CLINICAL STUDY PROTOCOL

Study Title: A Phase 3b, 42-day, Randomized, Double-Blind, Placebo−Controlled, Parallel Group Study to Evaluate the Safety and Tolerability of Nebulized Revefenacin and Nebulized Formoterol Fumarate [redacted] Administered in Sequence and as a Combined Solution in Subjects with Chronic Obstructive Pulmonary Disease

Study Short Title: A 42-day Parallel Group Safety Study of Revefenacin and Formoterol, administered in Sequence and as a Combination, in Subjects with COPD

Sponsor Study No.: 0167

Date: 16 April 2018, Amendment 1

Test Product: Revefenacin

US IND: [redacted]

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This study will be conducted according to the principles of Good Clinical Practice.

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: A Phase 3b, 42-day, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Tolerability of Nebulized Revefenacin and Nebulized Formoterol Fumarate [redacted] Administered in Sequence and as a Combined Solution in Subjects with Chronic Obstructive Pulmonary Disease

Study Short Title: A 42-day Parallel Group Safety Study of Revefenacin and Formoterol, administered in Sequence and as a Combination, in Subjects with COPD

Estimated Number of Study Centers and Countries or Regions: Approximately [redacted] in the United States

Background and Rationale: [redacted]

[redacted]

Objectives: The primary objective of the study is:

- To characterize the safety and tolerability of once-daily revefenacin inhalation solution when dosed sequentially with twice-daily formoterol inhalation solution compared to monotherapy formoterol, in a population of patients with moderate-to-very severe COPD over 21 days.

The secondary objective of this study is:

- To characterize the safety and tolerability of dosing a mixture of revefenacin inhalation solution and formoterol compared to dosing a mixture of placebo and

formoterol in a population of patients with moderate-to-very severe COPD over 21 days.

The exploratory objectives of the study are:

- [redacted]

Study Design: This is a randomized, double-blind, placebo-controlled, parallel-group study.

Each subject will receive treatment twice daily for a total of 42 days. There will be two treatment groups:

Treatment Group 1:

Days 1 to 21:

Revefenacin 175 mcg and formoterol 20 mcg sequentially administered via nebulizer in the morning. Revefenacin will be administered first (as a 3 mL solution) and then formoterol will be administered (as a 2 mL solution). Formoterol will be administered again in the evening.

Days 22 to 42:

After a 21 day period subjects on revefenacin 175 mcg and formoterol 20 mcg will be dosed for 21 days with a combination of revefenacin 175 mcg and formoterol 20 mcg administered as a combined solution and administered via a single nebulization (as a 5 mL solution). Formoterol 20 mcg will be administered (as a 2 mL solution) again in the evening.

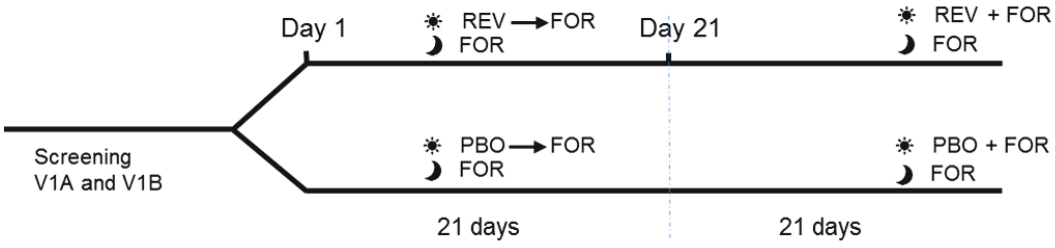
Treatment Group 2:

Days 1 to 21:

Placebo revefenacin and formoterol 20 mcg sequentially administered via nebulizer in the morning. Placebo will be administered first (as a 3 mL solution) and then formoterol will be administered (as a 2 mL solution). Formoterol 20 mcg will be administered (as a 2 mL solution) again in the evening.

Days 22 to 42:

After a 21 day period subjects on placebo revefenacin and formoterol 20 mcg will be dosed for 21 days with a combination of placebo revefenacin and formoterol 20 mcg administered as a combined solution and administered via a single nebulization (as a 5 mL solution). Formoterol 20 mcg will be administered (as a 2 mL solution) again in the evening.



All treatments will be administered via a [redacted] jet nebulizer using the [redacted] compressor.

Subjects who are currently on a stable dose of inhaled steroids will continue the use of these medications throughout the course of the study.

Subjects who are currently using LABA monotherapy (other than formoterol) will be switched to formoterol for the duration of the study. Those subjects on ICS/LABA fixed dose combinations must be able to switch to an identical dose of ICS monotherapy (or equivalent) to be eligible to enroll in the study.

Screening will involve either one or two visits, depending on whether a washout period is required. The first visit will be an Initial Screening Visit (Visit 1A) when informed consent will be obtained and the subject's existing COPD medication will be assessed to decide whether any adjustments are required to comply with the requirements of the protocol. The subject will start a washout period only after signing the informed consent form.

After completing the washout (if required), the subject will return for further screening assessments, including an Ipratropium Reversibility Visit (Visit 1B), electrocardiograms (ECGs) and vitals. It is only necessary to conduct the Initial Screening Visit (Visit 1A) and Ipratropium Reversibility Visit (Visit 1B) as separate visits if a washout is required. If a washout period is not required, these two visits may be performed as one visit.

If a washout period is required, the time from the Initial Screening Visit (Visit 1A) to Visit 1B will be at least 48 hours and no longer than 7 days.

At the Ipratropium Reversibility Visit (Visit 1B), the FEV_1 response to a nebulized dose of ipratropium (500 mcg) will be tested to determine the subject's reversibility status and GOLD category for airflow limitation.

All remaining inclusion and exclusion criteria will be reviewed at this Visit 1B

All subjects will be issued study-specific rescue medication (albuterol metered-dose inhaler or MDI) for use throughout the screening period. Subjects will be advised to avoid use of their rescue albuterol medication for at least 6 hours prior to each visit.

Subjects will come in 2 to 7 days after Screening for Visit 2 (Day 1 of dosing). Eligible subjects will be randomized to one of two treatment groups in the study.

The treatment period will involve 3 visits:

- Visit 2 (Day 1)
- Visit 3 (Day 21)
- Visit 4 (Day 42)

On visit days, subjects will attend the clinic for assessment of pre-dose vital signs, labs, ECGs, [redacted] and review of AEs and concomitant medications. Subjects will administer study medication under supervision at all clinic visits to assess nebulizer technique and to correct and retrain as required. ECGs and vital signs will be measured 60 minutes pre-dose and 10 minutes post-dose at these visits. [redacted]

[redacted] On all visits, subjects will return the unused vials of study medication and the study-specific rescue medication they have been issued.

At Visit 3 (Day 21), subjects will return for in-clinic dosing and [redacted]. Visit 3 will have a visit window of ±7 days. ECGs will be performed after the final supervised dose of the sequential administration of revefenacin (or placebo) and then formoterol at 10 minutes postdose, which should be near the peak plasma level of formoterol. The site will instruct the patient on how to mix the two solutions of study medication as a combined solution in the nebulizer. Subjects will administer the study drugs as a combined solution for the remainder of the treatment period (Day 22 to 42).

Subjects will return to clinic for Visit 4 (Day 42) for in-clinic supervised dosing [redacted]. Visit 4 will have a visit window of ±7 days. ECGs will be performed after the supervised final dose of the combined administration of revefenacin (or placebo) plus formoterol at 10 minutes postdose, which should be near the peak plasma level of formoterol.

Visit 5 will be a follow up phone call to take place 7 (±2) days after Visit 4 (Day 42) to assess the subject for any adverse events or changes in concomitant medications.

Subjects who experience moderate or severe acute exacerbations of COPD (AECOPD) will not be allowed to continue and will be withdrawn from the study.

Duration of Study Participation: Up to 63 days (including screening and any required washout period).

Number of Subjects per Group: Approximately 60 subjects will be enrolled into each of two treatment groups in a blinded 1:1 ratio (total of approximately 120 subjects).

Study Population:

Patients with moderate- to-very severe COPD who meet the criteria for study enrollment.

Inclusion Criteria

1. Subject is a male or female subject 40 years of age or older (age at Visit 1A).
2. Subject is willing and able to provide signed and dated written informed consent to participate at Visit 1A prior to initiation of any study related procedures.
3. Subject is capable of performing reproducible spirometry maneuvers as described by current American Thoracic Society (ATS) Guidelines and has a post-ipratropium FEV_1/FVC ratio <0.7 at Visit 1B.
4. Subject has moderate-to-very severe stable COPD with a post-ipratropium FEV_1 less than 80% of predicted normal at Visit 1B and a post-ipratropium FEV_1 >700 mL at Visit 1B.
5. Subject has a current or past cigarette smoking history (or equivalent for cigar or pipe smoking history) of at least 10 pack-years.

6. Subject must be willing and able to attend study visits according to the visit schedule and adhere to all study assessments/procedures.
7. Females of either child bearing potential or non-child bearing potential as follows:
    - Females of childbearing potential must have documentation of a negative urine pregnancy test at Visit 1B and again at Visit 2 (prior to randomization) if Visit 2 is > 7 days after Visit 1B. If a urine pregnancy test is positive, it must be confirmed via a second urine pregnancy test. All female subjects of childbearing potential must agree to use a highly effective method of birth control during the study and for at least 1 month after completion of study drug dosing.
        - A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as condom + diaphragm, condom + spermicide, diaphragm + spermicide, or intrauterine device [IUD] with documented failure rate of <1% per year, or oral/injectable/implanted hormonal contraceptives used in combination with an additional barrier method.
        - Females are considered to be not of childbearing potential if they have had a total hysterectomy and/or bilateral tubal ligation (documentation for either must be provided before enrollment) or are at least 2 years postmenopausal (>24 months since last menstrual period).

Exclusion Criteria:

1. Females who are pregnant, planning to become pregnant, or breastfeeding during the study.
2. Subject has a significant respiratory disease or disorder other than COPD that, in the opinion of the investigator, would interfere with the interpretation of data from this study including, but not limited to, restrictive lung disorders, benign or malignant tumors of the lung, chronic pulmonary infections such as tuberculosis, occupational lung disease such as silicosis or asbestosis, inflammatory disorders of the lung, alpha-1-antitrypsin deficiency, and/or abnormalities of the chest wall or musculature (e.g., scoliosis, myasthenia gravis, phrenic nerve palsy).
3. Subject has a history of cancer of any organ, treated or untreated in the 5 years prior to Visit 1A (excludes localized basal cell or squamous cell carcinoma of the skin; localized prostate cancer in situ of grade 1; localized cervical cancer in situ of grade 0).
4. Subject has a concurrent disease or condition that, in the opinion of the investigator, would interfere with study participation or confound the evaluation of safety, tolerability, or pharmacokinetics of the study drug.
5. Subject has a history of reactions or hypersensitivity to inhaled or nebulized anticholinergics, short-acting beta-agonists and long-acting beta-agonists.

6. Subject suffers from any medical condition that would preclude the use of inhaled anticholinergics, including narrow-angle glaucoma, symptomatic benign prostatic hyperplasia, bladder neck obstruction, or urinary retention.
7. Subject has a significantly increased risk of cardiovascular events, as assessed by the investigator, and indicated by a history at Visit 1A of myocardial infarction or unstable angina within the last 6 months, new, unstable or life threatening cardiac arrhythmia requiring intervention in the last 6 months, or New York Heart Association (NYHA) Class IV heart failure.
8. Subjects with clinically significant and uncontrolled hypertension, hypercholesterolemia or Type II diabetes mellitus, as assessed by the investigator.
9. Subject has been hospitalized for COPD or pneumonia within 8 weeks prior to Visit 1B.
10. Subject has used systemic corticosteroids within 8 weeks prior to Visit 1B.
11. Subject has used antibiotics for respiratory tract infections within 8 weeks prior to Visit 1B.
12. Subject is unwilling or unable to stop the use of prohibited medications during the washout (if required) and treatment period and follow-up period of the study.

Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment:

- Revefenacin 175 mcg inhalation solution or matching placebo by jet nebulizer taken daily (QD) for 42 days.

Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment:

- [redacted] (formoterol fumarate) 20 mcg administered by jet nebulizer taken twice daily (BID) every day for 42 days.

Reference Therapy, Dose, and Route of Administration; Regimen; Duration of Treatment:

- Placebo for TD-4208 solution for inhalation by jet nebulizer, QD administration every morning for 12 weeks.

Statistical Methods

Sample Size:

A sample size of n=60 per group was determined to be adequate to assess the safety and tolerability of sequential or combination revefenacin with formoterol to monotherapy formoterol. [redacted]

Study Endpoints:

The primary endpoint(s) of this study will assess the long-term safety and tolerability of revefenacin in the treatment of COPD:

- Frequency and severity of adverse events, including COPD exacerbations
- Vital signs
- Clinical laboratory evaluations
- 12-lead ECG changes from baseline
- Heart rate (as measured by ECG)

The exploratory endpoints of this study [redacted]

Analysis:

All safety data will be presented in listings. Descriptive summary tables will be provided for treatment-emergent adverse events, laboratory evaluations, vital signs, 12-lead ECG parameters, and concomitant medications.

[redacted]

SCHEDULE OF STUDY PROCEDURES

Table 1: Schedule of Study Procedures

	Screening[a]		Randomization Day 1 (Visit 2)	Day 21 (Visit 3) (± 7 days)	Day 42 (Visit 4) (± 7 days)	Day 49 (Visit 5) Telephone Follow Up (7 days± 2 days after Visit 4)	Early Termination/ Withdrawal
	(Visit 1A)	(Visit 1B)					
Informed Consent	■						
Medication and Medical History	■						
Washout of COPD Medications (as required)	■						
Physical examination		■		■	■		■
Height and Weight		■					
Vital Signs[b]		■	■	■	■		■
Inclusion/Exclusion Criteria Review	■	■	■				
Urine Pregnancy Test (Female subjects)[c]		■	■		■		■
Ipratropium Reversibility[d]		■					
Randomization			■				
Dispense study med			■	■			
Collect and reconcile returned study drug (with compliance assessment), and rescue medication				■	■		■

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

	Screening[a]		Randomization Day 1 (Visit 2)	Day 21 (Visit 3) (± 7 days)	Day 42 (Visit 4) (± 7 days)	Day 49 (Visit 5) Telephone Follow Up (7 days± 2 days after Visit 4)	Early Termination/ Withdrawal
	(Visit 1A)	(Visit 1B)					
Con Meds	■	■	■	■	■	■	■
AEs		■	■	■	■	■	■
Dispense Rescue Medication and training on use	■		■	■			
Dispense Daily diary and train on use	■	■	■	■			
Collect and Review Daily Diary (if applicable)		■	■	■	■		■
Hematology and serum chemistry			■	■	■		■
ECG [e]		■	■	■	■		
[redacted]			■	■	■		■
In-Clinic study drug dosing			■	■	■		

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

	Screening[a]		Randomization Day 1 (Visit 2)	Day 21 (Visit 3) (± 7 days)	Day 42 (Visit 4) (± 7 days)	Day 49 (Visit 5) Telephone Follow Up (7 days± 2 days after Visit 4)	Early Termination/ Withdrawal
	(Visit 1A)	(Visit 1B)					
Training on the self-administration of revefenacin/placebo and formoterol (sequentially at Visit 2 and combined at Visit 3)			■	■			
[redacted]			■	■	■		
Record Study Drug Use and Rescue Med Use on Daily diary[g]			■	■	■		

a Visit 1A and 1B will be conducted as one visit unless a washout is required in which case they will be conducted as separate visits. If a washout period is required, the time from the Initial Screening Visit (Visit 1A) to Visit 1B will be at least 48 hours and no longer than 7 days.
b Vital signs on Day 1, Day 21, and Day 42 are performed at 60 mins pre-dose and 10 mins post-dose. Subjects need to be resting in a semi-recumbent position approximately 5 minutes prior to assessment of vital signs.
c A repeat urine pregnancy test is required at randomization (Visit 2) if visit is > 7 days after visit 1B urine pregnancy test.
d [redacted]
e ECG will be performed 60 mins pre-dose and 10 mins post-dose at Visits 2, 3, and 4.
f One session will be done if subject is willing.
g Recorded by subject on the daily diary every day during the treatment period of the study.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
ACh	Acetylcholine
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
BID	twice daily
ANCOVA	analysis of covariance
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CFR	United States Code of Federal Regulations
COPD	chronic obstructive pulmonary disease
CRF	case report form
CSPV	Clinical Safety and Pharmacovigilance
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	United States Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GFR	glomelular filtration rate
GOLD	Global Initiative for Crohnic Obstructive Lung Disease
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization (Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IQR	interquartile range
IRB	Institutional Review Board
ITT	Intent-to-treat
LABA	long-acting $beta_2$ agonist
LAMA	long-acting muscarinic antagonist
LTOT	Long Term Oxygen Therapy

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
MDI	Metered-dose inhaler
M_1	muscarinic receptor 1 (subtype)
M_2	muscarinic receptor 2 (subtype)
M_3	muscarinic receptor 3 (subtype)
M_4	muscarinic receptor 4 (subtype)
M_5	muscarinic receptor 5 (subtype)
NYHA	New York Heart Association
Pack Years	Number of packs per day times number of years smoked
PI	principal investigator
PIFR	Peak Inspiratory Flow Rate
PP	per-protocol
PRN	Administration as needed
PT	preferred term
QD	daily
REB	research ethics board
RTSM	randomization and treatment supply management
QTcB	Bazett-corrected QT interval
QTcF	Fridericia-corrected QT interval
SABA	short-acting $beta_2$ agonist
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
sGaw	specific airway conductance
SOC	system organ class
SOP	standard operationg procedure
TBPH	Theravance Biopharma, Inc.
TEAE	treatment-emergent adverse event

1. INTRODUCTION

Pharmacologic treatment of chronic obstructive pulmonary disease (COPD) with bronchodilators is central to the management of both the symptoms and the long term risks of the condition. Long-acting inhaled bronchodilators are convenient and may be more effective for long-term symptom relief than short-acting bronchodilators; accordingly, widely-accepted treatment guidelines such as those produced by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend the use of long-acting muscarinic antagonist (LAMA) bronchodilators as first-line therapies for subjects with persistent COPD symptoms[1].

The use of dual bronchodilation has increasingly been recommended for the treatment of COPD. Recent GOLD guidelines have advocated stepping from monotherapy bronchodilator therapy to dual bronchodilator therapy for patients who remain symptomatic. More recently, the IMPACT study has demonstrated that triple therapy may have benefit above either ICS/LABA therapy or LAMA/LABA therapy.

1.1. Background and Rationale

[redacted]

1.2. Nonclinical Profile

Revefenacin is a novel, long-acting, anti-muscarinic agent being developed as an inhalation solution for administration via standard jet nebulizer for the treatment of COPD. A review of the nonclinical profile of revefenacin can be found in the current version of the revefenacin Investigator's Brochure (IB). A brief summary of the pertinent findings follows this section.

[redacted] is a long-acting beta-2 adrenergic receptor agonist that is United States Food and Drug Administration (FDA) approved for the nebulized treatment of COPD. For additional information on the efficacy and safety of [redacted] Inhalation Solution refer to prescribing information.

1.2.1. Pharmacology

[redacted]

[redacted] Overall, the pharmacology of revefenacin, when administered into the lungs, is consistent with that of a long-acting muscarinic antagonist and demonstrates good selectivity for lung versus systemic effects.

Safety pharmacology studies for revefenacin included assessments of potential effects on cardiovascular and respiratory function and for potential neurobehavioral effects. These studies are summarized in the IB.

1.2.2. Toxicology

The toxicology assessment of revefenacin included single-dose toxicity, repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, and local tolerance studies. The results of these studies are summarized in the IB.

1.3. Clinical Experience

[redacted]

[redacted]

1.4. Risks and Benefits

Subjects participating in this study may be at risk of experiencing adverse events related to muscarinic antagonism, including headache, mouth dryness, constipation, blurred vision, dizziness and urinary retention.

Subjects participating in this study may experience discomfort due to blood draws for laboratory testing.

Clinically significant bronchodilation has been observed in each of the study populations of COPD subjects thus far in the development program. Two replicate phase 3 efficacy studies [redacted] with a 3-month treatment period have demonstrated that the 88 mcg and 175 mcg doses of revefenacin were generally well-tolerated, with comparable rates of adverse events and serious adverse events across all treatment groups (active and placebo). The most commonly reported adverse events, across both trials and across all revefenacin treatment groups were COPD exacerbation, nasopharyngitis, cough, dyspnea and headache. There were no reports of blurred vision, narrow-angle glaucoma or worsening of urinary retention, all of which are commonly reported adverse events for this class of medication. In addition, reports of dry mouth were < 0.5% in the revefenacin treatment arms. A long term safety study [redacted] with a 1-year treatment period revealed a similar safety profile to what was observed to the efficacy studies.

Further detail regarding the safety profile for revefenacin is available in the revefenacin IB.

2. OBJECTIVES

The primary objective of the study is as follows:

- To characterize the safety and tolerability of once-daily revefenacin inhalation solution when dosed sequentially with twice-daily formoterol inhalation solution [redacted] compared to monotherapy [redacted] in a population of patients with moderate-to-very severe COPD over 21 days.

The secondary objective of this study is:

- To characterize the safety and tolerability of dosing a mixture of revefenacin inhalation solution and formoterol compared to dosing a mixture of placebo and formoterol in a population of patients with moderate-to-very severe COPD over 21 days.

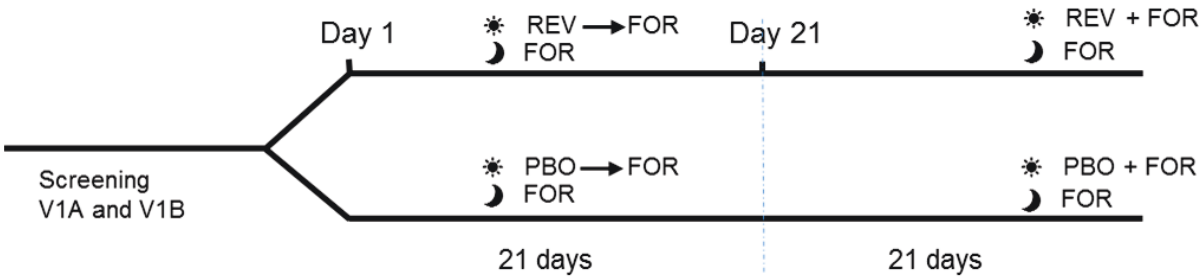
The exploratory objectives of the study are:

- [redacted]

3. STUDY DESIGN

3.1. Overview

Figure 1: Study Design Schema



3.2. Rationale for Study Design

This study is designed to provide safety data for the use of once-daily revefenacin administered sequentially with formoterol for 21 days then followed with dosing a mixture of revefenacin and formoterol for another 21 days. [redacted]

This will be a randomized, double-blind, placebo-controlled study to characterize the safety and tolerability of revefenacin inhalation solution administered via a standard jet nebulizer or placebo prior to formoterol, a LABA that is commercially available for nebulization. All subjects will have access to inhaled albuterol rescue inhalers as required. Subjects who are on a stable dose of inhaled corticosteroids will be permitted to continue the use of this concomitant medication throughout the study.

Subjects will be required to meet the standard spirometry definitions for moderate-to-very severe COPD (post-bronchodilator FEV_1/FVC ratio of <0.7 and a post-bronchodilator FEV_1<80% of predicted normal and a post-bronchodilator FEV_1 >700 mL, [NHANES III])[2].

3.3. Selection of Dose and Duration of Treatment

The selection of the 175 mcg dose of revefenacin for this study is based on the results of two twelve week studies conducted as part of the phase 3 program in the clinical development of revefenacin (Studies 0126 and 0127). The results of those studies showed that revefenacin, administered once daily via a standard jet nebulizer at doses of 88 mcg and 175 mcg to subjects with moderate-to-very severe COPD, demonstrated clinically and statistically significant improvements in trough FEV_1, over the entire treatment period. Revefenacin at 175 mcg demonstrated and replicated consistently greater improvements in FEV_1 across both studies, in concomitant LABA subjects and in more severe subjects than revefenacin at 88 mcg. Most common AEs, across all treatment groups, were exacerbations, cough, dyspnea, and headache. The AE profile did not differ from the expected safety/tolerability profile to date for revefenacin or other LAMAs. Revefenacin appears to be safe and well tolerated in the population of subjects in these studies.

3.4. Study Endpoints

The primary and secondary endpoints of this study will assess the long-term safety and tolerability of revefenacin in the treatment of COPD:

- Frequency and severity of adverse events, including COPD exacerbations
- Vital signs
- Clinical laboratory evaluations
- 12-lead ECG changes from baseline
- Heart rate (as measured by ECG)

The exploratory endpoints of this study [redacted]

3.5. Minimization of Bias

Bias will be minimized through the use of randomization and a double-blind study design, with respect to revefenacin and placebo.

3.5.1. Blinding

All study subjects, study investigators and their staff, and the Sponsor's staff involved in the conduct of the study will be blinded to treatment assignment with regard to revefenacin and placebo. Subjects will be assigned in random order to revefenacin or placebo according to the randomization schedule. The only personnel who will have access to the randomization schedule before database lock are:

- The nominated personnel at the Contract Research Organization responsible for generation of the randomization schedule.

In the event of an untoward safety observation, the investigator may unblind a subject's treatment assignment using the randomization and treatment supply management (RTSM). If possible, the investigator should first contact the Theravance Clinical Study Director before unblinding. The blind should be broken only if knowledge of the subject's study medication would affect subsequent treatment and such knowledge is required for the clinical management of the subject. Any investigator unblinding will be documented within the appropriate section of the subject's case report from (CRF) and will be captured in the RTSM.

Unblinding of individual study subjects or site staff on the basis of results from the study procedures (i.e., self-unblinding) is not considered to be either an expected or likely event.

3.5.2. Treatment Assignment

After a subject is screened and the investigator determines that the subject is eligible for enrollment, the subject will be randomized to one of the two treatment groups using RTSM (Day 1 visit [redacted]

4. STUDY POPULATION

The following inclusion and exclusion criteria must be satisfied before subjects are entered into the study:

4.1. Inclusion Criteria

1. Subject is a male or female subject 40 years of age or older (age at Visit 1A).
2. Subject is willing and able to provide signed and dated written informed consent to participate at Visit 1A prior to initiation of any study related procedures.
3. Subject is capable of performing reproducible spirometry maneuvers as described by current American Thoracic Society (ATS) Guidelines and has a post-ipratropium FEV_1/FVC ratio <0.7 at Visit 1B.
4. Subject has moderate-to-very severe stable COPD with a post-ipratropium FEV_1 less than 80% of predicted normal at Visit 1B and a post-ipratropium FEV_1 >700 mL at Visit 1B.
5. Subject has a current or past cigarette smoking history (or equivalent for cigar or pipe smoking history) of at least 10 pack-years.
6. Subject must be willing and able to attend study visits according to the visit schedule and adhere to all study assessments/procedures.
7. Female of either child bearing potential or non-child bearing potential as follows:
    - Female of childbearing potential must have documentation of a negative urine pregnancy test at Visit 1B and again at Visit 2 (prior to randomization) if Visit 2 is > 7 days after Visit 1B. If a urine pregnancy test is positive, it must be confirmed via a second urine pregnancy test. All female subjects of childbearing potential must agree to use a highly effective method of birth control during the study and for at least 1 month after completion of study drug dosing.
        - A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as condom + diaphragm, condom + spermicide, diaphragm + spermicide, or intrauterine device [IUD] with documented failure rate of <1% per year, or oral/injectable/implanted hormonal contraceptives used in combination with an additional barrier method.
        - Females are considered to be not of childbearing potential if they have had a total hysterectomy and/or bilateral tubal ligation (documentation for either must be provided before enrollment) or are at least 2 years postmenopausal (>24 months since last menstrual period).

4.2. Exclusion Criteria

1. Females who are pregnant, planning to become pregnant, or breastfeeding during the study.
2. Subject has a significant respiratory disease or disorder other than COPD that, in the opinion of the investigator, would interfere with the interpretation of data from this study including, but not limited to, restrictive lung disorders, benign or malignant tumors of the lung, chronic pulmonary infections such as tuberculosis, occupational lung disease such as silicosis or asbestosis, inflammatory disorders of the lung, alpha-1-antitrypsin deficiency, and/or abnormalities of the chest wall or musculature (e.g., scoliosis, myasthenia gravis, phrenic nerve palsy).
3. Subject has a history of cancer of any organ, treated or untreated in the 5 years prior to Visit 1A (excludes localized basal cell or squamous cell carcinoma of the skin; localized prostate cancer in situ of grade 1; localized cervical cancer in situ of grade 0).
4. Subject has a concurrent disease or condition that, in the opinion of the investigator, would interfere with study participation or confound the evaluation of safety, tolerability, or pharmacokinetics of the study drug.
5. Subject has a history of reactions or hypersensitivity to inhaled or nebulized anticholinergics, short-acting beta-agonists and long-acting beta-agonists.
6. Subject suffers from any medical condition that would preclude the use of inhaled anticholinergics, including narrow-angle glaucoma, symptomatic benign prostatic hyperplasia, bladder neck obstruction, or urinary retention.
7. Subject has a significantly increased risk of cardiovascular events, as assessed by the investigator, and indicated by a history at Visit 1A of myocardial infarction or unstable angina within the last 6 months, new, unstable or life threatening cardiac arrhythmia requiring intervention in the last 6 months, or New York Heart Association (NYHA) Class IV heart failure.
8. Subjects with clinically significant and uncontrolled hypertension, hypercholesterolemia or Type II diabetes mellitus, as assessed by the investigator.
9. Subject has been hospitalized for COPD or pneumonia within 8 weeks prior to Visit 1B.
10. Subject has used systemic corticosteroids within 8 weeks prior to Visit 1B.
11. Subject has used antibiotics for respiratory tract infections within 8 weeks prior to Visit 1B.
12. Subject is unwilling or unable to stop the use of prohibited medications during the washout (if required) and treatment period and follow-up period of the study.

5. STUDY DRUGS

All study drugs supplied by the Sponsor must be stored in a secure location accessible only to designated study personnel. The assignment of subjects to one of the treatment groups will be accomplished by randomizing the subject through the RTSM. Each drug kit will contain a unique kit number which will be provided by the RTSM on Day 1 to identify the study drug kits to dispense to a particular subject.

More information regarding study drug dispensing, administration, handling and storage are provided in a separate Pharmacy Manual.

5.1. Description of Study Drugs

5.1.1. Revefenacin and Placebo

Revefenacin has a molecular weight of [redacted] It is a [redacted]

Revefenacin and its placebo must be stored in a secure location accessible only to designated study personnel, [redacted]

Placebo inhalation solution is identical in appearance to the active [redacted]

Detailed instructions for administration will be provided in the Pharmacy Manual.

5.1.2. Formoterol

Formoterol will be provided in a carton containing 30 foil wrapped vials each containing 2 mL of a solution of 20 mcg/2 mL formoterol fumarate for inhalation by nebulization.

Formoterol should be stored in a secure location at room temperature (2°C to 25°C or 36°F to 77°F).

Detailed instructions for administration will be provided in the Pharmacy Manual.

5.2. Dosage and Administration

5.2.1. Revefenacin

Revefenacin will be administered immediately prior to administration of formoterol on the morning of Day 1 in the clinic. This will continue each day at home until Day 21. On the morning of Day 21 the subject will not administer the dose at home since this dose will be administered at the clinic. The subject will take the jet nebulizer, compressor and study drug home where dosing will occur every morning at approximately the same time and will be within the window of 6 am and 11 am. Revefenacin will be administered immediately before formoterol each day. Formoterol will be also be administered in the evening.

Training on the home use of the nebulizer will take place after the subject is randomized on Day 1 prior to discharge from the clinic. Subjects will be trained to administer the study drug until nebulization of the study drug solution is complete, which takes approximately 10 minutes and is evidenced by "spluttering" of the nebulizer. Administration will be once daily in the morning at approximately the same time each day and the time of administration will be recorded by the subject in their diary. This time will be chosen based on convenience for the subject and will remain the same for the duration of the study. The subject may receive additional instruction at the site based on the judgment of the investigator. Additional information on the training of the subject on home nebulization is contained in the Pharmacy Manual.

5.2.2. Formoterol

Formoterol will be sequentially administered on the morning of Day 1 in the clinic, i.e., immediately after the administration of revefenacin. This will continue each day at home until Day 21. On the morning of Day 21 the subject will not administer the dose at home since this dose will be administered at the clinic. Formoterol will also be administered approximately 12 hours after the morning dose each evening.

At the end of the Day 21 visit, training will be provided to the subject on how to administer the revefenacin and formoterol as a combined solution, rather than sequentially, as a single nebulization session. The first dose of the combination of revefenacin and formoterol will not begin however until the next morning at home on Day 22 and continue until Day 41. On the morning of Day 42 the subject will not administer the dose at home since this dose will be administered at the clinic.

Formoterol will be administered every evening throughout the study from Day 1 until Day 41. The time of the evening administration will be within the window of 6 pm and 11 pm.

The time of administration of the morning dose of revefenacin and formoterol (either sequentially or combined), and the evening dose of formoterol, will be recorded by the subject in their diary. Refer to the package insert for further information.

5.2.3. Agents for Rescue or Responsiveness Testing

5.2.3.1. Ipratropium

Ipratropium will be provided as a solution for administration via jet nebulizer for responsiveness testing during screening, at a dose of 500 mcg. Refer to the package insert for further information.

5.2.3.2. Albuterol

All patients will be supplied with study-specific rescue medication (albuterol MDI) at Visit 1A for use throughout the remainder of the study. Subjects will be advised to avoid use of their rescue medication for at least 6 hours prior to each visit.

Subjects will return the albuterol MDI at each of the following study visits (Visit 2, Visit 3 and Visit 4). Additional albuterol will be dispensed as needed.

The subject will be allowed to retain their albuterol MDI at the end of the study for their own use.

Refer to the package insert for further information.

5.3. Treatment Compliance

Compliance will be assessed in study subjects when accountability is performed as described in the next section. Compliance will be defined as subjects who are considered to have received 80-120% of the total number of doses that should have been administered in between study visits.

Compliance outside the 80-120% range will be documented in the electronic CRF (eCRF) as to reasons why, the number of doses that were outside this range, and whether any adverse event occurred as a result of the non-compliance.

5.4. Drug Accountability and Reconciliation

The investigator or designee is responsible for maintaining accountability records for all study drug(s) received from the Sponsor, in accordance with applicable government regulations and study procedures. The accountability record will include entries for receipt, distribution or dispensing, and the on-site destruction or return of the material(s) as specified by the sponsor. Unused and expired study drugs will be disposed of in accordance with written instructions from Sponsor.

Study drug accountability will be performed at Visit 3 (Day 21), Visit 4 (Day 42) and any unscheduled visit or early termination visit where study drug is returned, to document compliance with the dosing regimen. Subjects will be instructed to bring back all remaining study drug and all study drug packaging at each study visit for drug accountability. Treatment compliance will be assessed by subtracting the number of unused returned foil pouches from number of foil pouches that were supplied to the subject (for revefenacin and formoterol). If a subject does not return the unused foil pouches, it will be assumed that the subject administered the study drug. If a subject misses recording any dose of study drug based on the subject's diary, the site personnel should discuss the missing entries to determine if the missing entries are due to not recording the administration in the diary and make any necessary corrections to the diary while the subject is on site. Discrepancies between the subject's diary and the count of returned study drug should be documented in the source documents.

Albuterol count will be not be captured for this study. Subjects should return their albuterol inhaler(s) at each study visit, and returns should be documented on the accountability logs. Subjects will be allowed to retain their albuterol MDI at the end of the study for their own use.

6. STUDY PROCEDURES

6.1. Schedule of Study Procedures

The schedule of study procedures is summarized in (Table 1).

Throughout the study, investigators should conduct the order of the assessments for each study visit as indicated in the study procedures and strive to maintain consistency in this order. All study procedures for a visit must be completed on the same day. Any missed visits, test not done, or procedures that are not conducted must be reported as such on the eCRFs.

The scheduling of Visit 3 (Day 21 ± 7 days) and Visit 4 (Day 42, ± 7 days) is based on the date of occurrence of Visit 2 (Day 1 of the treatment period when the subject is randomized). The follow-up phone call should be scheduled 7 days after Visit 4, with a ± 2 day visit window.

6.2. Total Blood Volume

The total volume of blood to be drawn from each subject for safety laboratory assessments (hemogram/hemoglobin and clinical chemistry) will be approximately 13.5 mL. Additional samples may be necessary.

6.3. Procedures by Visit

Screening assessments and study procedures outlined in this section can only be performed after obtaining informed consent. Importantly, this includes any washout of a subject's current medication for the purpose of participation in the study or changing a subject's combination medication containing an inhaled steroid to inhaled steroid monotherapy [redacted]

Prior medical history should be obtained for the previous 2 years as part of screening the subject for eligibility into the trial. If these records have not been obtained, then documented efforts to obtain these records must be present in the source documents.

Participants in this study who, at the time of screening, are taking COPD medications requiring a washout will have two screening visits (1A and 1B). [redacted]

Subjects on LABAs (e.g., salmeterol, indacaterol, vilanterol, formoterol, arformoterol, olodaterol) must be prepared to stop these medications and switch to nebulized formoterol for the duration of the study. There is no washout period for LABAs, but the last dose of these medications should have been taken no sooner than 12 hours (for BID medications such

as salmeterol, formoterol or arformoterol) or 24 hours (for QD medications such as vilaterol and indacaterol) before the randomization visit.

Subjects on LABAs in combination with an ICS (e.g., fluticasone propionate, fluticasone fuorate, budesonide, ciclesonide, beclomethasone) will need to be switched to ICS monotherapy at the same or equivalent dose. Subjects must have been on a stable dose of ICS for at least 30 days prior to study entry. (A change from ICS/LABA to an equivalent ICS dose does not require this 30 day stability period). As with LABA monotherapy, if the subject is going to switch to an equivalent ICS monotherapy dose, this can occur on the day of randomization, assuming the last dose of LABA occurred as described above (12 or 24 hours prior to the visit as appropriate).

Subjects on TRIPLE therapy would need to follow rules for washing out of the LAMA primarily, switching to a LABA and an ICS during this period of time, and then switching to study medication for the LABA on the day of randomization as described above.

The first visit will be Screening Visit 1A. Informed consent will be obtained and the subject's existing COPD medication will be assessed to decide whether any adjustments are required to comply with the requirements of the protocol. If required, subjects will start a washout period only after signing the informed consent form. After completing the necessary washout period (if required) subjects will return for Screening Visit 1B within 7 days.

If a washout period is not required then the first two screening visits (Visit 1A and Visit 1B) may be conducted as one visit. The time period from Visit 1B (whether this is combined with Visit 1A or not) to randomization at Visit 2 will be 2 to 7 days. Review of the spirometry at Visit 1B by the central spirometry vendor will take approximately 2 business days and must be completed to determine if the spirometry meets the eligibility criteria before the subject can be randomized.

If a subject does not meet the eligibility criteria for reasons of a failed screening test due to a properly administered procedure, this test or procedure will not be allowed to be repeated and the subject should be screen failed. This includes spirometry, i.e., if a subject fails to meet any spirometry related criteria after the first attempt the subject should be screen failed. Repeat screening spirometry will only be considered if there is a technical issue (e.g., with the spirometer or with the software) or if the spirometry was not performed properly due to site error.

6.3.1. Visit 1A (Screening Visit) – (performed up to 7 days before Visit 1B)

The following procedures will be performed at this visit:

- Written informed consent after the nature of the study has been explained and before any study procedure is performed
- Concomitant and previous relevant medication and medical history including an assessment of the subject's COPD medication
- Review of inclusion and exclusion criteria
- If required, [redacted] subject will begin their washout. If subject is receiving a combination COPD medication containing

an inhaled steroid this may include changing this medication to an inhaled steroid monotherapy.

- Subject will be dispensed one albuterol MDI as a rescue bronchodilator
- Subject will be trained on and dispensed the daily diaries

6.3.2. Visit 1B – (if a washout is not required Visit 1A and 1B may be conducted as one visit)

Subject should not have taken their LABA for approximately 12 hours (if on BID therapy) or approximately 24 hours (if on QD therapy) prior to the dose of ipratropium at this visit. Additionally, subjects should have refrained from taking their study supplied albuterol for 6 hours prior to spirometry assessments. They should further refrain from using albuterol throughout the study visit.

- Predose of ipratropium
  - Complete physical examination
  - Height and weight
  - Vital signs (blood pressure or BP and HR) - subjects need to be resting in a semi-recumbent position approximately 5 minutes prior to assessment of vital signs Perform
  - ECG
- Review of inclusion and exclusion criteria
- A urine pregnancy test will be done for females of childbearing potential
- Ipratropium Reversibility - Spirometry reversibility testing pre- and postdose ipratropium [redacted] Spirometry will be performed predose and 45 minutes postdose (± 10 minutes).
- Concomitant Medications
- Adverse Events
- Collect and review Daily Diary (if diary was given at Visit 1a)
- Subject will be trained on and dispensed the daily diaries

6.3.3. Treatment and Follow-up Period

6.3.3.1. Visit 2 (Randomization Visit)

The time period from Visit 1B (whether this is combined with Visit 1A or not) to randomization at Visit 2 will be 2 to 7 days. The following procedures will be performed at Visit 2. The timing of predose procedures is relative to the start of study drug administration (start of nebulization of revefenacin). The timing of procedures postdose study drug administration is relative to the completion of nebulization of formoterol.

The sequence of events for the subject to follow at home will be as follows: recording the start time of study drug (start of nebulization of revefenacin) in the paper diary, followed immediately by nebulization of formoterol).

Subject should not have taken their LABA for approximately 12 hours (if on BID therapy) or approximately 24 hours (if on QD therapy) prior to taking it in the clinic. Additionally, subjects should have refrained from taking their short acting bronchodilators (study supplied albuterol) for 6 hours prior to ECG assessments. They should further refrain from using albuterol throughout the study visit.

It is important at study visits that [redacted] The sequence of study medication will be: nebulized revefenacin (or matching placebo) until the nebulizer sputters (emptying the nebulizer cup completely by tapping it on a clean dry surface until it is further emptied), then nebulized formoterol until the nebulizer again sputters.

The following procedures will be performed at the Randomization Visit:

- Vital signs
- Review of inclusion and exclusion criteria
- Urine pregnancy test if visit is > 7 days after visit 1B
- Randomization (subject eligibility must be confirmed by investigator before randomizing subject)
- Dispense study drug (RTSM will assign 1 kit of revefenacin or placebo (AM) and 2 kits of formoterol (AM and PM))
- Concomitant medications
- Adverse events
- Dispense Rescue Medication and training on use
- Collect and review Daily Diary and reconcile rescue medication as appropriate.
- Dispense Daily Diary and train on use
- Hematology and serum chemistry lab draw
- Perform predose ECG at 60 mins predose
- [redacted]
- Study drug dosing via nebulization of revefenacin/placebo followed immediately by nebulization of formoterol. Training on how to perform nebulization will be completed as part of these first doses, so that the subject can perform self-administration at home.
- Perform ECG 10 mins postdose
- [redacted]

- Record Study Drug use and any in-clinic rescue medication use on daily diary and/or in source documents

6.3.3.2. Visit 3 (Day 21 ± 7 days)

Subject should not have taken their albuterol for at least 6 hours prior to their ECG. They should further refrain from using albuterol throughout the study visit.

It is important at study visits that [redacted].

The following procedures will be performed at the Visit 3:

- Physical Exam
- Vital signs
- Dispense study drug (RTSM will assign 1 kit of revefenacin or placebo (AM) and 2 kits of formoterol (AM and PM))
- Collect and reconcile returned study drug (with compliance assessment) and rescue medication
- Dispense Daily Diary and train on use
- Concomitant medications
- Adverse events
- Dispense Rescue Medication and training on use
- Hematology and serum chemistry lab draw
- Perform predose ECG at 60 mins predose
- [redacted]
- Study drug dosing via nebulization of revefenacin/placebo followed immediately by nebulization of formoterol
- Perform postdose ECG at 10 mins postdose
- [redacted]
- Record Study Drug use and any in-clinic rescue medication use
- Before discharging the subject from clinic, they should be trained on how to self-administer a combined solution of revefenacin/placebo and formoterol in a single nebulization session. (The first dose of the combined solution, however, will not be administered until the next morning after the subject has returned home).

6.3.3.3. Visit 4 (Day 42 ± 7 days)

Subject should not have taken their albuterol for at least 6 hours prior to their ECG. They should further refrain from using albuterol throughout the study visit.

It is important at study visits that [redacted]

The following procedures will be performed at Visit 4:

- Physical exam
- Vital signs (BP and HR)
- Urine pregnancy test
- Collect and reconcile returned study drug (with compliance assessment) and rescue medication
- Concomitant medications
- Adverse events
- Collect and Review Daily Diary
- Hematology and serum chemistry lab draw
- Perform predose ECG at 60 mins predose
- [redacted]
- Study drug dosing via nebulization of combined dose of revefenacin/placebo mixed with formoterol
- Perform postdose ECG at 10 mins postdose
- [redacted]
- Record Study Drug use and any in-clinic rescue medication use

6.3.3.4. Visit 5 (Telephone Follow-up) (7 Days ± 2 days after Visit 4)

The following reviews with the subject will take place via telephone.

- Concomitant medications
- Adverse events

6.3.4. Early Termination

The following procedures will be performed at the Early Termination/Withdrawal Visit

- Physical exam
- Vital signs (BP and HR)
- Urine pregnancy test
- Collect and reconcile returned study drug and assess compliance

- Concomitant medications
- Hematology and serum chemistry lab draw
- Adverse events
- [redacted]
- Collect and review of Daily Diary
- Collect and reconcile rescue medication

In the instance of a subject terminating early due to an adverse event a telephone follow-up visit will be conducted 30 days afterwards to review concomitant medications and adverse events.

6.3.5. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the subject's request, or as deemed necessary by the investigator. The date and reason for the unscheduled visit should be recorded in the source documentation. The following activities may be completed at unscheduled visits as required or medically indicated:

- Medical history update
- Vital Signs
- Physical Exam
- Dispense replacement study drug or rescue albuterol
- Record concomitant medications
- Record adverse events
- [redacted]
- ECG
- Hematology and serum chemistry lab draw

6.4. Description of Study Assessments

6.4.1. Demographic and Baseline Assessments

After obtaining informed consent, each subject will be asked to provide a relevant medical history including medication history, concomitant medications, and demographic information including date of birth, sex, race, and ethnicity. The subject will also undergo a physical examination including vital signs, height, and weight and also will have the following assessments measured; [redacted] and a urine pregnancy test for females of child-bearing potential.

6.4.2. Assessments

6.4.3. Safety Assessments

6.4.3.1. Adverse Events

Adverse events will be reviewed and recorded from the signing of the informed consent through the last day of the follow-up visit. Adverse events may be observed by the site study personnel or spontaneously reported by the subject. Subjects will be reminded to call the site to report AEs that occur between visits.

6.4.3.2. Medical History

Complete medical history at screening will include evaluation for past and present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary, substance abuse, surgical history, or any other diseases or disorders.

6.4.3.3. Physical Examination

Physical examinations will include examination of the following: general appearance; head, ears, eyes, nose, and throat; neck, cardiovascular system, respiratory system, abdominal system, lymphatic system, dermatologic system, musculoskeletal system, and nervous system.

6.4.3.4. Vital Signs

Blood pressure (BP), and heart rate (HR), will be recorded only once in the eCRF for each protocol specified time point; at screening only, a second measurement may be obtained to rule out sustained elevation/decrease of either systolic or diastolic blood pressure. Subject need to be resting in a semi-recumbent position for approximately 5 minutes prior to assessment of vital signs. BP will be measured manually using a mercury sphygmomanometer or calibrated automatic blood pressure device. HR will be measured by palpation of the radial pulse over a 60-second period or by the automated blood pressure device.

6.4.3.5. Laboratory Tests

A central lab will be used for all laboratory assessments. Specimen collection times are specified in the Schedule of Study Procedures and all assessments will be performed non-fasting.

6.4.3.5.1. Hematology

Hematocrit and hemoglobin, red blood cell count; white blood cell count, including differential count of total neutrophils, eosinophils, basophils, monocytes, lymphocytes; mean corpuscular volume; mean corpuscular hemoglobin; and mean corpuscular hemoglobin concentration; and platelet count.

6.4.3.5.2. Serum Chemistry

Sodium, potassium, chloride, bicarbonate (if available), blood urea nitrogen (BUN), creatinine, magnesium, calcium, phosphate, total bilirubin, direct and indirect bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase, and glomerular filtration rate (GFR) (derived from serum creatinine).

6.4.3.6. ECG – 12-lead

ECGs will be done singly following a 5-minute semi-recumbent rest at:

- Screening Visit 1B
- Visit 2 (Randomization Visit): 1 hour pre-dose, and 10 minutes post-dose.
- Visit 3 (Day 21) and Visit 4 (Day 42): 1 hour pre-dose and 10 minutes post-dose.

The time window for the 1 hour pre-dose spirometry will be ± 10 minutes. The time window for the 10 minutes post-dose spirometry will be +10 minutes only (with no – window).

6.4.3.7. Pregnancy

Urine pregnancy tests will be performed in women of child bearing potential. A positive urine pregnancy test will be confirmed with a second urine test. If the subject is an early termination or withdrawal, a urine pregnancy test will also be performed at the early termination visit.

[redacted]

6.5. Concomitant Medications

Inhaled maintenance steroid therapy will be continued at the allowed maintenance dose throughout the treatment and washout periods. Albuterol will be allowed as required (or "PRN") during the study. Albuterol should be withheld for at least 6 hours before the

ECG [redacted]
Only study supplied albuterol should be used during the subject's participation in the study.

If subjects have used albuterol within 6 hours of the ECG at the Visit 2, the visit should be rescheduled. At each of the remaining visits, if this occurs, the visit will still be conducted, however this will be considered a protocol deviation.

Subjects who are receiving a LABA or LABA/ICS (either QD or BID) may be enrolled into the study provided that the dose has been stable for at least 30 days prior to Screening and the steroid component is ≤1000 mcg/day equivalent to fluticasone propionate.

Subjects on LABAs (e.g., salmeterol, indacaterol, vilanterol, formoterol, arformoterol, olodaterol) must be prepared to stop these medications and switch to nebulized formoterol for the duration of the study. There is no washout period for LABAs, but the last dose of these medications should have been taken no sooner than 12 hours (for BID medications such as salmeterol, formoterol or arformoterol) or 24 hours (for QD medications such as vilaterol and indacaterol) before the randomization visit.

Subjects on LABAs in combination with an ICS (e.g., fluticasone propionate, fluticasone fuorate, budesonide, ciclesonide, beclomethasone) will need to be switched to ICS monotherapy at the same or equivalent dose. Subjects must have been on a stable dose of ICS for at least 30 days prior to study entry. (A change from ICS/LABA to an equivalent ICS dose does not require this 30 day stability period). As with LABA monotherapy, if the subject is going to switch to an equivalent ICS monotherapy dose, this can occur on the day of randomization, assuming the last dose of LABA occurred as described above (12 or 24 hours prior to the visit as appropriate).

The triple therapy will need to be switched to a LABA and ICS therapy during the 48 hour washout of the LAMA component. Then on Day 1 the subject will be switched again to receive an equivalent ICS monotherapy as the study treatment administration will be in place of their LABA. The ICS monotherapy should be continued for the duration of the treatment period.

LABA and LABA/ICS drugs include the following examples:

- fluticasone propionate/salmeterol combination product
- budesonide/formoterol fumarate dihydrate combination product
- fluticasone furoate/vilanterol combination product
- mometasone/formoterol

The initiation of new treatment for COPD during this study is strictly prohibited. If the subject experiences worsening of symptoms that requires additional therapy other than increased use of study supplied albuterol (i.e., an exacerbation of their COPD) they should be withdrawn from the study and, if the event qualifies, report this event as a serious adverse event.

[redacted] Subjects will be permitted to restart their routine medications after the completion of Visit 4.

[redacted]

[redacted]

[redacted]

6.6. Restrictions

Subjects are to observe the following requirements from Screening through to Day 42:

- No use of recreational drugs
- No use of medicinal marijuana
- No use of excessive alcohol during the study period
- No participation in another investigational drug study
- No donation of ≥500 mL blood (or equivalent)

During study visits (i.e., when the subject is in clinic), smoking, exercise, or caffeine intake or large meals should be restricted (further details provided in the 0167 Study Manual).

6.7. Discontinuation

6.7.1. Subject Discontinuation

Any subject (or his or her legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn or who meets any of the following criteria:

- Subjects who experience a COPD exacerbation that is considered severe or results in a serious adverse event
- Subjects who discontinue study drug for more than 7 days, regardless of the reason

A subject's participation in the study may be discontinued at any time at the discretion of the investigator and in accordance with his or her clinical judgment. When possible, the tests and evaluations listed for the termination visit should be carried out. If a subject withdraws before completing the study, the reason for withdrawal is to be documented on the CRF.

The Sponsor will be notified of all subject withdrawals.

Reasons for which the investigator or the Sponsor may withdraw a subject from the study or a subject may choose to terminate participation before completion of the study include, but are not limited to, the following:

- Adverse event
- Subject's choice
- Major violation of the protocol
- Termination of the study by the Sponsor
- Other (e.g., subject personal circumstances)

Table 3: Severity Criteria for COPD Exacerbations

COPD exacerbation is defined as a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with SABAs, antibiotics, systemic steroids, or hospitalization.

Severity of COPD exacerbation	Criteria
Mild	A deterioration of COPD symptoms, in the judgment of the investigator, managed with an increased use of SABA but not requiring the use of antibiotics or oral or systemic corticosteroids.
Moderate	A deterioration of COPD symptoms, in the judgment of the investigator, based on any one of the following criteria: • An acute change in symptoms with purulent sputum requiring treatment with a course of antibiotics for lower airway disease • An acute change in symptoms requiring treatment with a course of oral steroid for lower airway disease • Subjects meeting the above criteria may receive treatment in a hospital setting as long as the duration of the visit is <1 day
Severe	A deterioration of COPD symptoms that results in hospitalization for emergency treatment of the COPD and the duration of the visit is ≥1 day.

Subjects who experience a mild or moderate COPD exacerbation (one or more) may continue in the trial. However, COPD exacerbations that are severe or result in a serious adverse event, will be discontinued from the trial.

The Sponsor will be notified of all subject withdrawals.

Subjects who discontinue study drug early because of an adverse reaction should be encouraged to continue their participation in the follow-up safety assessments. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason.

6.7.2. Subject Replacement

[redacted]

6.7.3. Study Discontinuation

The Sponsor reserves the right to discontinue this study at any time for any reason.

Certain circumstances may require the premature termination of the study, if the principal investigator and the Sponsor feel that the type, number and/or severity of AEs justify discontinuation of the trial, as for example, when several cases of similar serious adverse events (SAEs) considered related by both the investigator and the Sponsor occurs. The Sponsor reserves the right to discontinue this study at any time for any reason.

6.8. Pregnancy

If a female subject becomes pregnant during the study, the clinical study director (or designee) must be notified immediately and the subject discontinued from the study.

The Investigator must report this to the Sponsor using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the pregnancy.

If not all information requested on the **Pregnancy Reporting Form** is available at the time of the initial report, follow-up reports must be completed and submitted within 24 hours of the Investigator's becoming aware of any new information. The Investigator is required to follow up on the pregnancy until it has completed.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. The outcome of the pregnancy and the status of the newborn (if applicable) will be reported on the **Pregnancy Reporting Form** within 24 hours of the Investigator's becoming aware of that information.

6.9. COPD Exacerbations

Exacerbations of COPD that are considered severe or result in a serious adverse event are cause for withdrawal from the study and will be captured as a reason for study termination.

7. ADVERSE EVENTS

7.1. Definitions

The definitions below are based on International Conference on Harmonization (ICH) guideline E2A, "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".

7.1.1. Adverse Events (AE) for the Purposes of This Study

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

- AEs may be new events
- Preexisting events that increase in frequency, severity or change in nature or seriousness during or as a consequence of participation in clinical studies.
- Pre- or post-treatment complications that occur as a result of a protocol-mandated procedure (such as a biopsy).
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigation (e.g., laboratory results, x-ray findings).
- AEs may result from an overdose of the study medication.

Whenever possible, the diagnosis (rather than a series of terms related to a diagnosis) should be recorded as the AE term.

An AE does not include the following:

- All COPD exacerbations (mild, moderate and severe) will be qualified as an Adverse Event. Please see definitions of COPD exacerbations in Table 3.
- Medical or surgical procedures (such as surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an adverse event
- Preexisting diseases or conditions present or detected before signing an informed consent form that do not worsen
- Situations where an untoward medical occurrence has not occurred (such as hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of either study drug or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation

Any medical condition or clinically significant laboratory abnormality with an onset date prior to the time the subject signed the informed consent form is considered to be preexisting and should be documented in the medical history CRF.

Pregnancy is not an AE; however, if a female subject becomes pregnant during the conduct of the study, Theravance Biopharma will be notified according to the procedures for SAE reporting as outlined in Section 7.4.3. Follow-up information regarding the outcome of the pregnancy and any fetal or neonatal sequelae will be obtained and documented.

7.1.2. Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation. "Life-threatening" refers to a situation in which the patient was at risk of death at the time of the event; it does not refer to an event which might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization
- Note: "Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure, scheduled treatments, or routine check-ups do not meet this criterion. Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are as follows:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm
  - Blood dyscrasias or convulsions that do not result in hospitalization
  - Development of drug dependency or drug abuse

7.1.3. Additional Considerations for Serious Adverse Events

- Death is an outcome of an adverse event and not an adverse event in itself. Deaths of unknown cause for which the investigator cannot identify a cause of death will be captured as death of unknown cause or death not otherwise specified.
- All deaths, regardless of cause, must be reported for subjects if the death occurs while the subject is participating in the study.

- "Occurring at any dose" does not imply that the subject is receiving study drug at the time of the event; dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.

7.2. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Abnormal laboratory findings (such as clinical chemistry or hematology) or other abnormal assessments (such as ECGs, X-rays, or vital signs) that are considered clinically significant in the judgment of the investigator must be recorded as AEs or SAEs if they meet the definition of an adverse event (or serious adverse event), as described in Sections 7.1.1 (Adverse Event) and 7.1.2 (Serious Adverse Event).

If there are any AE questions, the investigator is encouraged to contact the Sponsor to discuss.

7.3. Assessment of Adverse Events

All AEs will be assessed by the investigator and recorded in the case report form, including the dates of onset and resolution, severity, relationship to study drug, outcome, and action taken with study medication.

7.3.1. Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The severity of AEs will be assessed according to the following definitions:

- **Mild**: the AE is noticeable to the patient and/or the Investigator, but does not interfere with routine activity.
- **Moderate**: the AE interferes with routine activity, but responds to symptomatic therapy or rest.
- **Severe**: the AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.

7.3.2. Causal Relationship to Study Medication

The Investigator's assessment of causality is based on clinical judgment regarding the reasonable possibility that the study medication caused the event and may include consideration of some or all of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, co-morbid conditions, other drugs, and environmental factors.
- The temporal association between drug exposure and onset of the AE.

- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study medication.
- Whether the AE resolved or improved with decreasing the dose or stopping the study medication ("dechallenge") or recurred or worsened upon re-exposure to the study medication ("rechallenge").

The causal relationship between the study medication and the AE will be described using one of the following categories:

- **Not Related:** Evidence exists that the adverse event has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

7.4. AE Reporting and Recording

7.4.1. AE Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical trials is crucial for the protection of patients and is mandated by regulatory agencies. Sponsor has established standard operating procedures in compliance with regulatory requirements worldwide to ensure appropriate reporting of safety information. All clinical trials sponsored by TBPH will be conducted in accordance with these procedures.

7.4.2. AE and SAE Recording

All AEs, regardless of seriousness, severity, or causal relationship to study medication, will be recorded from signing informed consent through the last study visit (or last subject contact in the case of a follow-up telephone call). AEs will be recorded on the AE page of the CRF. SAEs, regardless of relationship to study medication will be recorded from signing informed consent through the last study visit (or last subject contact in the case of a follow-up telephone call). Additionally, investigators may report SAEs assessed as related to study medication through 30 days following the last study visit (or last subject contact in the case of a follow-up telephone call). All SAEs will be recorded on both the SAE Report Form and the AE page of the CRF and should include the following:

Description of event:

- Signs and symptoms due to a common etiology should be reported as a single diagnosis; for example, cough, runny nose, sneezing, sore throat, and head congestion would be reported as "upper respiratory infection".
- A diagnosis or description must be as specific and as complete as possible (e.g., "lower extremity edema" instead of "edema").
- Hospitalization or surgical procedures should not be used as adverse event terms (e.g., if a subject was hospitalized for cholecystectomy due to cholecystitis, the adverse event term should be recorded as cholecystitis, and not as the procedure, cholecystectomy).
- "Death" should not be used as an adverse event term unless the cause of death is unknown. For events with a fatal outcome, the cause of death should be the adverse event term (e.g., if a subject died of an acute myocardial infarction, the adverse event term should be recorded as "Myocardial Infarction" and the event outcome as fatal).
  - Relationship to study medication: The Investigator will make an assessment of the causal relationship of the study medication to the AE using the guidelines in Section 7.3.2.
  - Severity: The severity of the AE will be assessed using the guidelines in Section 7.3.1.
  - Outcome: The outcome of AEs will be recorded.
  - Therapeutic measures: Measures taken for the treatment or management of the AEs will be recorded.

7.4.3. SAE Reporting Timeline

SAEs will be reported to Clinical Safety and Pharmacovigilance within 24 hours of the time the Investigator or his/her designee becomes aware that an SAE has occurred, whether or not the event is considered to be related to study medication. If the initial SAE is reported by telephone, a written report signed by the Investigator must be submitted within 24 hours.

The SAE Report Form must be completed in accordance with the SAE Report Form Completion Guidelines. If all information on the SAE Report Form is not available at the time of the initial report, follow-up SAE reports will be completed and submitted.

To report an SAE, complete and email or fax the Serious Adverse Event Report Form to the following:

Theravance Clinical Safety and Pharmacovigilance (CSPV):

Email: [redacted]

For medical questions regarding an SAE, contact the Sponsor medical monitor by telephone as follows:

Sponsor Medical Monitor Contact Information:

[redacted]

Telephone: [redacted]
Email: [redacted]

For fatal or life-threatening events, fax copies of hospital case reports, autopsy reports, and other documents when requested. Additional information may be requested from the investigator to ensure the timely completion of accurate safety reports.

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the study drug and is unexpected/unlisted based on the current revefenacin IB. In this case, all investigators will receive notification of the event. The investigator is responsible for notifying the Institutional Review Board or Ethics Committee and documenting the notification, as required by local regulatory authorities and in accordance with the local institutional policy.

7.5. Adverse Event Follow-up

A subject experiencing an AE or SAE will be followed by the investigator or his/her trained delegate(s) through the follow-up visit or until the investigator and/or the Sponsor has determined that the AE or SAE has resolved or a stable clinical endpoint is reached, whichever is longer. The Sponsor may request follow-up of certain adverse events until resolution and documentation of assessments made during this period.

The investigator must take all therapeutic measures necessary for resolution of an SAE. Any medications necessary for treatment of the SAE must be recorded in the concomitant medication section of the case report form.

8. STATISTICAL CONSIDERATIONS

8.1. General Considerations

All individual data will be listed as measured. All statistical summaries and analyses will be performed using SAS software (SAS Institute, Cary, North Carolina, USA).

Continuous data will be summarized using [redacted]

Categorical data will be summarized using the frequency [redacted]

Any changes to the protocol-specified analyses will be pre-specified in the Statistical Analysis Plan prior to data lock.

8.2. Sample Size and Power

[redacted]

8.3. Analysis Sets

The Safety analysis set will include all randomized subjects receiving at least one dose of study drug summarized by actual drug received. These subjects will be analyzed according to their actual treatment received, regardless of their randomized treatment. The Safety analysis set will be the primary analysis for safety analyses.

The Intent-to-Treat (ITT) analysis set will include all randomized subjects. Subjects in this set will be analyzed according to their randomized treatment assignments, regardless of treatment received.

A per-protocol (PP) analysis will also be implemented and be considered supportive to the ITT analysis. The PP analysis set included all subjects in the ITT analysis set who did not violate the key inclusion/exclusion criteria through Day 42. Subjects who received the incorrect treatment (compared to their randomized treatment) at any time point will be excluded from this subset. For subjects who received proscribed medications during the 42-days treatment period, all data collected after the first occurrence of receiving proscribed medication will be excluded from the PP analysis. The key inclusion/exclusion criteria pertaining to the PP analysis and the list of proscribed medications will be included in the statistical analysis plan (SAP).

8.3.1. Examination of Subgroups

The following subgroups are pre-defined at baseline:

- Baseline smoking status [redacted]
- Age [redacted]
- Current ICS use [redacted]
- Reversibility to (not reversible) to ipratropium,
- Sex [redacted]

Selected analyses as defined in the SAP will be conducted using the subgroup examination sets. Additional subgroups may be defined in the SAP.

8.3.2. Major Protocol Analysis Deviations

The following protocol deviations are defined as major and would be considered to have an impact on the analysis of data.

[redacted]

Additional criteria may be specified in the SAP.

8.4. General Analyses

8.4.1. Demographics Characteristics

Demographics and baseline characteristics (including age, sex, race, ethnicity, height, weight, and body mass index [BMI]) will be summarized for the ITT analysis set.

8.4.2. Screening Summaries

A summary of pulmonary function at screening, including reversibility, and at baseline using the ITT analysis set will be provided.

8.4.3. COPD Clinical History and Smoking History

A summary of the COPD clinical characteristics/history and smoking history using the ITT analysis set will be provided.

8.4.4. Select Medical History

A summary of select medical history/characteristics using the Safety analysis set will be provided characterizing co-morbidities and disease severity.

8.5. Safety Analyses

For all safety analyses, the safety analysis population will be used.

Safety variables to be summarized include vital signs, adverse events, clinical laboratory results (hematology and chemistry), and corrected QT interval (QTcF) from standard safety digital ECGs. Vital signs will be summarized in terms of observed values and changes from baseline.

8.5.1. Extent of Exposure

A subject's data for the extent of exposure to study drug will be generated from the study drug administration page of the CRF. Dosing information for individual subjects will be listed. Using drug administration data, estimates of exposure to revefenacin and/or formoterol will be summarized. Dose discontinuations and reasons for study drug discontinuation will be listed and summarized.

8.5.2. Adverse Event Data

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will present by system organ class (SOC), preferred term (PT) and severity, the frequency and percentage of subjects reporting each observed event.

Adverse events observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from adverse events observed after study drug administration (i.e., treatment-emergent adverse events [TEAEs]).

A TEAE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus the number of days in the follow-up period. AEs observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from TEAEs.

All AEs and all TEAEs will be listed by subject. The frequency of subjects who experience TEAEs will be summarized overall and by treatment group. AEs will also be summarized by relationship to treatment (study drug) and severity.

A listing will be provided for all subjects who experience an SAE. Data listings will also be provided for subjects who discontinued the study due to any AE, as well as for a SAE.

8.5.3. Concomitant Medications

Medications will be summarized both prior and during the treatment period. Medications will be summarized in the following classes, COPD bronchodilator, ICS and non-COPD medications.

8.5.4. Laboratory Data

Laboratory data will be summarized in terms of observed values, changes from baseline, values relative to normal ranges, and changes from baseline relative to normal ranges. Listings will flag laboratory values that are outside of normal range.

Clinical laboratory test results will be listed by subject. Reference ranges provided by the laboratory for each parameter will be used to evaluate the clinical significance of laboratory test results. Values falling outside of the relevant reference range will be flagged, as appropriate, in the data listings. Abnormalities in clinical laboratory test results will be listed in a separate listing.

8.5.5. Vital Signs Data

Vital Signs data will be summarized in terms of observed values (by time point), changes from baseline (by time point), and counts and percentages within appropriately defined categories (Table 4).

Table 4: Outlier Threshold for Vital Signs

Heart Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
<40 >110	<85 >160	<45 >100

8.5.6. ECG Data

The QTcF, PR interval, QT interval, QRS duration, and HR from standard digital ECGs will be summarized in terms of observed values, changes from baseline, and counts and percentages within appropriately defined categories (Table 5).

Table 5: ECG Test Outlier Thresholds

Heart Rate (bpm)	Heart Rate Change from Baseline (bpm)	PR Interval (msec)	PR Percentage Change From Baseline (%)	QRS Interval (msec)	QT_cF (msec)	QT_cF change from Baseline (msec)
>120	≥20	≥ 200	≥ 15	≥ 120	Males:	≤ 30
>130	≥30	≥ 220	≥ 25		< 430	>30, ≤ 60
		Optional:			≥ 430	> 60
		≥ *240*			≥ 450	
		≥ *260*			≥ 470	
		≥ *280*			≥ 480	
		≥ *300*			≥ 500	
					Females:	
					< 450	
					≥ 450	
					≥ 470	
					≥ 480	
					≥ 500	

Treatment emergent ECG abnormalities are defined as those not present at baseline, or those that worsened after treatment, e.g., borderline at baseline, but were prolonged after treatment. QTcF {and QTcB} will also be summarized by the following categories, Normal (males <430, females <450), Borderline (males (≥430, <450); females (≥450, <470)) and Prolonged (males ≥450, females ≥470).

When multiple values exist for the same nominal time point (e.g., triplicate reading), the average of the readings taken for ECG parameters will be used in the data analysis, including the outlier analysis stated below.

There will be no imputation of missing data. Subjects without post-baseline measurement for a given treatment period will be excluded from the summary statistic (e.g., denominator of the summary statistic) for that time point.

All recorded values for the ECG parameters will be presented in a by-subject listing.
A separate listing of subjects with values of QTcF > 500 msec or an increase > 60 msec will be provided, as necessary.

Cumulative distribution plots will be provided for maximum change in QTcF by day.

8.6. Other Analyses

For other analyses, the ITT population will be used. In select analyses, the PP and subgroup examination sets may be used.

8.6.1. Other Endpoints

[redacted]

[redacted]

8.6.5. Multiplicity Adjustment

[redacted]

8.7. Missing Data Handling

[redacted]

8.8. Data Monitoring Committee

No data monitoring committee is planned for this study.

9. STUDY ADMINISTRATION

This study will be conducted in compliance with all applicable regulations.

9.1. Principal Investigator Responsibilities

Before beginning the study, the principal investigator (PI) at each site must provide to the Sponsor or its designee a fully executed and signed Form FDA 1572 and, if applicable, a financial disclosure form. For applicable studies, financial disclosure forms must also be completed for all subinvestigators who will be directly involved in the treatment or evaluation of research subjects in this study. (A subinvestigator is defined in ICH E6 as any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions [e.g., associates, residents, research fellows].)

The PI will ensure the following:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- He or she will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- He or she has read and understands the information in the Revefenacin IB, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/independent ethics committee (IEC) complies with the requirements of 21 CFR Part 56, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC. Additionally, he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

9.2. Institutional Review Board/Independent Ethics Committee

Before beginning study-specific research, the investigator will obtain written confirmation that the IRB, IEC, or Research Ethics Board (REB) is properly constituted and compliant with ICH and good clinical practice (GCP) requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to the Sponsor or its designee. The protocol, informed consent form (ICF), IB, and any other appropriate written information provided to the subjects that the IRB/IEC/REB may require to fulfill its responsibilities will be submitted to the IRB/IEC/REB in advance of the study. The Sponsor or its designee must approve the ICF and all subject recruitment materials before they are submitted to the IRB/IEC/REB. The study will not proceed until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol and the ICF are obtained by the investigator and copies are received by the Sponsor or its designee. If possible, the approval document should refer to the study by study protocol title and the Sponsor study number, identify the documents reviewed, and include the date of the review and approval. The written approval of the IRB/IEC/REB will be retained as part of the study file. The study may proceed before approval of consent forms and other study documents translated to a language other than the native language of the clinical site, provided that written IRB/IEC/REB approval of the translated documents is obtained before they are used. Any amendments to the protocol should be reviewed promptly.

The investigator must provide the appropriate periodic reports on the progress of the study to the IRB/IEC/REB and the Sponsor in accordance with local IRB/IEC/REB requirements and applicable governmental regulations, whichever is strictest.

9.3. Informed Consent

A properly written and executed ICF, in compliance with-ICH E6 (GCP Guideline, Section 4.8), 21 CFR §50, and other applicable local regulations, will be obtained for each subject before enrollment of the subject into the study. The investigator will prepare the ICF or revise the template ICF and provide the documents to the Sponsor (or designee) for approval before submission to the IRB/IEC/REB. The Sponsor and the IRB/IEC/REB must approve the documents before they are implemented.

The investigator will provide copies of the signed ICF to each subject (or the subject's legally authorized representative) and will maintain the original in the subject's record file.

9.4. Data Recording and Quality Assurance

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used.

A CRF (approved by the Sponsor) is required and should be completed (in English) for each randomized subject. The investigator has ultimate responsibility for the accuracy, authenticity, completeness, and timely collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms. The investigator must review and sign the CRFs to attest that the data contained on the CRFs are correct.

Electronic data capture (EDC) technology will be used for this study. All clinical information requested in this protocol will be recorded on the electronic case report forms approved by the Sponsor, or via other data collection methods, e.g., electronic laboratory data transfer. Study site personnel will enter (in English) study data into the CRFs for each randomized subject. Training on the EDC application will be completed and documented before access to the EDC system is given.

In the event of a CRF data change (e.g., correction of an error or addition of new information), corrections will be made to the CRF. Corrections to the CRFs, including the reason for change, will be automatically documented through the EDC system's audit trail.

The investigator is responsible for reviewing all CRFs, verifying them for accuracy, and approving them via an electronic signature. The investigator is designated as the signatory coordinating investigator.

An electronic copy of the CRF casebooks will be sent to the site for retention with other study documents after full completion of the study, i.e., after database lock.

The investigator is responsible for maintaining accurate, authentic, complete, and up-to-date records for each subject. The investigator is also responsible for ensuring the availability of any original source documentation related to the study (including any films, tracings, computer discs, tapes, and worksheets). In most cases the source is the subject's medical record. Data collected on the CRFs must match the source documents.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded in the CRF and for which the CRF will stand as the source document.

9.5. Document Retention

Until otherwise notified by the Sponsor, an investigative site must retain in a controlled manner all study documents required by the Sponsor and by the applicable regulations. The investigative site must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) and any original source documents that are electronic, as required by applicable regulations.

The investigator must consult the Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location or disposition of the study files. If an investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study documents, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian and must approve this transfer of responsibility.

9.6. Confidentiality

The investigator or designee must explain to each subject, before enrollment into the study, that, for evaluation of study results, the subject's confidential medical information obtained during the study may be shared with the study sponsor, the study sponsor's affiliated companies, the study sponsor's designated service providers, regulatory agencies, and the institutional review board (IRB) or independent ethics committee (IEC). The investigator (or designee) is responsible for obtaining written permission to use confidential medical information in accordance with country-specific regulations (such as the Health Insurance Portability and Accountability Act in the United States) from each subject or, if appropriate, the subject's legally authorized representative. If permission to use confidential medical information is withdrawn, the investigator is responsible for documenting that no further data from the subject will be collected.

Subject medical information obtained during this study is confidential, and disclosure to unauthorized third parties is prohibited. The pertinent sections of data protection laws will be complied with in full. Study records containing subject information will only be identified by the subject identification number, subject initials, date of birth, and study number, and not by the subject's full name, except the subject consent form, which is archived at the study center only. The subject's name will not be used in any public report of the study.

During the course of the study, a confidential subject identification list will be maintained by the investigator and archived at the investigative site.

Before and during the conduct of the study, no study-related details may be disclosed, i.e., placed on the internet, published, or otherwise publicized, or provided to a third party without prior written permission from the Sponsor. The policy for publication of data after completion of the study is described in Section 9.9 (Publication).

9.7. Access to Data and Documents

Upon receipt of the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Study data recorded on the CRFs must be verifiable to the source data. All original recordings, laboratory reports, and subject records generated by this study must be available to the Sponsor, representatives of the Sponsor, the IRB/IEC/REB, and applicable regulatory authorities, and they may be used for submission to regulatory authorities. In addition, all source data should be attributable (signed and dated), consistent with local medical practice. The investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representatives) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent.

9.8. Quality Control: Study Monitoring and Auditing

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP and standard operating procedures (SOPs) for compliance with applicable government regulations. The investigator agrees to allow these monitors direct access to the clinical data and supplies, dispensing, and storage areas and, if requested, agrees to assist the monitors. The investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Members of the Sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA or other Regulatory Agencies, including IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the investigator should notify the Sponsor immediately. The investigator will ensure that the auditors have access to the clinical supplies, study site facilities, laboratory and all data (including original source documentation) and all study files are available, if requested.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an investigator, institution, institution staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued noncompliance may result in termination of the investigator's involvement in the study. The IRB/IEC/REB and relevant regulatory authority will be informed.

9.9. Publication

The Sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and presentation at seminars or conferences. The Sponsor will retain the ownership of the data collected in this study. The investigator will provide any proposed manuscript or abstract to the Sponsor before submission for publication or presentation of any results or data obtained in this study.

Additional details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Study Agreement between the Sponsor and the investigator.

10. REFERENCES

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Available at: https://www.ncbi.nlm.nih.gov/pubmed/27418551

The above references are available upon request.

11. APPENDICES

APPENDIX 1. PROTOCOL SIGNATURE FORM

Protocol Signature Form

Protocol #:	0167
Protocol Title:	A Phase 3b, 42-day, Randomized, Double-Blind, Placebo−Controlled, Parallel Group Study to Evaluate the Safety and Tolerability of Nebulized Revefenacin and Nebulized Formoterol Fumarate [redacted] Administered in Sequence and as a Combined Solution in Subjects with Chronic Obstructive Pulmonary Disease
Version:	1.0
Version Date:	16 April 2018, Amendment 1

I have read the protocol described above and agree to conduct this study in accordance with procedures described therein. I also agree to conduct the study in compliance with all applicable regulations.

Investigator's Name (print)

Investigator's Signature Date