CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Study to Compare Once Daily Nebulized Revefenacin with Spiriva Once Daily Delivered via the [redacted] on Lung Function in Subjects with Chronic Obstructive Pulmonary Disease and a Low Peak Inspiratory Flow Rate
Study Short Title:	Revefenacin PIFR Study in COPD
Sponsor Study No.:	0149
Date:	04 April 2017, [redacted]
Test Product:	REVEFENACIN
US IND:	[redacted]
Sponsor:	Theravance Biopharma R&D, Inc. c/o Theravance Biopharma US, Inc. 901 Gateway Boulevard South San Francisco, California 94080 Telephone: (650) 808-6000 Facsimile: (650) 808-4181
Clinical Study Director/Medical Monitor:	[redacted] Theravance Biopharma US, Inc. Telephone: [redacted]

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

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: A Phase 3b, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Study to Compare Once Daily Nebulized Revefenacin with Spiriva Once Daily Delivered via the [redacted] on Lung Function in Subjects with Chronic Obstructive Pulmonary Disease and a Suboptimal Peak Inspiratory Flow Rate

Study Short Title: Revefenacin Suboptimal PIFR Study in COPD

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

Background and Rationale:

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

PROTOCOL SYNOPSIS (CONTINUED)

[redacted] either via nebulization with revefenacin or via dry powder inhaler with tiotropium.

Objectives: The primary objective of the study is as follows:

- To characterize the relative efficacy on trough FEV_1 of revefenacin administered once daily via nebulization compared to tiotropium administered once daily via [redacted] in a population of subjects with moderate to very severe COPD and suboptimal PIFR.

The secondary objectives of the study are as follows:

- Characterize relative efficacy of Trough FVC and IC post 28th dose on Day 29
- Characterize relative efficacy of Peak FEV_1, FVC on Day 29 (0-4 hours)
- Characterize relative efficacy of Peak FEV_1, FVC on Day 1 (0-4 hours)
- Characterize relative use of rescue albuterol use

PROTOCOL SYNOPSIS (CONTINUED)

Study Design:

This is a randomized, double-blind, double-dummy, parallel group study.

Each subject will receive study treatment once daily in the morning for the length of study duration, up to 29 days and all subjects will be allowed to continue on their current regimen of concomitant ICS/LABA therapy of their choice, either QD or BID administration. There will be two treatment groups (revefenacin 175 mcg and tiotropium 18 mcg). Revefenacin solution for inhalation (3 mL) will be administered using the [redacted] jet nebulizer. Tiotropium will be administered using the [redacted] device with the drug and placebo capsules blinded using precedent blinding methods.

Subjects will be assessed during screening for low PIFR using the [redacted] device [redacted] to measure PIFR set to [redacted] resistance for inclusion to the study and set to the [redacted] resistance for descriptive purposes. Subjects with PIFR lower than [redacted] set to the [redacted] resistance, defined in this study as suboptimal PIFR, and who meet all eligibility criteria will be randomized.

Once screening criteria have been met, subjects will have baseline characteristics and medical history collected. At Visit 1B reversibility to ipratropium will be evaluated and PIFR measurements will be collected set to both the [redacted] and to [redacted] resistance.

At Visit 2 (Day 1), eligible subjects will be randomized to one of two groups in the study. Spirometry, including FVC and FEV_1, will be assessed at baseline (-45 and -15 minutes predose), 1 hour, 2 hour, and 4 hour post dosing. Hyperinflation, as measured by inspiratory capacity (IC) will also be assessed at -45 mins predose. This will be done by a Slow Vital Capacity (SVC) maneuver immediately after the FVC maneuver. Maximal Inspiratory Pressure (MIP) will be performed following the SVC.

At Visit 3 (Day 29), subjects will return for final in-clinic dosing and spirometry assessments.

Safety assessments, including collection of adverse events will be performed at every visit.

A supply of rescue medication (albuterol MDI or nebulized) for use in the study and a 28-day supply of study medication will be provided for each subject.

Duration of Study Participation: Up to 50 days

Number of Subjects per Group: Approximately 100 subjects will be enrolled in each of two treatment groups (total of 200).

Study Population:

Subjects with COPD with suboptimal peak inspiratory flow rates (PIFR <60L/min to [redacted] resistance using the [redacted] device)

PROTOCOL SYNOPSIS (CONTINUED)

Inclusion Criteria

1. Subject is a male or female subject 40 years of age or older with a diagnosis of COPD.
2. Subject has <60 L/min of PIFR as measured by [redacted] device with resistance set to [redacted] at screening at Visit 1B.
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 and post-ipratropium predicted FEV_1 < 80% at screening and FEV_1 >400mL.
4. Subject has a current or past cigarette smoking history (or equivalent for cigar or pipe smoking history) of at least 10 pack-years.
5. Subject is willing and able to provide signed and dated written informed consent to participate prior to initiation of any study related procedures.
6. Subject is willing and able to adhere to all study assessments/procedures
7. Women of either non-child bearing potential or child bearing potential, provided that:
   - 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.

     (Women 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.)
8. Subject (or caregiver) based on the investigator's assessment is able to properly prepare and administer study medication administered either by nebulizer or [redacted].

Exclusion Criteria:

1. Subject has a concurrent disease or condition that, in the opinion of the investigator, would interfere with continued study participation or confound the evaluation of safety and tolerability of the study drug.
2. Subject has a history of reactions or hypersensitivity to inhaled or nebulized anticholinergics
3. 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.
4. A clinically significant abnormal lab for any of the following tests that, in the investigators opinion, would likely interfere with the successful completion of the study.

PROTOCOL SYNOPSIS (CONTINUED)

Historical labs performed within the last 90 days are acceptable; if not available, then labs for these tests will be performed at Visit 1A.

- creatinine
- hematocrit

5. For subjects requiring a washout of a LAMA, Subject has ≥75 L/min of PIFR as measured by [redacted] device with resistance set to [redacted] at screening at Visit 1A
6. For subjects not requiring a washout of a LAMA, Subject has ≥60 L/min of PIFR as measured by [redacted] device with resistance set to [redacted] at screening at Visit 1A
7. Subject has been hospitalized for COPD or pneumonia within 8 weeks prior to Visit 1A.
8. Subject has a COPD exacerbation requiring treatment (other than increased use of study supplied albuterol) during the screening period.
9. Subject has used systemic corticosteroids within 8 weeks prior to Visit 1A.
10. Subject has used antibiotics for respiratory tract infections within 8 weeks prior to Visit 1A.

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

Revefenacin solution for inhalation by jet nebulizer. Daily (QD) administration every morning for 29 days.

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

Tiotropium dry powder administered using capsules with the [redacted] device. Daily (QD) administration every morning for 29 days (dose 18 µg). Tiotropium will be blinded in a manner similar to that used in other trials, namely by using a color matched capsule containing placebo and using a foil overlay on the blister pack. Thus the product will appear while in packaging to be identical.

Study Evaluations

Safety Assessments:

Adverse events, vital signs, physical examinations, and rescue medication usage.

Efficacy Assessments:

Pulmonary function tests (FVC, FEV_1 and IC) measured by spirometer in the clinic. Rescue bronchodilator medication use will be collected daily as a binary measure and through drug accountability (via a dose counter).

Clinical Outcomes Assessments:

Baseline and Transition Dyspnea Index (BDI/TDI).

PROTOCOL SYNOPSIS (CONTINUED)

Statistical Methods

Efficacy endpoints will be evaluated using the following hypothesis testing schema: Revefenacin will be compared to tiotropium. The null hypothesis for the treatment comparison will be that there is no difference between the LS mean of revefenacin and tiotropium. The alternative hypothesis will be that there is a difference.

Sample Size:

[redacted], approximately 100 subjects will be randomized per treatment group (N=200 subjects in total).

[redacted]

Study Endpoints:

The primary study endpoint is trough FEV_1 post the 28th dose on Day 29

The secondary endpoints are:

- Trough FVC and IC post 28th dose on Day 29
- Peak FEV_1, FVC on Day 29 (0-4 hours)
- Rescue albuterol use (incidence of albuterol use)

[redacted]

The safety endpoints are:

- Adverse events
- Vital signs
- Concomitant medications

Analysis:

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

[redacted]

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

SCHEDULE OF STUDY PROCEDURES

Table 1: Schedule of Study Procedures

Procedures	Screening[a]		Randomization Day 1 (Visit 2)	Treatment Period (29 days)	Day 29 (Visit 3) ± 5 days	Follow-Up/ Phone call 7 days after last visit ± 2 days	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		■			■		■
Inclusion/Exclusion Criteria Review	■	■	■				
Urine Pregnancy Test (Female subjects)[b]	■		■		■		■
Ipratropium Reversibility[c]		■					
Subject training on the maneuver for MIP		■					
Randomization			■				
Collect and review Daily Diary		■	■		■		■

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

Procedures	Screening[a]		Randomization Day 1 (Visit 2)	Treatment Period (29 days)	Day 29 (Visit 3) ± 5 days	Follow-Up/ Phone call 7 days after last visit ± 2 days	Early Termination/ Withdrawal
	(Visit 1A)	(Visit 1B)					
Dispense study med			■				
Collect and reconcile returned study drug (with compliance assessment), and rescue medication					■		■
Con Meds		■	■		■	■	■
AEs		■	■		■	■	■
Dispense Rescue Medication and training on use	■		■				
Dispense Daily diary and train on use	■	■	■				
Local lab tests for creatinine and hematocrit (if historical tests within the last 3 months are not available)	■						
BDI [d] and mMRC			■				
TDI [d]					■		■
PIFR	■[e]	■[e]			■[e]		■[f, g]

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

Procedures	Screening[a]		Randomization Day 1 (Visit 2)	Treatment Period (29 days)	Day 29 (Visit 3) ± 5 days	Follow-Up/ Phone call 7 days after last visit ± 2 days	Early Termination/ Withdrawal
	(Visit 1A)	(Visit 1B)					
Predose Spirometry (FEV_1, FVC) at 45 and 15 minutes predose			■		■		■[f, g]
IC measured with a SVC maneuver at 45 minutes predose[g]			■		■		■
MIP[h]			■		■		■[f]
LABA dosing (if applicable)			■	■	■		
Training on the use of the [redacted] and nebulizer devices by watching a training video			■				
In-Clinic study drug dosing			■		■		

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

Procedures	Screening[a]		Randomization Day 1 (Visit 2)	Treatment Period (29 days)	Day 29 (Visit 3) ± 5 days	Follow-Up/ Phone call 7 days after last visit ± 2 days	Early Termination/ Withdrawal
	(Visit 1A)	(Visit 1B)					
Record Study Drug Use and Rescue Med Use on Daily diary			■	■	■		
Postdose Spirometry (FEV_1, FVC,) at 1, 2, and 4 hours postdose			■		■		

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.

b A repeat urine pregnancy test is required at randomization (Visit 2) if visit is > 7 days after visit 1A urine pregnancy test.

c Spirometry measurements predose and 45 min postdose for ipratropium reversibility.

d BDI (Baseline Dyspnea Index), TDI (Transitional Dyspnea Index).

e PIFR will be measured at Visit 1A, only set to [redacted] resistance. PIFR will be measured at V1B set to [redacted] and [redacted] resistance and also at day 29 and early term visits. Subjects requiring a LAMA washout with ≥75 L/min set at [redacted] resistance will be excluded per exclusion criteria #5 at Visit 1A. Subjects not requiring a LAMA washout with ≥60 L/min set at [redacted] resistance will be excluded (per exclusion criteria #6) at Visit 1A. PIFR will be measured again at Visit 1B for inclusion criteria #2.

f Measurements will be done if subject is willing.

g IC will be measured by a separate slow vital capacity (SVC) maneuver performed immediately after the FVC maneuver at -45 minutes only on Day 1 and Day 29 only. Similarly, at an ET visit where an FVC maneuver is done 30 minutes apart, the SVC will only be performed immediately after the first FVC.

h MIP will be performed immediately after the SVC maneuver at -45 minutes only on Day 1 and Day 29 only.

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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
AUC	area under concentration curve
BDI/TDI	Baseline Dyspnea Index / Transitional Dyspnea Index
BP	blood pressure
COPD	chronic obstructive pulmonary disease
CRF	case report form
DPI	dry powder inhaler
ECG	Electrocardiogram
EDC	electronic data capture
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
HR	heart rate
IB	Investigator's Brochure
IC	Inspiratory capacity
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
IRB	Institutional Review Board
ITT	Intent-to-treat
LABA	long-acting $beta_2$ agonist
LAMA	long-acting muscarinic antagonist
LTOT	Long Term Oxygen Therapy
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
MDI	Metered-dose inhaler
MIP	Maximal Inspiratory Pressures
mMRC	Modified Medical Research Council Questionnaire
M_1	muscarinic receptor 1 (subtype)
M_2	muscarinic receptor 2 (subtype)
M_3	muscarinic receptor 3 (subtype)

Abbreviation	Description
M_4	muscarinic receptor 4 (subtype)
M_5	muscarinic receptor 5 (subtype)
NEB	nebulizer
PIFR	Peak Inspiratory Flow Rate
PRN	Administration as needed
SVC	Slow Vital Capacity

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 the Treatment of 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}. For some patients, bronchodilator therapy is most effectively provided using a nebulizer device. Revefenacin is designed as a once-daily agent to be administered using a standard jet nebulizer.

1.1 Background and Rationale

[redacted]

1.2 Nonclinical Profile

Revefenacin is a 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). The following is a brief summary of the pertinent findings.

1.2.1 Pharmacology

[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 Investigator's Brochure.

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 Investigator's Brochure.

1.3 Clinical Experience

[redacted]

[redacted]

[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 repeated blood sampling.

During the single dose study in which revefenacin was administered as a dry powder, the most common adverse events were dysgeusia and headache.

In Study [redacted] a single nebulized dose (350 or 700 mcg) of revefenacin was administered to COPD subjects according to a crossover design. The study also involved ipratropium and placebo. Adverse events were generally mild and occurred with similar frequencies in all periods of the study – including the placebo period. The most common adverse events were headache and dyspnea. In Study [redacted] subjects with COPD received doses ranging between 22 and 700 mcg (or placebo) once daily for 7 days. Each subject was assigned to 5 different treatment periods with a 2-week washout between each period. A range of adverse events occurred in this population most of which were consistent with the underlying disease state (COPD) and not unanticipated in a study of this duration. There were no deaths in this study. [redacted]. Other adverse events were generally mild and occurred with similar frequencies in all treatment periods including the placebo period. The most common adverse events reported in this study were headache, cough and dyspnea.

In Study [redacted] the most common adverse event was dyspnea. There was one serious adverse event, a death, in the study. [redacted] The investigator assessed the event as unrelated to study medication.

[redacted]

[redacted]

[redacted]

Clinically significant bronchodilation has been observed in each of the study populations of COPD subjects thus far in the development program, however revefenacin is an investigational drug and its benefits and risks continue to be evaluated in phase 3. Two replicate phase 3 studies 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 treatment groups were exacerbations, 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, and in addition, [redacted]

2 OBJECTIVES

The primary objective of the study is as follows:

- To characterize the relative efficacy on trough FEV_1 of revefenacin administered once daily via nebulization compared to tiotropium administered once daily via [redacted] in a population of subjects with moderate to very severe COPD and suboptimal PIFR.

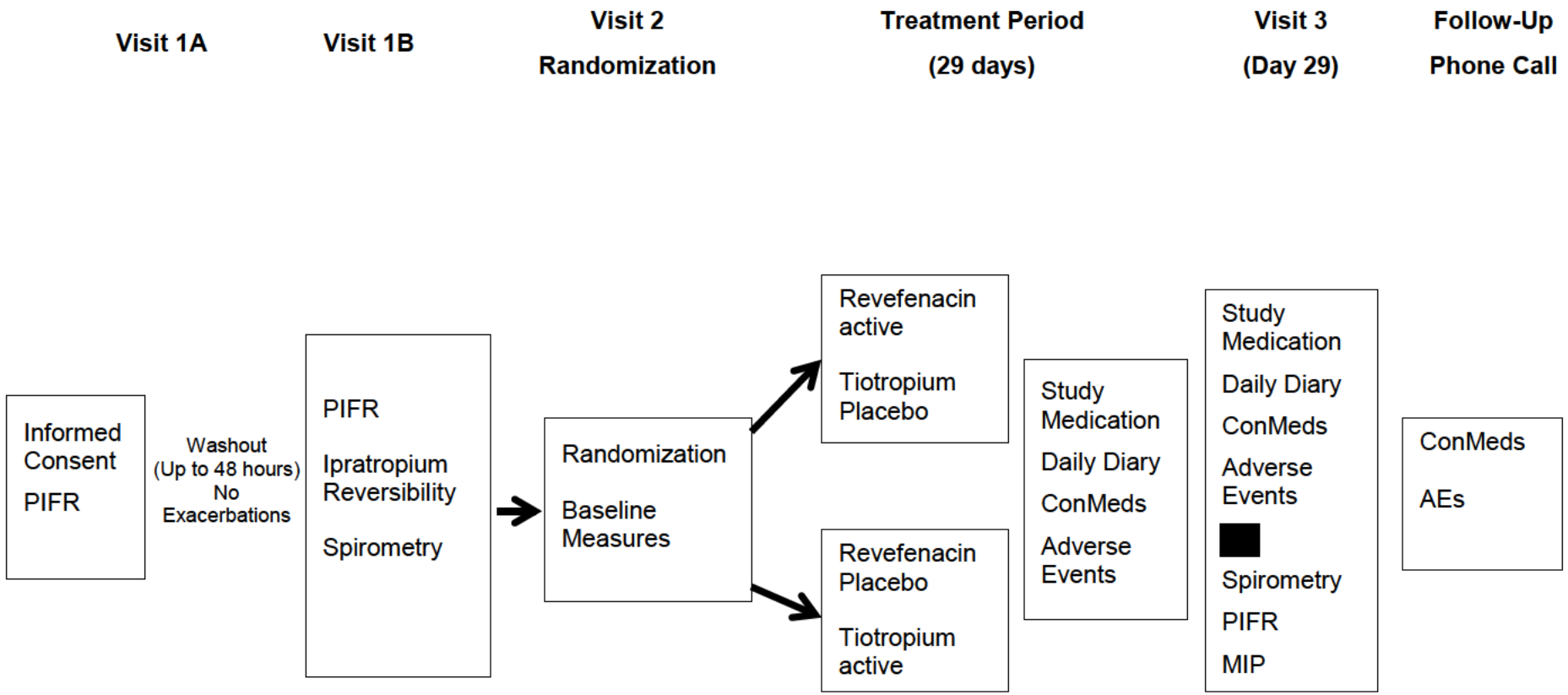
The secondary objectives of the study are as follows:

- Characterize relative efficacy of Trough FVC and IC post 28th dose on Day 29
- Characterize relative efficacy of Peak FEV_1, FVC and IC on Day 29 (0-4 hours)
- Characterize relative efficacy of Peak FEV_1, FVC and IC on Day 1 (0-4 hours)
- Characterize relative use of rescue albuterol use

3 STUDY DESIGN

3.1 Overview

Figure 1: Study Design Schema



3.2 Rationale for Study Design

This is a Phase 3b study to assess revefenacin at a dose of 175 mcg administered once-daily for 29 days using the jet nebulizer that was utilized in the earlier studies of the program. This study is intended to provide data in patients with moderate to severe COPD who have sub-optimal PIFR, where nebulized delivery of revefenacin could provide more benefit, as measured by spirometry and dyspnea symptoms than a DPI [redacted] to support the use in this demographic as a bronchodilator for the treatment of subjects with COPD. The 175 mcg dose selected from the Phase 3 studies has an optimal benefit:risk ratio to further characterize the use in this specific patient population.

The study is designed as a double blinded, double-dummy, parallel-group study, with 100 subjects randomized to each treatment group [redacted] Randomization allows for an unbiased assessment of treatment effects across revefenacin and tiotropium. The duration of treatment is limited, and all subjects will have study specific rescue medication (albuterol via MDI or via nebulization) provided for the full duration of the study, including during the screening (via MDI only) and follow-up periods. Subjects who have an exacerbation that requires treatment (other than increased use of study supplied albuterol) during the study period will be discontinued.

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 >400 mL, [NHANES III]) {5}. Subject should meet a PIFR of <60 L/min as measured by [redacted] device with resistance set to [redacted] at screening at Visit 1B.

3.3 Selection of Doses and Duration of Treatment

The selection of the 175 mcg dose of revefenacin for this study is based on the results of two (2) twelve week studies conducted as part of the phase 3 program in the clinical development of revefenacin [redacted] The results of those studies showed that revefenacin, administered once daily via a standard jet nebulizer at doses of 88 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 study endpoint is trough FEV_1 on Day 29.

The secondary endpoints are:

- Trough FVC and IC post 28th dose on Day 29
- Peak FEV_1, and FVC on Day 29 (0-4 hours)
- Rescue albuterol use (incidence of albuterol use)

[redacted]

The safety endpoints are:

- Adverse events
- Vital signs
- Concomitant medications

3.4.1 Minimization of Bias

Bias will be minimized through the use of randomization and a double-blind double-dummy study design.

3.4.2 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 the tiotropium comparator arm. Subjects will be assigned in random order to tiotropium or revefenacin 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 IWRS. 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 IWRS.

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.

3.4.3 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 IWRS (Day 1 visit) with the following stratification factors: [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 with a diagnosis of COPD
2. Subject has <60 L/min of PIFR as measured by [redacted] with resistance set to [redacted] at screening at Visit 1B.
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 and post-ipratropium predicted FEV_1 < 80% at screening and FEV_1>400mL.
4. Subject has a current or past cigarette smoking history (or equivalent for cigar or pipe smoking history) of at least 10 pack-years.
5. Subject is willing and able to provide signed and dated written informed consent to participate prior to initiation of any study related procedures.
6. Subject is willing and able to adhere to all study assessments/procedures
7. Women of either non-child bearing potential or child bearing potential, provided that:
   - 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.

   (Women 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.)
8. Subject (or caregiver) based on the investigator's assessment is able to properly prepare and administer study medication administered either by nebulizer or [redacted]

4.2 Exclusion Criteria

1. 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 and tolerability of the study drug.
2. Subject has a history of reactions or hypersensitivity to inhaled or nebulized anticholinergics.
3. 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.
4. A clinically significant abnormal lab for any of the following tests that, in the investigators opinion, would likely interfere with the successful completion of the study. Historical labs performed within the last 90 days are acceptable; if not available, then labs for these tests will be performed at Visit 1A.
    - creatinine
    - hematocrit
5. For subjects requiring a washout of a LAMA, Subject has ≥75 L/min of PIFR as measured by [redacted] device with resistance set to [redacted] at screening at Visit 1A
6. For subjects not requiring a washout of a LAMA, Subject has ≥60 L/min of PIFR as measured by [redacted] with resistance set to [redacted] at screening at Visit 1A
7. Subject has been hospitalized for COPD or pneumonia within 8 weeks prior to Visit 1A.
8. Subject has a COPD exacerbation requiring treatment (other than increased use of study supplied albuterol) during the screening period.
9. Subject has used systemic corticosteroids within 8 weeks prior to Visit 1A.
10. Subject has used antibiotics for respiratory tract infections within 8 weeks prior to Visit 1A.

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 IWRS. Each drug kit will contain a unique kit number which will be provided by the IWRS 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

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

[redacted]

Revefenacin and its placebo must be stored in a secure location accessible only to designated study personnel, at temperatures stated in the Pharmacy Manual.

Detailed instructions for administration will be provided separately and provided to the study subject.

5.1.2 Tiotropium

Tiotropium will be provided in blister cards which consists of [redacted] dry powder capsules or matching placebo administered using the [redacted] device.

Tiotropium and its placebo should be stored in a secure location at room temperature (15°C to 30°C or 59°C to 86°F).

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

5.2 Dose Administration

5.2.1 Revefenacin

Revefenacin will be administered on the morning of Day 1 in 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 after tiotropium each day.

Training on the home use of the nebulizer will take place after the subject is randomized on Visit 2 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 Tiotropium

Tiotropium will be administered on the morning of Day 1 in the clinic. Tiotropium will be administered immediately prior to revefenacin on Day 1 and on each day at home.

The subject will take the [redacted] device and the tiotropium dry powder capsules home where dosing will occur every morning at approximately the same time. This time will be chosen based on convenience for the study subject and will be within the window of 6 am and 11 am. The time of administration will be recorded by the subject in their diary. At each of the remaining study visits subjects will be required to bring their [redacted] device and unused tiotropium capsules back to the clinic for in-clinic dosing on visit days. At each study visit subjects will be dispensed sufficient tiotropium capsules for home dosing until the time the subject returns for their next study visit.

Training on the home use of the [redacted] device will take place at Visit 2 after the subject is randomized. 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 the use of the [redacted] device is contained in the Package Insert.

5.2.3 Agents Used for Rescue Medication

5.2.3.1 Albuterol

Albuterol will be provided as a MDI or as a solution for nebulization for rescue medication on an as-needed basis and administered at a dosage of 90 mcg per puff or via nebulization at a dosage of 2.5 mg every 6-8 hours. Subjects will be provided with one MDI at Visit 1A. At Visit 2 (Day 1) subjects must decide whether to receive albuterol via MDI or nebulization for the remainder of the study. This method of administration must remain the same until the subject completes the study. If the subject chooses albuterol via nebulization at Visit 2 then the MDI dispensed at Visit 1A should be retrieved. If the subject chooses to continue with albuterol via MDI, then the MDI at Visit 1A may be kept. Please see 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. [redacted]

[redacted]

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 29) 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. [redacted]

[redacted]

Albuterol use will be captured using the dose counter on the albuterol inhaler. If a subject forgets to return the albuterol inhaler at a study visit, the study coordinator should contact the subject by telephone after the subject returns home to obtain the value of the counter as reported by the subject.

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 electronic case report forms (eCRFs).

The scheduling of Visit 3 (Day 29, ± 5 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 3, with a ± approximate 2 day visit window.

6.2 Procedures by Visit

6.2.1 Screening

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 (see Table 2 for specific washout periods required).

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). Long acting bronchodilators requiring a washout include LAMAs (tiotropium [redacted] glycopyrronium bromide, aclidinium [redacted]), umeclidinium ([redacted]) or any other approved LAMA; combination LAMA/LABA products [redacted] olodaterol/tiotropium or any other approved combination LAMA/LABA); and roflumilast (Table 2). The effects of the long acting agent will be washed out between Visit 1A and Visit 1B and this washout period will be at least 48 hours and no longer than 7 days. Subjects not taking these long acting bronchodilators, or other COPD medications requiring a washout at screening, can be randomized 3 to 7 days after the

screening visit. As part of the screening visit, the investigator should review subjects' most recent lab work (within the previous 3 months) to ensure that subjects are stable and to confirm that creatinine and hematocrit values are normal and/or not clinically significant. If historical lab tests containing these tests have not been performed within 3 months, then local labs should be performed at Visit 1A. The local lab results (either historical or performed at Visit 1A) must be present in the source documents.

Subjects on LABAs (e.g. salmeterol, indacaterol, vilanterol, formoterol, arformoterol, olodaterol) either alone or in combination with an ICS (e.g. fluticasone propionate, fluticasone fuorate, budesonide, ciclesonide, beclomethasone) will not need to be washed out before enrolling in the study and will be allowed to be randomized on this background therapy.

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 3 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.

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

Subjects should not have taken their LABA for approximately 12 hours (if on BID therapy) or approximately 24 hours (if on QD therapy) prior to performing the measurement for PIFR at Visit 1A. Additionally, subjects should not have taken albuterol or any other short acting bronchodilator for approximately 6 hours prior to the PIFR measurements. If this has occurred subjects may still be consented however should return to have Visit 1A performed on a separate day.

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, based on the washout periods specified in Table 2, 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
- PIFR – subjects requiring a washout of a LAMA with ≥75 L/min of PIFR as measured by [redacted] device with resistance set to [redacted] will be screen failed at Visit 1A
- PIFR – subjects not requiring a washout of a LAMA with ≥60 L/min of PIFR as measured by [redacted] device with resistance set to [redacted] will be screen failed at Visit 1A
- A urine pregnancy test will be done for females of childbearing potential
- Subject will be trained on and dispensed the diaries
- Local lab tests for creatinine and hematocrit if historical local labs within 3 months of Visit 1A are not available

6.2.1.2 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
    - PIFR measurements with resistance set to [redacted] and [redacted] resistance (Subjects with ≥60 L/min of PIFR with resistance set to [redacted] will be screen failed at Visit 1B)
    - Complete physical examination
    - Height and weight
    - Vital signs (BP and HR) - subjects need to be resting in a semi-recumbent position approximately 5 minutes prior to assessment of vital signs
- Ipratropium Reversibility - Spirometry reversibility testing pre- and postdose ipratropium after withholding bronchodilators as specified in Table 2. Spirometry will be performed predose and 45 minutes postdose (± 10 minutes).
- Subject training on the MIP maneuver
- Concomitant Medications
- Adverse Events
- Review of inclusion and exclusion criteria
- Collect and review Daily Diary (if applicable) and dispense Daily Diary

6.2.2 Treatment and Follow-up Period

6.2.2.1 Visit 2 (Randomization Visit)

The following procedures will be performed at Visit 2. The timing of predose procedures is relative to the start of study drug administration (using the [redacted] The timing of procedures postdose study drug administration is relative to the completion of nebulization of revefenacin.

All attempts should be made to perform the spirometry FVC maneuver at the required time points (i.e. the FVC maneuver will take priority over other protocol procedures and if necessary the timing of the other protocol procedures are approximate and may be adjusted

to accomplish this requirement). Such adjustments will not be considered protocol deviations as long as the appropriate reason is documented in the source documents.

The sequence of events for the subject to follow at home will be as follows: recording the start time of study drug (i.e. use of [redacted]) in the paper diary, then administering the [redacted] first, followed immediately by nebulized revefenacin.

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 spirometry assessments. They should further refrain from using albuterol throughout the study visit.

It is important at study visits that the trough FEV_1 is done before receiving study drug (and before taking LABA if applicable). If the subject is taking a LABA this must be taken immediately before the study drug. For subjects that are taking a LABA, the sequence will be LABA, followed immediately by tiotropium/placebo ([redacted]; then nebulized revefenacin/placebo. The following procedures will be performed at the Randomization Visit:

- Review of inclusion and exclusion criteria
- Urine pregnancy test if visit is > 7 days after visit 1A
- Randomization (subject eligibility must be confirmed by investigator before randomizing subject)
- Collect Daily Diary and reconcile rescue medication as appropriate. Dispense Daily Diary
- Concomitant medications
- Adverse events
- Subjects will be given the choice to receive rescue albuterol either as an MDI or as nebules for nebulization for the remainder of the study. This will be assigned in IWRS and dispensed accordingly and subjects will be trained on their administration. (If the subject chooses to receive nebules at this visit, the MDI dispensed at Visit 1A should be retrieved.)
- Dispense study drug (IWRS will assign 1 kit of each drug)
- Administer BDI
- Complete modified Medical Research Council Questionnaire (mMRC)
- Predose FEV_1, FVC via spirometry to be done 45 minutes and 15 minutes prior to the start of study drug dosing

- Predose IC via spirometry to be done 45 minutes prior to the start of study drug dosing post the FVC maneuver
- MIP
- If appropriate, Administer LABA containing product (for those on existing LABA-containing therapy)
- Study drug dosing via [redacted] (tiotropium or placebo) followed immediately by study drug dosing via nebulizer (revefenacin or placebo). Training on the specific devices will be performed before the first dose is administered and as part of receiving the first dose.
- Postdose Spirometry (FEV_1, FVC) at 1, 2, and 4 hours postdose
- Record Study Drug use and any in-clinic rescue medication use

6.2.2.2 Visit 3 (Day 29)

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 albuterol for at least 6 hours prior to their spirometry. They should further refrain from using albuterol throughout the study visit.

It is important at study visits that the trough FEV_1 is done before receiving study drug (or and before taking LABA if applicable). If the subject is taking a LABA this must be taken immediately before the study drug.

The following procedures will be performed at Visit 3:

- Physical Exam
- Vital signs (BP and HR) - subjects need to be resting in a semi-recumbent position approximately 5 minutes prior to assessment of vital signs.
- Urine pregnancy test
- Collect and review Daily Diary
- Collect and reconcile returned study drug and assess compliance
- Concomitant medications
- Adverse events
- Complete TDI
- Predose FEV_1, and FVC, via spirometry to be done 45 minutes and 15 minutes predose.
- Predose IC via spirometry to be done 45 minutes predose and immediately post the FVC maneuver.
- MIP – to be done immediately post the IC measurement

- PIFR – to be done immediately post the FVC maneuver at 15 minutes predose. Subjects will complete PIFR measured by [redacted] device with resistance set to [redacted] followed by PIFR set at the [redacted] resistance.
- If appropriate, Administer LABA containing product (for those on existing LABA-containing therapy)
- Study drug dosing via [redacted] (tiotropium or placebo) followed immediately by study drug dosing via nebulizer (revefenacin or placebo).
- Postdose Spirometry (FEV_1, FVC) at 1, 2 and 4 hours postdose.
- Record Study Drug use and any in clinic rescue medication use
- Collect and reconcile rescue medication as appropriate. Document the number of rescue puffs (if MDI) or nebules (if nebulized) that were used. The number of rescue nebules used will equal the number dispensed less the number still available to the subject.

6.2.2.3 Visit 4 (Telephone Follow-up) (7 Days ± 2 days after Visit 3)

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

- Concomitant medications
- Adverse events

6.2.3 Early Termination/Withdrawal Visit

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

- Physical exam
- Vital signs (BP and HR)
- Urine pregnancy test
- Collect and review of Daily Diary
- Collect and reconcile returned study drug and assess compliance
- Collect and reconcile rescue medication
- Concomitant medications
- Adverse events
- Complete TDI
- PIFR - subjects will complete PIFR measured by [redacted] device with resistance set to [redacted] followed by PIFR set at the [redacted] resistance.
- MIP
- Spirometry (FEV_1, FVC) at two time points 30 minutes apart. A SVC maneuver to measure IC is only performed immediately after the first spirometry maneuver.

(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.)

6.2.4 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
- Record concomitant medications
- Record adverse events
- Spirometry
- PIFR
- MIP

6.3 Description of Study Assessments

6.3.1 Demographic and Screening 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; PIFR, FEV_1, FVC (as part of spirometry for ipratropium reversibility), and a urine pregnancy test for females of child-bearing potential.

6.3.2 Efficacy Assessments

6.3.2.1 Spirometry

Spirometry, using a flow-volume loop for all respiratory flow measurements, will be completed as follows during the course of the study. Measurements will be done according to methods described separately in the Spirometry Manual; this Manual is based on ATS Guidelines.

- At Visit 1B (as part of ipratropium reversibility)
- At Visits 2 and 3

The time window for the 45 and 15 minute predose spirometry will be ± 10 minutes, which applies to the end time of the session. The time window for the 1, 2 and 4 hour postdose spirometry will be ± 10 minutes, which applies to the start time of the session. IC will be measured by a separate slow vital capacity maneuver and only be performed immediately after the 45 minute predose FVC maneuver at Visit 2 and 3.

A central spirometry vendor will be used to provide standardized training on spirometry, qualification of the spirometry technician, and quality control of the spirometry throughout the study.

PIFR and MIP will be measured at time points shown in the schedule of procedures using methods described in the Spirometry Manual. As PIFR will be measured with a device that involves taking a visual reading using a graduated scale, a second person at the site will be asked to verify the reading and this verification will be noted in the source documents.

6.3.3 Safety Assessments

6.3.3.1 Adverse Events

Adverse events will be reviewed and recorded from the time of first dose of study medication 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.

6.3.3.2 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.

6.3.3.3 Physical Examination

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

6.3.3.4 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. 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.

6.3.3.5 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.

6.4 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 first spirometry performed at each study visit until all spirometry is completed. 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 spirometry measurement the visit must be rescheduled. Use of albuterol as a rescue inhaler will be documented in a medication diary and recorded in the eCRF.

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. Once enrolled it is important to standardize administration of the subject's LABA or LABA/ICS together with the study drug. These subjects should administer their LABA or LABA/ICS in the morning immediately prior to the administration of study drugs. This administration should be documented in the source documents on study visit days and subjects should be instructed to follow the same procedure while at home between study visits. If subjects have used their LABA or LABA/ICS on the morning prior to their in-clinic visit instead of taking it immediately

prior to study drug at Visit 2, this visit will be rescheduled and the subject will be trained on the importance of not taking this the morning of the study visit.

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.

Table 2 lists the medications that require washout prior to Randomization. These medications are also prohibited throughout the study. Subjects will be permitted to restart their routine medications after the completion of Visit 3.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

6.5 Restrictions

Subjects are to observe the following restrictions from Screening through to Day 29:

- Use of recreational drugs
- Medicinal marijuana
- Excessive alcohol during the study period
- Participation in another investigational drug study
- 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 0149 Study Manual).

6.6 Discontinuation

6.6.1 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. 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. All efforts should be made however to minimize discontinuations from the study. If a subject withdraws consent from participation in the study, the sponsor retains the right to use the subject's data through to the date the subject withdraws consent.

Exacerbations of COPD as part of the disease under study should not be recorded as adverse events unless they are Serious Adverse Events (e.g. they are life threatening, require or prolong hospitalization, etc.).

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
- COPD Exacerbation requiring treatment (other than increased use of study supplied albuterol)
- Subject choice (i.e. withdrew consent)
- Major deviation of the protocol
- Lost to follow-up
- Termination of the study by the Sponsor
- Other

Subjects who discontinue study drug early because of an adverse reaction should be encouraged to continue their participation in the follow-up safety assessments. A telephone follow-up visit will be conducted 30 days after discontinuation to review concomitant medications and adverse events if the discontinuation was due to an AE. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. This will consist of at least 3 telephone calls followed by a registered letter to the subject.

6.6.2 Subject Replacement

[redacted]

6.6.3 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 SAEs (SUSARs) 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.

6.7 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.

If the female partner of a male subject becomes pregnant, the Investigator must attempt to obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

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.

6.8 COPD Exacerbation

Exacerbations of COPD requiring treatment other than increased use of study supplied albuterol are cause for withdrawal from the study and will be captured as a reason for study termination.

7 ADVERSE EVENTS

7.1 Regulatory Definition of an Adverse Event

In the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice, Section 1.2 defines an adverse event (AE) as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily 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 (investigational) product, whether or not considered related to the medicinal (investigational) product.

7.2 Adverse Event Definition for the Purposes of This Study

For the purposes of this clinical study, adverse events will be defined as follows:

An adverse event (AE) is any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with the study treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not considered related to the study drug (investigational product).

Preexisting events that increase in frequency or severity or change in nature during or as a consequence of participation in clinical studies will also be considered as adverse events. An AE may also include pre- or post-treatment complications that occur as a result of a protocol-mandated procedure (such as a biopsy).

Any medical condition or clinically significant laboratory abnormality with an onset date prior to the first dose of study medication is considered to be preexisting and should be documented in the medical history CRF, if applicable for the study.

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:

- COPD Exacerbation as that is the disease under study, unless such exacerbation qualifies as an SAE. (See SAE below)
- 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 to first dose of study medication 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

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.

Clinical severity should be recorded and graded using mild, moderate or severe as described below.

Mild	= Awareness of signs or symptoms, but easily tolerated
Moderate	= Discomfort sufficient to cause interference with usual activities
Severe	= Incapacitation with inability to work or perform usual activities

The relationship to study drug therapy should be assessed using the following definitions:

- **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).
- **Possibly/Probably 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.

These criteria in addition to good clinical judgment should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

7.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)

- In-patient-hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events)
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Other: 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

Additional Considerations for Serious Adverse Events

- Death is an outcome of an adverse event and not an adverse event in itself. In reports of death due to disease progression, where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study drug(s).
- 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.
- “Life-threatening” means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- “In-patient-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.
- The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

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

Abnormal assessments (such as vital signs) that are associated with signs and/or symptoms or 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 7.2 (Adverse Event Definition for the Purposes of This Study) and 7.4 (Serious Adverse Events).

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

7.6 Serious Adverse Event Reporting

Any SAE that occurs after a subject has signed the informed consent form through the follow-up visit, regardless of causal relationship, must be reported to the Sponsor within 24 hours of the investigator's knowledge of the event. To report an SAE, complete the SAE report form and submit as described on the form. For medical questions regarding an SAE, contact the medical monitor by telephone as follows:

Sponsor Medical Monitor Contact Information:

[redacted]
[redacted]
Telephone: [redacted]
Email: [redacted]

As an alternate, contact:

[redacted]
Telephone: [redacted]
Email: [redacted]

For fatal or life-threatening events, email or fax copies of hospital case reports, autopsy reports, and other documents when requested to:

Theravance Clinical Safety and Pharmacovigilance (CSPV):

Email: [redacted]
Fax:

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 Investigator's Brochure. 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.

7.7 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 [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] approximately 100 subjects will be randomized per treatment group (N=200 subjects in total).

[redacted]

A total of 50 or more subjects with GOLD grade 4 will be enrolled.

8.2.1 Randomization Strata

Randomization will be conducted using the following stratum to ensure balance in subjects:

- Concomitant LABA use [redacted])
- Baseline PIFR set to [redacted] resistance [redacted]
- GOLD airway limitation grade ([redacted])

8.3 Analysis Sets and Subgroups

8.3.1 Analysis Sets

The Intent-to-Treat (ITT) analysis set will include all randomized subjects receiving at least one dose of study drug and at least one post-baseline FEV_1 assessment. The ITT analysis set will be the primary analysis set for the summarization of efficacy analyses.

The Per-protocol (PP) analysis set will include all subjects in the ITT analysis set with no major protocol analysis deviations.

The Safety (Safety) analysis set will include all subjects receiving at least one dose of study drug summarized by actual drug received. The Safety analysis set will be the primary analysis for General and Safety analyses.

8.3.2 Examination of Subgroups

The following subgroups are pre-defined at baseline:

- Baseline smoking status [redacted],
- Age [redacted]
- Sex [redacted]
- Current LABA-product containing use [redacted],
- Baseline post bronchodilator % predicted FEV_1 [(≥ [redacted]
- Baseline PIFR set to [redacted] resistance [redacted]
- Baseline PIFR set to [redacted] resistance [redacted]
- Baseline PIFR set to HandiHaler® resistance [redacted]
- Consistency of Screening PIFR at Visits 1B and 3 [redacted]
- BMI [redacted]

Selected efficacy analyses, as defined in the statistical analysis plan (SAP), will be conducted using the subgroup examination sets. Additional subgroups may be defined in the SAP.

8.3.3 Major Protocol Deviations

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

[redacted]

8.4 General Analyses

8.4.1 Demographics and Other Baseline Characteristics

Demographics (including age, sex, race, ethnicity, height, weight, and BMI) and baseline characteristics (concomitant LABA use) will be summarized for the Safety analysis set.

8.4.2 Screening and Baseline Spirometry

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.

8.4.5 Reversibility

Reversibility to ipratropium is defined as a post-bronchodilator increase of 12% and at least a 200 mL increase in FEV_1 relative to the pre-bronchodilator response at the relative screening visit.

8.5 Efficacy Analyses

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

8.5.1 Efficacy Endpoints

The primary study endpoint is trough FEV_1 post the 28th dose on Day 29.

The secondary endpoints are:

- Trough FVC and IC post 28th dose on Day 29
- Peak FEV_1 and FVC on Day 29 (0-4 hours)
- Rescue albuterol use (incidence of albuterol use)

[redacted]

- [redacted] s FEV_1, FVC (0-4 hours) on Days 1 and 29
- TDI on Day 29

8.5.2 Primary Efficacy Evaluation

[redacted]

The following hypothesis testing schema will be employed to assess the primary endpoint: the null hypothesis for the treatment comparison will be that there is no difference between the mean responses at a given dose level of revefenacin and the mean response on the tiotropium treatment in trough FEV_1. The alternative hypothesis will be that there is a difference.

[redacted]

[redacted]

8.5.3 Secondary Efficacy Endpoints

8.5.3.1 Trough FVC and IC

[redacted]

8.5.3.2 Peak FEV_1 and FVC

Peak pulmonary functions will be summarized [redacted]

8.5.3.3 Rescue Medication Endpoints

Rescue medication endpoints will be summarized using a similar methodology as the primary endpoint where [redacted]

8.5.3.4 Clinical Outcomes Assessments

[redacted]

8.5.3.5 [redacted]

[redacted]

8.5.4 Impact of Rescue Medication Use on Spirometry Data

The use of a COPD rescue medication [redacted] will confound the estimation of treatment effect. [redacted]

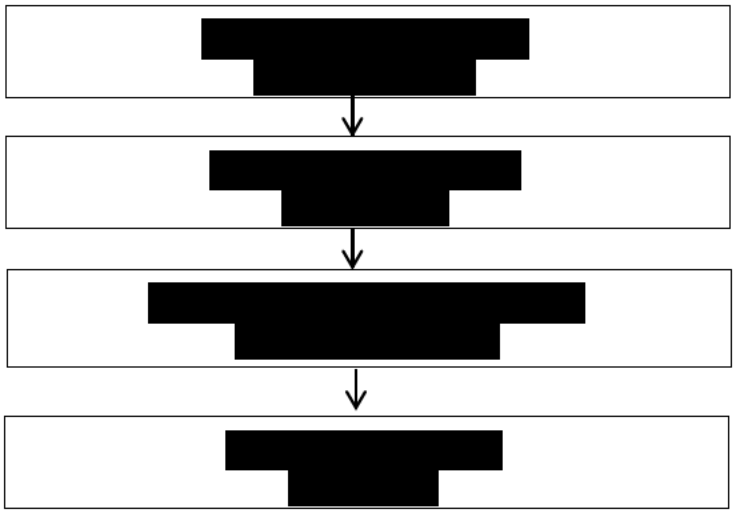
8.5.5 Multiplicity Adjustment

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

8.6 Safety Analyses

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

Safety variables to be summarized include vital signs and adverse events. Vital signs will be summarized in terms of observed values and changes from baseline.

8.6.1 Extent of Exposure

A subject's data for the extent of exposure to study drug will be generated from study drug accountability. Dosing information for individual subjects will be listed. [redacted]

8.6.2 Adverse Event Data

8.6.2.1 Adverse Events

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.

A treatment-emergent adverse event (TEAE) will be defined as any AE that [redacted] AEs observed during the period from obtaining informed consent to the first dose of study drug are to be captured as medical history.

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.

8.6.3 Concomitant Medications

Medications will be summarized both prior and during the 1-month treatment period. Medications will be summarized as COPD bronchodilator, ICS and non-COPD medications.

8.6.4 Vital Signs Data

[redacted]

[redacted]

[redacted]

8.7 Missing Data Handling

[redacted]

[redacted]

[redacted]

8.8 Data Monitoring Committee

No data monitoring committee is planned for this study.

Monitoring of trial data to ensure the safety of subjects will take place by the ongoing periodic review of tables and listings of the safety data collected during the conduct of the trial. These meetings will take place approximately monthly once the trial has been initiated.

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 sub-investigators who will be directly involved in the treatment or evaluation of research subjects in this study. (A sub-investigator 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 Investigator's Brochure, 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/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 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.

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 designated service providers, regulatory agencies, and the institutional review board (IRB) or independent ethics committee (IEC). Suppliers used in the study will also have access to some of the subjects' medical information as part of providing their services in the study (e.g. central spirometry). 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

The following references are available upon request.

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6. Jarvis S, Ind PW, Shiner RJ. Inhaled therapy in elderly COPD patients; time for re-evaluation? Age Ageing. 2007 Mar;36(2):213-8

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8. Chee Hong Loh, MD; Tina Lovings, RCP; Jill Ohar, MD. Long Acting Nebulized Agents Decrease Readmissions in Patients With Suboptimal Peak Inspiratory Flow. Chest. 2016;150(4_S):925A. doi:10.1016/j.chest.2016.08.1025

Appendix 1: Signature Page

Protocol Signature Form

Title: A Phase 3b, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Study to Compare Once Daily Nebulized Revefenacin with Spiriva Once Daily Delivered via the [redacted] on Lung Function in Subjects with Chronic Obstructive Pulmonary Disease and a Low Peak Inspiratory Flow Rate

Study No.: 0149

Date: 04 April 2017

I have read the forgoing protocol and agree to conduct this study in accordance with the current protocol. I also agree to conduct the study in compliance with all applicable regulations.

_____
Investigator's Name (print)

_____ _____
Investigator's Signature Date