visits after the Day 1 visit, subjects will be instructed to bring all remaining study drug materials to the site; study drug will be dispensed at each visit.

- Ivacaftor will be prepared and dispensed by an unblinded pharmacist.

- Subjects will be instructed to continue their standard COPD medication regimen.

Table 1. Schedule of Assessments [a]8 hr PK (pre, 1, 2, 4, 8, hr samples). [b] peak and trough PK only, [c]random PK, [d]only if indicated.

Assessment	Screen (Day -28 to -1) Visit 1	Day 1 Visit 2	Day 28 (± 2) Visit 3	Day 56 (± 2) Visit 4	Day 84 (± 2) Visit 5	Follow Up (Day 98 ± 2) Visit 6
Informed Consent	X					
Medical History & Concomitant Medications	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X
Safety Labs	X		X	X	X	X[d]
CFTR Genotyping	X					
Urine Pregnancy Test		X	X	X	X	X
Serum Pregnancy Test	X					
Blood Biomarker Collection		X	X	X	X	X
Spirometry	X	X	X	X	X	X
Sweat Chloride	X	X	X	X	X	X
MCC	X				X	
Patient report outcome questionnaires		X	X	X	X	X
Pharmacokinetics		X[a]	X[b]	X[c]	X[b]	X
Drug Administration		X	X	X		
Drug Dispensing & Drug Return		X	X	X		
Ocular exam	X					
6 minute Walk test		X			X	

4.1 Safety Assessments:

All other blood samples for laboratory assessments will be collected at the times specified in the table. All blood samples will be collected while subjects are in a seated or supine position and will be analyzed at the UAB Outreach Laboratory (a CLIA and Clinical Research Certified Laboratory).

The clinical laboratory test panels will include the following:

Hematology:

- Hemoglobin
- Hematocrit

- Red blood cell (RBC) count
- Platelet count
- White blood cell (WBC) count
- Differential (absolute and percent)
    - Eosinophils
    - Basophils
    - Neutrophils
    - Lymphocytes
    - Monocytes

Serum Chemistry:

- Glucose
- Blood urea nitrogen (BUN)
- Creatinine
- Sodium
- Potassium
- Calcium
- Inorganic phosphate
- Total bilirubin
- Alkaline phosphatase
- Serum aspartate transaminase (AST)
- Serum alanine transaminase (ALT)
- Lactate dehydrogenase (LDH)
- Gamma-glutamyl transpeptidase (GGT)
- Total protein
- Albumin
- Indirect bilirubin
- Hemoglobin A1c
- Amylase
- Lipase

Urine Pregnancy test (for females only)

Coagulation studies:

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- PT International Normalized Ratio (PT INR)

4.2 Other Assessments:

CFTR genotyping (for eligibility evaluation). Commercially available CFTR genotype analysis that includes 49 mutations including the 23 recommended by the ACGME and reflex testing for the intron 7 polythymidine sequence (e.g. 5T variant analysis). Depending on results and funding, we may also perform CFTR sequencing to evaluate for less common CFTR variants.

Phamacokinetic levels of ivacaftor: Serum ivacaftor levels will be measured by gas chromotagraphy/MS/MS on human serum, using a protocol established at UAB. Evaluation will be conducted at the times listed in Table 4-1. PK levels will be evaluated at the planned interim analysis (see below) and upon completion of the study.

Ocular exam: Ocular exam to assess for the presence of cataracts will be performed during screening window for patients without a known prior history of cataracts or an ocular exam within the last year prior to screening.

Serum biomarker collection

Routine biomarker collection facilitated by the UAB Pulmonary Biorepository will be held for long-term storage for future analysis:

- Buffy coat
- Plasma
- Serum

5.0 SELECTION OF STUDY POPULATION

Inclusion Criteria:

- Male or Female age 40-80
- A Clinical diagnosis of COPD as defined by GOLD
- At Least a 10 pack year smoking history
- Exhibit symptoms of chronic bronchitis as defined by the Medical Research Council
- FEV1% predicted ≥ 35% and ≤70% Post Bronchodilator
- Clinically stable in the last 4 weeks with no evidence of COPD exacerbation
- Weight of 40 kg-120 kg
- Willingness to use at least one form of acceptable birth control including abstinence, condom with spermicide, or hormonal contraceptives from time of signing ICF through study follow up visit
- Willing to monitor blood glucose if known history of diabetes mellitus requiring insulin or medical therapy
- Element of CFTR Dysfunction, as defined by Sweat Chloride > 30 mEq/L)

Exclusion Criteria

- Current Diagnosis of Asthma
- Known Diagnosis of Cystic Fibrosis
- Daytime use of Oxygen Therapy
- Documented history of drug abuse within the last year
- Subjects should not have a pulmonary exacerbation or changes in therapy for pulmonary disease within 28 days before receiving the first dose of study drug.
- Cirrhosis or elevated liver transaminases > 3X ULN
- GFR < 50 estimated by Cockroft-Gault
- Any illness or abnormal lab finding that, in the opinion of the investigator might confound the results of the study or pose an additional risk in administering study drug to the subject.
- Pregnant or Breastfeeding
- Subjects taking moderate or strong inhibitors or inducers of CYP3A4, including certain herbal medications and grapefruit juice. (Excluded medications and foods including the drugs and foods listed in the IRB HSP application.)
- Uncontrolled Diabetes
- Recent (e.g 1year) arterial thrombotic events (peripheral arterial disease, thrombotic stroke)

- Clinically significant arrhythmias requiring anti-arrhythmic agent(s) or conduction abnormalities that in the opinion of the investigator that affect patient safety such as the abnormalities listed below (patients with stable coronary artery disease are eligible)
    - Angina symptoms
    - History of MI
    - Revascularization procedure in the last year prior to screening
    - Clinically significant congestive heart failure (known LVEF <= 45%, cor pulmonale, diastolic heart failure, etc)

6.0 Statistical Analysis Plan

Safety analysis will be conducted by descriptive statistics. Pharmacodynamic analysis will be evaluated within group for the ivacaftor treatment group for changes between screening/day 1 and day 84. We will also compare findings between groups. The primary outcome measure is safety; the primary efficacy outcome measure is MCC (AUC_{60}) and change in FEV1 (% predicted). Secondary outcome measures including change in other measures of spirometry, PROs, exacerbation frequency, and 6MWD will also be analyzed. These data will be used to test the null hypothesis of no change using a paired t-test unless the distributions are notably skewed, in which case the non-parametric Wilcoxon signed-rank test will be implemented. Between group comparisons and composite time-dependent changes based on multiple measures (e.g. sweat chloride, MCC, FEV1, etc.) will be conducted as secondary analyses using the two-group t-test (or the non-parametric Wilcoxon rank-sum test if needed) and analysis of covariance models. The dose groups will be compared simultaneously using analysis of variance (or the nonparametric Kruskal-Wallis test if needed). Longitudinal analyses will consist primarily of mixed models repeated measures analyses. An appropriate structure for the covariance matrix will be selected for these models using the final data. When a model term is statistically significant, the Tukey-Kramer multiple comparisons test will be used to determine which specific pairs of means are significantly different. Interaction terms may be included in some models. All statistical tests will be two-sided and will use $\alpha=0.05$. Power analysis for measurements of MCC, CFTR function measured by sweat chloride, and FEV1 (% predicted) are provided below. The off drug effect will be measured by using data from the follow-up visit to assess the change from on drug to washout at the follow up visit.

6.1 Power and Sample Size Calculations

The size of the study was chosen based on the ability to detect a meaningful within subject change in MCC and FEV1, while also providing a study population suitable to detect safety signals and determine clinical and physiologic outcome measures for future studies. The sample size was calculated for the target population (e.g. those with chronic bronchitis, which is associated with CFTR dysfunction[13-16]) based on prior experience with the CFTR endpoints and our knowledge of anticipated activity of ivacaftor in CF airway epithelia, which is substantiated based on the close relationship between CFTR activity *in vitro* and potential difference findings *in vivo* in CF subjects.[17-25] Choice of endpoints and sample size have also been informed by the pilot study.[12] Based on experience with ivacaftor using MCC imaging[26], and our preliminary data demonstrating sweat test abnormalities among COPD smokers (including repeated measures), our study also has sufficient power to detect changes in these parameters.[27,28] Although we do not have sufficient data from the Pilot Study to perform an estimated sample size for changes in FEV1 with ivacaftor, we know from prior experience in COPD the variance of FEV1 in populations of this sort. Sample size calculations for key primary and secondary endpoints are shown in Table 2.

		Power based on response magnitude of	Within-

Assay (unit)	Detectable difference		50% of the difference between COPD and normal		subject reproducibility (SD)
	80% Power	90% Power	Efficacy	Power	
MCC ($AUC_{60\ min}$)	3.9%	4.5%			7%[29,30]
Spirometry (FEV_1)[d]	2.8%[b]	3.2%			5%[31]
Sweat Chloride (mmol/L)	2.3	2.6	9.9 mmol/L	>99%[a]	4 mmol/L[18,32]

Table 2. Power and sample size of the proposed study. All calculations are based on within subject changes observed with prior experience (as indicated by references in Table) or preliminary data, n=27 active treatment patients among all doses assignments and accounting for 10% drop-out rate, a two-sided paired t-test, and α=0.05. [a]Power=80% between-groups at SD=12.8 mmol/L and 90% at SD=11.1 mmol/L. [b]Power=80% to detect 3.9% change in FEV_1% between groups; this corresponds to 5.1% relative improvement in FEV_1 assuming ~55% FEV_1% predicted upon enrollment, a typical mean value for COPD studies at our center with similar enrollment criteria. These two between-group calculations (a and b) assume a two-sided two-group t test. [c]This is a conservative estimate based on extensive experience in NPD; within group SD is < 3 at our center. [d]Based on experience testing ivacaftor in CF patients, LCI exhibits even greater power than spirometry, so we have an excellent sample size to detect a meaningful effect.[28]

7.0 Removal of Subjects in the Study

A subject may be discontinued from the study at any time if the subject, or investigator determines that it is not in the best interest of the subject to continue participation. A subject who prematurely discontinues treatment will be asked to return for a follow-up visit approximately 4 weeks following administration of the last dose of ivacaftor.

A subject will be discontinued from the study for any of the following reasons:

- A female subject has a confirmed pregnancy or, in the case of a male subject, his female partner becomes pregnant.
- A subject experiences an arrhythmia or conduction abnormality including, but not limited to, prolonged QTcF interval, where the severity is categorized as CTCAE version 4.0 Grade 3 or higher.
- A subject experiences MI/unstable angina or stroke/Cerebrovascular accident

A subject experiences

- an elevated alanine transaminase (ALT) or aspartate transaminase (AST) of >8 × ULN or
- ALT or AST >5 × ULN for more than 2 weeks or
- total bilirubin >2 × ULN and/or clinical jaundice, in association with elevation of ALT or AST >3 × ULN and no convincing alternative etiology (e.g., viral hepatitis, alcohol ingestion) for the Elevated transaminase is identified, regardless of whether ALT or AST levels had improved

A subject may be discontinued from the study for any of the following reasons:

- A subject develops a medical condition that requires prolonged concomitant therapy with a prohibited medication.
- A subject experiences a prolonged interruption of study drug.
- A subject develops a life-threatening adverse event, or a serious adverse event (SAE) that places them at immediate risk.
- A subject is noncompliant with study requirements.

- A subject experiences an increase in liver function tests (LFTs) to 3 × ULN (if the baseline LFTs are normal) or an increase that exceeds an absolute value of 5 × ULN

8.0 Lost to Follow-Up

Subjects will be considered lost to follow-up if the following occurs:

- A subject misses 2 consecutive study visits.
- A subject is unable to be contacted by telephone subsequent to the 2 consecutive missed visits (3 documented attempts by telephone within 2 weeks following the second missed visit).
- A subject does not respond to the registered letter sent after the 3 attempted telephone contacts

9.0 Study Drug Administration and Management

Ivacaftor should be administered every 12 hours. It is recommended that subjects take ivacaftor approximately 30 minutes after of the start of a meal or snack. Whenever possible subjects should take ivacaftor at the same time each day. On day 1 subjects who meet all inclusion and exclusion criteria will be enrolled in the study. In this study, all subjects will receive 150 mg ivacaftor BID or placebo. The research pharmacist will provide logs of investigation product and maintain those in a study binder.

9.1 Role of Vertex IIS regarding provision of study drug and placebo

- Vertex Pharmaceuticals will provide ivacaftor and matching placebo to randomize up to approximately 50 subjects to achieve approximately 40 completers (35 active patients and 15 placebo treated patients for 84 days, assuming 5 dropouts in the ivacaftor group and 5 dropouts in the placebo group). This will provide sufficient compound for lost samples, if they occur.

10.0 Packaging and Labeling

Ivacaftor will be supplied as a tablet for oral administration, film-coated, 150 mg. Drug and placebo will be provided from Vertex Pharmaceuticals.

11.0 Study Drug Supply, Storage and Handling

Ivacaftor tablets must be stored at room temperature, 15-30 degrees Celsius. While at the site, ivacaftor must be stored in a secure, temperature-monitored area of limited access. On day 1 a 28 day supply (+/-2 days) supply of ivacaftor will be dispensed to the subject. The drug will be dispensed an additional 28 day supply at day 28 and 56, with all drug being returned to the site at the day 84 visit.

12.0 Drug Accountability

Study drug may be dispensed only under the supervision of the investigator or delegate and only to study subjects. The pharmacist or designated site staff will maintain information regarding the dates and amounts of study drug received, dispensed to the subjects, and returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site.

13.0 Disposal

The site staff or pharmacy personnel will retain all materials returned by the subjects until the drug accountability has been performed. Following completion of drug accountability, all study drug materials may be destroyed at the site according to their institutional policies and or/SOP.s

14.0 Blinding and Unbinding

The study pharmacist in this study will be an unblinded pharmacist. Should an event occur requiring unblinding of the investigative team, the PI and the Co-I will confer. The unblinded pharmacist at that time may unblind the PI if it is deemed necessary.

15.0 Prohibited Medications and Other Restrictions

In vitro studies showed that ivacaftor is mainly metabolized by CYP3A4. In vivo, ketoconazole, a strong CYP3A inhibitor, when co-administered with a single 150-mg dose of Ivacaftor significantly inhibited the metabolism of ivacaftor, which resulted in significantly higher systemic exposure of ivacaftor (AUC increased to 8.5-fold and Cmax increased to 2.7-fold), confirming that Ivacaftor is a sensitive CYP3A substrate.[33] Based on this, moderate or strong inhibitors and inducers of CYP3A4 will not be allowed in this study. This includes grape fruit juice and Seville orange products.

16.0 Collection Period of Adverse Events

An adverse event is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease that occurs during the study, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency after obtaining informed consent and assent (where applicable). Any abnormal findings in clinical laboratory assessments, ECGs, vital signs, or physical examination that are judged by the investigator to be clinically significant must also be reported as adverse events. Planned/elective hospital admissions or surgical procedures are not to be considered adverse events.

16.1 Documentation of Adverse Events

All subjects will be queried, using non-leading questions, about the occurrence of adverse events at each visit. In addition, all spontaneously reported adverse events will be collected. All adverse events will be recorded in the eCRF and source document. Adverse events should be reported and documented in accordance with the procedures outlined below. All adverse events occurring during the study must be documented in the relevant eCRF and source documents. The following data must be documented for each adverse event:

- Description of the event
- Classification of “serious” or “not serious”
- Date of first occurrence and date of resolution (if applicable)
- Severity (see Section 16.2 and Table 16-1)
- Causal relationship to study drug (see Section 16.3)
- Action taken (see Section 16.4)

• Outcome (see Section 16.5)
• Concomitant or other treatment given (see Section 16.6)

When possible, a constellation of signs and/or symptoms should be identified as one overall event or diagnosis.

Any adverse event judged by the investigator to be related to the study drug that is continuing at the Follow-up Visit will be followed until it has been resolved, returned to baseline, or become stable or a chronic condition.

16.2 Adverse Event Severity

The investigator must determine and record the severity of all serious and non-serious adverse events. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.019 should be used for grading the severity of adverse events. Adverse events of CTCAE Grades 4 and 5 should be documented as "life-threatening" in the eCRF and source documents. In considering the severity of an adverse event in a pediatric subject, the investigator should consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the CTCAE. An adverse event that does not appear in the CTCAE should be determined according to the definitions in Table 16-1. A copy of the CTCAE will be provided as and attachment to the protocol.

Table 16-1 Grading of Adverse Event Severity

Mild (Grade 1)	Awareness of the event; may cause minimal interference with the subject's daily life.
Moderate (Grade 2)	Discomfort enough to cause a noticeable impact on the subject's daily life.
Severe (Grade 3)	Incapacitation or significant impact on the subject's daily life.
Life-Threatening (Grade 4)	Subject in immediate risk of death from the event as it occurs. It does not Include an event that, if it were to occur in a more severe form, might cause death.

16.3 Adverse Event Casuality

The investigator will assess the relationship of the adverse event, if any, to the study drug. Causality should be classified using the categories presented in Table 16-2.

Table 16-2 Classifications for Adverse Event Causality

Related	Event follows a reasonable temporal association from administration of study drug without significant alternative etiology. May be supported by improvement upon study drug discontinuation and/or a positive re-challenge.
Possibly Related	Event follows a reasonable temporal association from administration of study drug and may have been produced by the

	subject's clinical state or other factors. Information on drug withdrawal (dechallenge) may be lacking or unclear.
Unlikely Related	Event may or may not follow a clear temporal association with study drug administration and is probably produced by the subject's clinical state or other factors. Also includes clinical events for which there is insufficient information or contradictory information which prohibits a proper assessment.
Not Related	No relationship between the event and administration of the study drug.

16.4 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the adverse event. The action taken should be classified according to the categories shown in Table 16-3.

Table 16-3 Classifications for Study Drug Action Taken with Regard to an Adverse Event

Drug Interrupted	Study drug administration stopped in response to an adverse event. If study drug administration is not re-started, this action changes to"drug withdrawn."
Drug Withdrawn	Study drug administration permanently discontinued in response to an adverse event.
Dose Not Changed	Study drug dose not changed in response to the adverse event.
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances such as when the subject has died, or the investigational treatment had been completed before the adverse event, or adverse event occurred before the investigational treatment started
Unknown	Action taken is unknown, e.g., a subject hospitalized at a hospital not under thecare of the investigator and the investigator has no knowledge whether study drug was continued or not.

16.5 Adverse Even outcome

The investigator will document the outcome of the adverse event using the categories shown in Table 16-4.

Table 16-4 Classifications for Outcome of an Adverse Event

Recovered/Resolved	Resolution of an adverse event with no

	residual signs or symptoms.
Recovered/ Resolved With Sequelae	Resolution of an adverse event with residual signs or symptoms.
Not Recovered/ Not Resolved (Continuing)	Either incomplete improvement or no improvement of an adverse event, such it remains ongoing.
Fatal	Outcome of an adverse event is death. "Fatal" should be used when death is at least possibly related to the adverse event.

16.6 Clinically Significant Abnormal Study Assessments

A clinically significant worsening from baseline of any abnormal study assessment, such as laboratory test, ECG, physical examination, and vitals signs, should be considered an adverse event and recorded accordingly. If possible, a diagnosis for the clinically significant study assessment should be provided by the investigator (e.g., urinary tract infection or anemia). In the absence of a diagnosis, the abnormal study assessment itself is listed as the adverse event (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the subject has 1 or more of the following:

• Concomitant signs or symptoms related to the abnormal study assessment
• Further diagnostic testing or medical/surgical intervention
• A change in the dose of study drug or is discontinued from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria.

16.7 Treatment Given

The investigator will describe whether any treatment was given for the adverse event. "Yes" is used if any treatment was given in response to an adverse event, and may include treatments such as other medications, hospitalization, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an adverse event.

16.8 Elevation of Liver Function Test Parameters

Subjects with new ALT or AST elevations of >3 x ULN and clinical symptoms be followed closely, including repeat confirmatory testing within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST level, as clinically indicated.

Study drug administration will be interrupted immediately and the DSMB Chair will be notified if any of the following criteria is met:

• ALT or AST >8 × ULN
• ALT or AST >5 × ULN for more than 2 weeks
• Total bilirubin >2 × ULN and/or clinical jaundice, in association with elevation of ALT or AST >3 × ULN

A thorough investigation of potential causes should be conducted and the subject will be followed closely for clinical progression.

If no convincing alternative etiology (e.g., viral hepatitis, alcohol ingestion) for the elevated transaminases is identified, regardless of whether ALT or AST levels have improved, the subject will be discontinued from the study, in consultation with the Medical Monitor

An early termination visit should be scheduled as soon as possible. In addition to the early termination visit assessments specified in the protocol, a blood sample should be obtained for pharmacokinetic analysis. Subjects discontinued for elevated transaminases should be followed until their transaminases normalize or return to baseline. If a convincing alternative etiology for the elevated transaminases is identified and the subject's symptoms and laboratory findings have improved, the investigator will consider resuming study drug treatment in consultation with the PI.

16.9 Definition of COPD Exacerbation.

We will monitor the incidence and severity of COPD exacerbations to measure safety of ivacaftor and estimate whether a reduction in COPD exacerbations is plausible with effective CFTR potentiation by ivacaftor, and to develop sample size estimates for future studies. For the purposes of this protocol, COPD exacerbations will be defined as follows: a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness, requiring treatment with antibiotics and/or systemic steroids for at least three days.

17.0 Ongoing Safety Monitoring during the Trial

The PI is primarily responsible for reviewing safety data which will be monitored on a continual basis throughout the performance of the study as well as conducting interim safety analyses 10, 20, and 30 study subjects have completed 84 days of the study (see *Safety Monitoring* and *Interim Safety Analysis* below).

The PI will monitor and provide recommendations concerning safety and tolerability based on his/her evaluation of emerging trends and risks in reported SAEs and AEs which capture abnormal vital signs, physical exam findings, and abnormal laboratory tests.

The PI will review all SAEs in real time and conduct appropriate reporting to the IRB and Vertex Pharmaceuticals as required, within 24 hrs at maximum.

The PI will make the following determinations with the site Investigator reporting the SAE:

- Does the reported adverse event meet one of the FDA's definitions for serious?
- Is the event unexpected?
- Is the event related to study drug?

18.0 Interim Analysis

18.1 Interim Safety Analysis

Interim safety analysis will include blinded review of AEs, ECGs, and safety labs by the PI and will be conducted after completion of 10, 20, and 30 subjects. The interim safety analysis will include an interim safety report prepared by the PI for all Co-Investigators to review. This report will include a summary of the following:

- Demographics and baseline characteristics
- Enrollment
- Adverse events
- Withdrawals
- Exacerbation and hospitalization rates

18.3 Interim Efficacy Analysis

No interim efficacy analyses are planned for the study.

19.0 Source Document Monitoring and Study Management

Source document review will be conducted by the investigative team. Prior to each interim safety analysis, an independent Research Coordinator will confirm source documentation and review findings with the primary Research Coordinator and PI, and document findings in the study binder. Paper source documentation will be used for the study and stored in a secure location. Data will be input into a study specific RedCap database upon completion of each study subject.

20.0 PK and PK/PD Analysis

Intensive PK Analysis will be conducted at UAB by Dr. E. Acosta's laboratory using LC/MS/MS method already established at our laboratory and described in the pilot study.[12] Calculated PK parameters include: area-under-the-curve (AUC_{12}), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), oral clearance (CL/F), terminal apparent distribution volume (V_z/F), and elimination half-life ($t_{1/2}$). Subsequently, intensive data and sparse plasma concentrations will be combined to create a population PK model to assess covariates, such as age, weight, sex, smoking status, etc. as previously conducted by our group for NIH and industry sponsored studies. PK/PD analyses between ivacaftor levels and CFTR activity in the sweat gland will reveal new insights into the degree that wild-type CFTR can be activated by the CFTR potentiator ivacaftor.

20.1 Role of Vertex IIS regarding PK analysis

- To facilitate PK studies planned at UAB, we also request pure ivacaftor powder and stable isotope labeled internal standard for assay development and validation. We request 2-5 mg of each.

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