Protocol Number: 0180

Official Title: A Phase 4, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Study Comparing Improvements in Lung Function in Adults With Severe to Very Severe Chronic Obstructive Pulmonary Disease and Suboptimal Inspiratory Flow Rate Following Once-Daily Treatment Over 12 Weeks With Either Revefenacin Inhalation Solution Delivered Via Standard Jet Nebulizer or Tiotropium Delivered Via a Dry Powder Inhaler (Spiriva® HandiHaler®)

NCT Number: NCT05165485

Document Date: 27 February 2023

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 4, Randomized, Double-Blind, Double-Dummy, Parallel-Group Study Comparing Improvements in Lung Function in Adults With Severe to Very Severe Chronic Obstructive Pulmonary Disease and Suboptimal Inspiratory Flow Rate Following Once-Daily Treatment Over 12 Weeks With Either Revefenacin Inhalation Solution Delivered via Standard Jet Nebulizer or Tiotropium Delivered via a Dry Powder Inhaler (Spiriva® HandiHaler®)
Study Short Title:	PIFR-2 Study
Sponsor Study No.:	0180
Date:	27 Feb 2023, Amendment 4 (FINAL) Supersedes: 09 Feb 2022, Amendment 3
Test Product:	Revefenacin
US IND:	119840
Sponsor:	Theravance Biopharma Ireland Limited Ten Earlsfort Terrace Dublin 2 D02 T380 Ireland
Clinical Study Director:	[redacted] [redacted] Theravance Biopharma US, Inc. Telephone: [redacted] Email: [redacted]

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

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: Study 0180: A Phase 4, Randomized, Double-Blind, Double-Dummy, Parallel-Group Study Comparing Improvements in Lung Function in Adults With Severe to Very Severe Chronic Obstructive Pulmonary Disease and Suboptimal Inspiratory Flow Rate Following Once-Daily Treatment Over 12 Weeks With Either Revefenacin Inhalation Solution Delivered via Standard Jet Nebulizer or Tiotropium Delivered via a Dry Powder Inhaler (Spiriva® HandiHaler®)

Study Short Title: PIFR-2 Study

Estimated Number of Study Centers and Countries or Regions: Approximately 70 centers in the United States (US)

Background and Rationale: Revefenacin is an orally inhaled muscarinic antagonist which is approved by the US Food and Drug Administration (FDA) for the maintenance treatment of chronic obstructive pulmonary disease (COPD).

Long-acting bronchodilators can be delivered via a metered-dose inhaler (MDI), dry powder inhaler (DPI) or nebulizer. Successful use of a nebulizer requires the patient to breathe normally (tidal breathing) to successfully deliver the medicine, whereas use of MDIs and DPIs requires more complex coordination of actuation of the device and / or an appropriate inhalation technique (slow inhalation in case of MDI; forced inhalation in the case of DPI) to successfully deliver the medicine. Therefore, nebulized administration may have several advantages over DPI or MDI administration in some patients. In patients who are not able to properly engage the DPI or MDI delivery mechanism (Hand-Breath Coordination), patients with cognitive impairment that makes use of an MDI/DPI challenging, and patients with muscle weakness or manual dexterity issues, nebulized therapy may yield a more consistent dose due to fewer user errors and a more consistent delivery of the therapy. It may also be significantly easier for a care partner to administer medications via a nebulizer.

Furthermore, several studies have suggested that adults with COPD who have more severe disease and limited inspiratory flow rates may receive more benefit from nebulized therapy than from therapy with the same mechanism of action delivered as a powder for inhalation. In a study by Mahler et al, a nebulized long-acting beta-2-agonist (LABA; arformoterol, BROVANA®) was more effective in improving forced vital capacity (FVC) than an analogous LABA delivered via a DPI (salmeterol, SEREVENT DISKUS®) in participants with a Peak Inspiratory Flow Rate (PIFR) of less than 60 L/min using an In-Check™ device set to the resistance of the DISKUS® device (approximately 23 kPa/L/min).[1]

More recently, Mahler et al demonstrated in a randomized, double-blind, double-dummy study of revefenacin inhalation solution via a nebulizer and tiotropium powder for inhalation (Spiriva® HandiHaler®), that in participants with moderate to very severe COPD and suboptimal PIFR, as defined above, there was a trend toward greater improvement in forced expiratory volume over one second (FEV_1) with revefenacin inhalation solution than with tiotropium powder for inhalation over 4 weeks of treatment.[2] In the subgroup of participants with severe to very severe COPD (FEV_1 < 50% of normal at baseline), there was a clinically important improvement of 75 mL with revefenacin compared to an improvement of 28 mL with tiotropium (nominal p = 0.0302), and a responder analysis of the previous study suggested that participants would be twice as likely to achieve an improvement from baseline of

100 mL with revefenacin compared with tiotropium. In a post hoc analysis, the largest differences were seen in those participants with a PIFR <55 L/min. The clinical significance of this magnitude of change is further supported by the recent FDA approval of BEVESPI® based on differences of 56 mL and 54 mL for the combination product over the monotherapy components. Similarly, in the ANORO® program, an improvement of 52 mL for the combination of umeclidinium and vilanterol was observed over umeclidinium.

It is important to explore the most effective treatments for severe to very severe COPD patients with suboptimal PIFR, as in the more recent study participants with lower PIFR appeared to be more symptomatic at baseline, suggesting either that disease is worse than predicted by expiratory flow limitation alone, or that there may be a lack of efficacy using nonnebulized therapy at baseline, or both. Furthermore in another study, Loh et al showed that participants with a suboptimal PIFR (i.e., <60 L/min using In-Check™ at DISKUS resistance) at hospital discharge from an acute exacerbation of COPD had fewer days to hospital readmission and a trend toward more readmissions than those who had an optimal PIFR. Such participants discharged and prescribed nebulizer maintenance therapy also had fewer hospital readmissions compared to participants discharged on DPI/MDI maintenance therapy.[3]

The purpose of this study is to use lung function to compare the efficacy of once-daily administration of nebulized revefenacin inhalation solution (YUPELRI®) with once-daily administration of tiotropium inhalation powder (Spiriva® HandiHaler®) over 12 weeks in adults with low PIFR measured by the In-Check™ device, defined as < 55 L/min when the device is set to DISKUS® resistance and severe to very severe expiratory airflow limitation (i.e., FEV_1 < 50% of normal).

Objectives:

The primary objectives of the study are as follows:

- To characterize the relative efficacy on change from baseline in trough FEV_1 on Day 85 of revefenacin inhalation solution administered once daily via nebulization (YUPELRI®) compared to tiotropium powder for inhalation administered once daily (Spiriva® HandiHaler®) in adults with severe to very severe COPD who have impaired expiratory flow (i.e., FEV_1 < 50% of predicted normal) and suboptimal PIFR (i.e., PIFR < 55 L/min via In-Check™ device set to DISKUS resistance) following 84 days of dosing.
- To evaluate the safety and tolerability of revefenacin inhalation solution administered in adults with severe to very severe COPD, impaired expiratory flow, and suboptimal PIFR

The secondary objective(s) of the study are as follows:

- To evaluate the relative efficacy of once-daily revefenacin via nebulization compared to tiotropium administered once daily via HandiHaler® on average FEV_1 across Days 30, 60, and 85

- To evaluate the relative efficacy of once-daily revefenacin via nebulization compared to tiotropium administered once daily via HandiHaler® on trough FVC on Day 85
- To evaluate the relative efficacy of once-daily revefenacin via nebulization compared to tiotropium administered once daily via HandiHaler® on trough FEV_1 on Day 30
- To evaluate the relative efficacy of once-daily revefenacin via nebulization compared to tiotropium administered once daily via HandiHaler® on trough FEV_1 on Day 60
- To evaluate the relative efficacy of once-daily revefenacin via nebulization to tiotropium administered once daily via HandiHaler® in achieving improvements in lung function of ≥ 80 mL, as measured by trough FEV_1 on Day 85
- To evaluate time to first CompEx (composite endpoint for moderate or severe exacerbations of COPD) event

The exploratory objective(s) of the study are as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Study Design: This is a randomized, double-blind, double-dummy, parallel-group study evaluating efficacy and safety of revefenacin vs. tiotropium in adults with severe to very severe COPD and suboptimal PIFR. Participants will visit the clinic for up to 2 screening visits and eligible participants will visit the clinic for a randomization visit, up to 2 intermediate on-treatment visits, and a final or early termination visit. Unscheduled visits may also be required.

During screening, participants are required to "wash out" from certain medications, or to take a different dose. Such medications include, but are not limited to, long-acting muscarinic antagonists (LAMA), LABA, LAMA/LABA, LABA/inhaled corticosteroids (ICS), and LAMA/LABA/ICS (see complete list in Table 2). Participants will be assessed for suboptimal PIFR using the In-Check™ device set to DISKUS resistance in addition to other inclusion and

exclusion criteria, undergo ipratropium reversibility testing, receive rescue medication, receive an electronic diary (eDiary) device, have their adverse events and other concomitant medications reviewed. Participants will also undergo physical examinations (including vital signs, height, and weight measurements). Participants will also undergo clinical laboratory testing if results from the previous 3 months are unavailable. Women of childbearing potential will have a urine pregnancy test. Participants who are required to wash out from medications will have these procedures conducted over 2 screening visits 5 to 9 days apart; participants not required to wash out will have these procedures conducted in a single visit.

At the randomization visit on Day 1 (3 to 7 days after screening), eligible participants with PIFR < 55 L/min, post ipratropium 30% $\leq$ FEV_1 < 50% of predicted normal (using National Health and Nutrition Examination Survey-predicted equations) and absolute FEV_1 > 500 mL, or FEV_1 <30% predicted normal and absolute FEV_1 > 700 mL, and who meet all other inclusion criteria will be randomized to revefenacin (revefenacin 175 mcg/tiotropium placebo) or tiotropium (tiotropium 18 mcg/revefenacin placebo) in a 1:1 ratio. Enrollment of participants with Global Initiative for Chronic Obstructive Lung Disease airflow category 4 (GOLD 4; FEV_1 <30% of predicted normal) will be capped at 30% to reflect what is expected in the population with severe to very severe COPD. Participants will be trained on the use of the DPI device and nebulizer prior to receiving their first dose of study medication. Participants will undergo baseline lung function tests, clinical outcomes assessments, and have their diaries, concomitant medications, and adverse events reviewed. [redacted]

Participants will return to the clinic on Days 30 and 60 ± 7 days each (Visits 3 and 4 respectively). Diaries will be reviewed to assess compliance with regard to their completion. Study drug and rescue medication will be accounted for and new supplies will be dispensed. Adverse events and concomitant medications will be reviewed, and women of childbearing potential will undergo urine pregnancy testing. Clinical outcomes will be measured, and lung function will be assessed. [redacted] Participants will administer their study medication in the presence of study center personnel not involved in the measurement of efficacy parameters.

Participants will self-administer study medication once daily in the morning for 84 days, except on Days 30 and 60, when participants will return to the study center for assessments prior to taking their study medication.

Participants will return to the clinic on Day 85 ± 7 days (Visit 5) for final assessments. Study drug and rescue medication will be accounted for; diaries, concomitant medications, and adverse events will be reviewed. Participants will undergo a physical examination including vital signs. Clinical outcomes will be measured and lung function will be assessed. [redacted] Women of childbearing potential will undergo urine pregnancy testing. Participants who discontinue from the study prior to this visit will undergo the same procedures at an early termination visit.

At 7 ± 2 days after the last visit, participants will be contacted by telephone for an assessment of their adverse events.

Revefenacin (or matching placebo) will be administered as a 3-mL inhalation solution using the PARI LC Sprint® jet nebulizer and using a mouthpiece. Tiotropium (or matching placebo) will be administered as a dry powder using the HandiHaler® device. Participants will take study drug via DPI first, and then via nebulizer.

A supply of rescue medication (albuterol MDI) for use in the study and a supply of study medication will be provided for each participant at each visit, except at Visit 1B for participants requiring 2 screening visits, and at Visit 5 or at early termination.

The primary efficacy assessment is FEV_1 as measured by spirometry.

Secondary efficacy assessments are FVC, also measured by spirometry, and use of rescue medication as measured by daily participant diaries.

Safety assessments, including collection of AEs, measurement of vital signs (heart rate and blood pressure), urine pregnancy testing for women of childbearing potential, and review of concomitant medications, will be performed at every visit.

[redacted]

Duration of Study Participation: Up to 120 days including up to 10 days for washout (if necessary) and spirometry review prior to randomization, 84 days of dosing, a final visit after the last dose, and a follow-up telephone contact approximately 7 days after the last dose. The duration of study participation could vary based on time windows associated with each visit.

Number of Participants per Group: Approximately 183 participants with $FEV_1 < 50\%$ of normal and PIFR < 55 L/min will be randomized to each treatment group (366 participants total) to ensure 146 participants per treatment group (292 participants total) are evaluable for the primary analysis at the end of study.

[redacted] the sample size may be increased to a maximum of 488 [redacted]

Study Population:

Participants with diagnosed COPD, a post ipratropium $30\% \leq FEV_1 < 50\%$ of predicted normal (using National Health and Nutrition Examination Survey-predicted equations) and absolute $FEV_1 > 500$ mL, or $FEV_1 < 30\%$ predicted normal and absolute $FEV_1 > 700$ mL, and a PIFR <55 L/min assessed using In-Check™ device set to DISKUS resistance will be eligible for enrollment.

Inclusion Criteria:

Unless otherwise noted, all participants must meet the following criteria:

1. Participant is a male or female 40 years of age or older.
2. Participant is female and is nonpregnant and nonlactating. A woman of childbearing potential must have a documented negative urine pregnancy test at screening.

   Women are considered not to be 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.
3. During the study and for 30 days after receiving the last dose of study drug, women of childbearing potential and men capable of fathering children must agree to use highly effective birth control measures or agree to abstain from sexual intercourse.

   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.
4. Participant has a diagnosis of COPD, specifically, a post-ipratropium FEV_1/FVC ratio <0.7.
5. Participant has a post ipratropium 30% $\leq$ FEV_1 < 50% of predicted normal (using National Health and Nutrition Examination Survey-predicted equations) and absolute FEV_1 > 500 mL, or FEV_1 <30% predicted normal and absolute FEV_1 > 700 mL.
6. Participant has a PIFR <60 L/min as measured by an In-Check™ device with resistance set to DISKUS at Visit 1A (if not combined with Visit 1B) and < 55 L/min as measured by an In-Check™ device with resistance set to DISKUS at Visit 1B and Visit 2 prior to randomization.
7. Participant is capable of performing reproducible spirometry maneuvers [redacted] as described by current American Thoracic Society (ATS) Guidelines.
8. Participant is an active or former smoker with a cigarette smoking history (or equivalent for cigar or pipe smoking history) of at least 10 pack-years.
9. Participant or legal guardian is willing and able to provide signed and dated informed consent to participate prior to initiation of any study related procedures.
10. Participant is willing and able to adhere to all study assessments/procedures. Care partner assistance is acceptable.
11. Participant is willing and able to adhere to all restrictions during their study participation as follows:
    - 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)

12. Participant (or care partner) based on the investigator's assessment is able to properly prepare and administer study medication administered from both nebulizer and HandiHaler® according to their respective Instructions for Use.

Exclusion Criteria:

1. Participant 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. Participant has a history of reactions or hypersensitivity to inhaled or nebulized anticholinergics.
3. Participant 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. Participant has Moderate to Severe Hepatic impairment (Child-Pugh B or C) or Severe Renal Insufficiency (i.e. a glomerular filtration rate <30 mL/min/1.72m^2).
5. Participant has been hospitalized for COPD or pneumonia within 8 weeks prior to Visit 1.
6. Participant is receiving a LABA or LABA/inhaled corticosteroid (ICS; either QD or BID) at a dose that has been stable for ≤ 30 days prior to screening.
7. Participant has used systemic corticosteroids within 8 weeks of Visit 1.
8. Participant has used antibiotics for respiratory tract infections within 8 weeks of Visit 1, or is using antibiotics prophylactically.
9. Participant received COVID-19 vaccine within 2 weeks prior to Visit 1.

Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment: Revefenacin solution (175 mcg in 3 mL) for inhalation by jet nebulizer, administered by oral inhalation once every morning for up to 84 days. Revefenacin matching placebo will be administered to the participants in the tiotropium treatment group.

Reference Therapy, Dose, and Route of Administration; Regimen; Duration of Treatment: Tiotropium dry powder capsule (Spiriva®, 18 mcg) administered by oral inhalation once every morning using the HandiHaler® device for up to 84 days. Tiotropium matching placebo will be administered to the participants in the revefenacin treatment group.

Study Evaluations

Primary and Secondary Efficacy Assessments:

- Lung function tests (FEV_1, FVC) will be measured by spirometer at the study center.

Clinical Outcomes Assessments:

- Efficacy
  - Daily use of rescue medication (i.e., albuterol MDI)
  - Daily nocturnal awakenings as recorded in participant diaries
  - PEF measured by participant using portable meter
  - Evaluating Respiratory Symptoms in COPD (E-RS:COPD) assessment for daily breathlessness, cough/sputum, and chest symptoms
- Exploratory
  - [redacted]

[redacted]

Safety Assessments:

Safety will be assessed via the reporting of adverse events (AEs) including exacerbations of COPD, physical examination findings, vital sign measurements, urine pregnancy tests (for women of childbearing potential), and concomitant medications.

Statistical Methods

Efficacy endpoints will be evaluated by comparing revefenacin to tiotropium. For each of the primary and secondary efficacy endpoints, the null hypothesis for the treatment comparison will be that there is no difference between the responses of revefenacin and tiotropium. The alternative hypothesis will be that there is a difference.

Sample Size:

[redacted]

[redacted] The total number of subjects will be capped up to a maximum sample size of 488 subjects. [redacted]

Study Endpoints:

The primary study endpoint is change from baseline in trough FEV_1 on Day 85 following 84 days of dosing.

The secondary endpoints are as follows:

- Trough overall treatment effect (OTE) on FEV_1 over 85 days
- Change from baseline in Trough FVC on Day 85
- Change from baseline in Trough FEV_1 on Day 30
- Change from baseline in Trough FEV_1 on Day 60
- 80-mL response, defined as at least an 80-mL improvement in trough FEV_1 on Day 85
- Time to first CompEx (composite endpoint for exacerbations of COPD) event

  A CompEx event is defined as the first occurrence of a moderate or severe exacerbation, or clinically relevant deteriorations based on objective measures of deterioration in peak expiratory flow (PEF), rescue medication use, COPD symptoms, and nocturnal awakening.[5,6]

  A moderate exacerbation is defined as an increase in symptoms that requires treatment with antibiotics and/or oral corticosteroids and a severe exacerbation is defined as a deterioration of COPD symptoms that results in hospitalization for emergency treatment of the COPD and the duration of the visit is ≥1 day, as recorded via CRF.

  Clinically relevant deteriorations will be defined in the statistical analysis plan (SAP).

Exploratory endpoints are:

[redacted]

The safety endpoints are the incidence of AEs (including exacerbations of COPD), and vital signs (heart rate and blood pressure).

Analysis:

Analysis Sets

The full analysis set (FAS) is the primary analysis set for general and efficacy analyses and will include all randomized participants who:

- Receive at least one dose of study drug (revefenacin or tiotropium)

Participants will be analyzed according to their randomized treatment group.

The safety analysis set is the primary analysis set for safety analyses and will include all participants who are randomized and receive at least one dose of study drug. Participants will be analyzed according to their treatment actually received.

Analysis of Primary Efficacy Endpoint

For the primary endpoint, a repeated measures mixed effects model (RMMM) will be used to estimate treatment differences. The model will include fixed class terms for randomized treatment groups, ipratropium reversibility (reversible/not reversible), smoking status (current/former smoker), concomitant LABA or ICS/LABA use (Yes/No), GOLD (3/4), sex (woman/man), age (<65/≥65), and continuous covariates for baseline PIFR set to DISKUS® resistance and baseline FEV_1, as well as a time effect (visit) and its interaction terms with treatment and the baseline values of the covariates. Within-subject correlation will be modelled using an unstructured variance-covariance matrix. The Kenward and Roger method for approximating the denominator degrees of freedom will be used. Least-squares (LS) means and 95% confidence intervals (CIs) for LS mean differences between revefenacin and tiotropium will be calculated and presented in tabular and graphical format. Nominal p-values and CIs will be reported.

If the 2-sided 95% CI for the Day 85 FEV1 revefenacin vs. tiotropium treatment policy estimand difference lies above zero, the primary endpoint will be considered to have been met and a tipping point analysis systematically varying assumptions about unobserved responses.

Analysis of Secondary [redacted] Efficacy Endpoints

The following endpoints can all be estimated from the same model outlined for the primary analysis:

- Change from baseline in Trough FEV_1 on Day 30
- Change from baseline in Trough FEV_1 on Day 60
- Trough overall treatment effect (OTE) on FEV_1 over 85 days

Change from baseline in trough FVC on Day 85 will be analyzed using similar methodology as the primary endpoint.

A responder analysis based on Day 85 trough FEV_1 will be conducted using a logistic regression model with a similar set of covariates as the primary efficacy endpoint. A summary of responders will be presented with frequency distributions (counts and percentages), observed LS percentages, and revefenacin:tiotropium odds ratios.

Cox proportional hazards model will be used to derive hazard ratios and analyze time to first event for CompEx COPD.

A statistical hierarchy will be used to test the hypotheses of the primary and secondary endpoints to control the study-wise type 1 error rate at 5%.

All efficacy endpoints will also be reported with nominal p-values, unless specified otherwise.

Missing values for the primary and secondary spirometry efficacy endpoints will not be imputed except for the responder analysis and any additional sensitivity analyses specified in the SAP.

[redacted]

Analysis of Safety Data

All safety data will be presented in listings. Descriptive summary tables will be provided for extent of exposure, treatment-emergent AEs, vital signs, and concomitant medications. Changes from baseline in heart rate and blood pressure measurements will be summarized.

SCHEDULE OF STUDY PROCEDURES

Table 1: Schedule of Study Procedures

Procedures	Visit 1A	Visit 1B (5 ± 2 to 7 ± 2 days after Visit 1A[a])	Day 1 (Visit 2) Randomization (3 to 7 days after screening completed)	Day 30 (Visit 3) ± 7 days	Day 60 (Visit 4) ± 7 days	Day 85 (Visit 5) ± 7 days	Follow-Up Phone call 7 days after last visit ± 2 days	Early Termination / Withdrawal	Unscheduled Visit
Informed Consent[b]	X								
Medical and Medication History	X								X
Washout of COPD Medications[a]	X								
Physical Examination		X[c]				X		X	X
Height and Weight		X[c]							
Vital Signs		X[c]	X			X		X	X
Inclusion / Exclusion Criteria	X	X	X						
Urine Pregnancy Test	X		X[d]	X	X	X		X	
Ipratropium Reversibility[e]		X							
Randomization			X[f]						
Dispense eDiary		X							
Review eDiary			X	X	X	X		X	
Dispense Study Drug			X	X	X				
Dispense Rescue Medication	X		X	X	X				
Study Drug/Rescue Medication Accountability			X	X	X	X		X	
Concomitant Medications	X	X	X	X	X	X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Local Lab Tests for creatinine. hematocrit, ALT, AST, bili, alk phos[g]	X								
BDI			X						
TDI				X	X	X		X	
PIFR	X	X[h]	X						
MIP			X						
CAT			X	X	X	X		X	
Predose Spirometry (FEV_1, FVC) at 45 and 15 min predose		X[i]	X	X	X	X[j]		X[j]	X[j]
PEF[k]		X	X	X	X	X		X	X
E-RS: COPD[l]		X	X	X	X				
Nocturnal Awakenings Question		X	X	X	X	X		X	X
Plethysmography (IC, FRC, TLC) at 45 and 15 min predose[m]			X			X[j]			

Procedures	Visit 1A	Visit 1B (5 ± 2 to 7 ± 2 days after Visit 1A[a])	Day 1 (Visit 2) Randomization (3 to 7 days after screening completed)	Day 30 (Visit 3) ± 7 days	Day 60 (Visit 4) ± 7 days	Day 85 (Visit 5) ± 7 days	Follow-Up Phone call 7 days after last visit ± 2 days	Early Termination / Withdrawal	Unscheduled Visit
LABA Dosing (if applicable)			X	X	X	X			
Study Drug Dosing[n]			X	X	X				
Train on HandiHaler®, Nebulizer			X						
Dispense PEF Meter/Train Participants on Use		X							

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Alk phos, alkaline phosphatase; BDI, Baseline Dyspnea Index; bili, bilirubin; COPD, chronic obstructive pulmonary disease; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; eDiary, electronic diary; E-RS: COPD, Evaluating Respiratory Symptoms in COPD assessment; FEV_1, forced expiratory volume; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; INR; International Normalized Ratio; LABA, long-acting beta-2 agonist; MIP, maximal inspiratory pressure; PEF, peak expiratory flow; PIFR, peak inspiratory flow rate; TDI, Transitional Dyspnea Index; TLC, total lung capacity

a For participants who require washout of certain COPD medications as specified in Table 2. For participants not requiring washout, Visit 1B can be combined with Visit 1A if participant does not require washout of COPD medications.

b The research site will follow institutional and government guidelines/precautions regarding Coronavirus Disease 2019 (COVID-19) to reduce the risk of infection for study participants and study staff.

c Performed/collected prior to ipratropium dosing. Vital signs (heart rate and blood pressure) will be measured after resting in a semi-recumbent position for approximately 5 minutes.

d Performed if visit is more than 7 days after Visit 1A.

e Consult study manual

f Participant eligibility must be confirmed by investigator before randomizing the participant.

g If data from any time during the previous 3 months are not available. Collection of INR and albumin to determine Child-Pugh score for exclusion is at the discretion of the investigator.

h Participants who required a washout of a LAMA must have PIFR < 55 L/min at this visit.

i 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) at this visit (whether or not it is combined with Visit 1A).

j There is no dosing at this visit. Spirometry and plethysmography will be performed at 2 time points 30 minutes apart.

k Performed after predose spirometry at the study center during all study visits beginning with Visit 1B. Participants will receive the portable meter and be trained on its use at Visit 1B for subsequent use at home between visits.

l Before bedtime on the evening prior to the visit

m Measured in participants enrolled at selected centers capable of performing these assessments. Assessments will be done immediately after PIFR assessment.

n Between 6:00 am and 11:00 am local time

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
Alk phos	alkaline phosphatase
BID	twice daily
BDI	Baseline Dyspnea Index
Bili	bilirubin
BP	blood pressure
CAT	Chronic Obstructive Pulmonary Disease Assessment Test
CFR	(United States) Code of Federal Regulations
CI	confidence interval
CompEx	Composite endpoint for severe exacerbations of chronic obstructive pulmonary disease
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
(e)CRF	(electronic) case report form
DPI	dry powder inhaler
eDiary	electronic diary
EDC	electronic data capture
E-RS:COPD	Evaluating Respiratory Symptoms in COPD (assessment)
FAS	full analysis set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FRC	forced residual capacity
FVC	forced vital capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	heart rate

Abbreviation	Description
IB	Investigator's Brochure
IC	inspiratory capacity
ICF	informed consent form
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICS	inhaled corticosteroid
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
LABA	long-acting beta-2 agonist
LAMA	Long-acting muscarinic antagonist
MAR	missing at random
MDI	metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
MIP	Maximal inspiratory pressure
OTE	Overall treatment effect
PEF	peak expiratory flow
PIFR	peak inspiratory flow rate
PI	principal investigator
PRN	as needed
QD	once daily
REB	Research Ethics Board
RMMM	repeated measures mixed effects model
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SOP	standard operating procedure
TDI	Transitional Dyspnea Index
TLC	total lung capacity
US	United States

1. INTRODUCTION

1.1. Background and Rationale

Revefenacin is an orally inhaled muscarinic antagonist which is approved by the US Food and Drug Administration (FDA) for the maintenance treatment of chronic obstructive pulmonary disease (COPD).

Long-acting bronchodilators can be delivered via a metered-dose inhaler (MDI), dry powder inhaler (DPI) or nebulizer. Successful use of a nebulizer requires the patient to breathe normally (tidal breathing) to successfully deliver the medicine, whereas use of MDIs and DPIs requires more complex coordination of actuation of the device and / or an appropriate inhalation technique (slow inhalation in case of MDI; forced inhalation in the case of DPI) to successfully deliver the medicine. Therefore, nebulized administration may have several advantages over DPI or MDI administration in some patients. In patients who are not able to properly engage the DPI or MDI delivery mechanism (Hand-Breath Coordination), patients with cognitive impairment that makes use of an MDI/DPI challenging, and patients with muscle weakness or manual dexterity issues, nebulized therapy may yield a more consistent dose due to fewer user errors and a more consistent delivery of the therapy. It may also be significantly easier for a care partner to administer medications via a nebulizer.

Furthermore, several studies have suggested that adults with COPD who have more severe disease and limited inspiratory flow rates may receive more benefit from nebulized therapy than from therapy with the same mechanism of action delivered as a powder for inhalation. In a study by Mahler et al, a nebulized long acting beta-2-agonist (LABA; arformoterol, BROVANA) was more effective in improving forced vital capacity (FVC) than an analogous LABA delivered via a DPI (salmeterol, SEREVENT DISKUS®) in participants with a Peak Inspiratory Flow Rate (PIFR) of less than 60 L/min using an In-Check™ device set to the resistance of the DISKUS® device (approximately 23 kPa/L/min).[1]

More recently, Mahler et al demonstrated in a randomized, double-blind, double-dummy study of revefenacin inhalation solution via a nebulizer and tiotropium powder for inhalation (Spiriva® HandiHaler®), that in participants with moderate to very severe COPD and suboptimal PIFR, as defined above, there was a trend toward greater improvement in forced expiratory volume over one second (FEV_1) with revefenacin inhalation solution than with tiotropium powder for inhalation over 4 weeks of treatment.[2] In the subgroup of participants with severe to very severe COPD (FEV_1 < 50% of normal at baseline), there was a clinically important improvement of 75 mL with revefenacin compared to an improvement of 28 mL with tiotropium (nominal p = 0.0302), and a responder analysis of the previous study suggested that participants would be twice as likely to achieve an improvement from baseline of 100 mL with revefenacin compared with tiotropium. In a post hoc analysis, the largest differences were seen in those participants with a PIFR <55 L/min. The clinical significance of this magnitude of change is further supported by the recent FDA approval of BEVESPI® based on differences of 56 mL and 54 mL for the combination product over the monotherapy components. Similarly, in the ANORO® program, an improvement of 52 mL for the combination of umeclidinium and vilanterol was observed over umeclidinium.

It is important to explore the most effective treatments for severe to very severe COPD patients with suboptimal PIFR, as in the more recent study participants with lower PIFR appeared to be more symptomatic at baseline, suggesting either that disease is worse than predicted by expiratory flow limitation alone, or that there may be a lack of efficacy using nonnebulized therapy at baseline, or both. Furthermore in another study, Loh et al showed that participants with a suboptimal PIFR (i.e., <60 L/min using In-Check™ device at DISKUS resistance) at hospital discharge from an acute exacerbation of COPD had fewer days to hospital readmission and a trend toward more readmissions than those who had an optimal PIFR. Such participants discharged and prescribed nebulizer maintenance therapy also had fewer hospital readmissions compared to participants discharged on DPI/MDI maintenance therapy.[3]

The purpose of this study is to use lung function to compare the efficacy of once-daily administration of nebulized revefenacin inhalation solution (YUPELRI®) with once-daily administration of tiotropium inhalation powder (Spiriva® HandiHaler®) over 12 weeks in adults with low PIFR measured by the In-Check™ device, defined as < 55 L/min when the device is set to DISKUS® resistance and severe expiratory airflow limitation (i.e., FEV_1 < 50% of predicted normal).

1.2. Nonclinical Profile

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

Revefenacin is a potent and selective antagonist of human M_1 through M_5 muscarinic receptors, with kinetic selectivity for the M_3 vs. M_2 subtype. When administered by inhalation to conscious guinea pigs, revefenacin was an antagonist of acetylcholine-induced bronchoconstriction and demonstrated a duration of action comparable to that of tiotropium (>24 hours) at a potency equivalent- dose. In the rat, inhaled revefenacin was superior to tiotropium with respect to lung selectivity, which was determined by examination of the ratio of pilocarpine-induced antisialagogue activity and the 24-hour bronchoprotective activity of revefenacin. Revefenacin also demonstrated a 24-hour duration of activity in a dog model of methacholine-induced bronchoconstriction. Overall, the pharmacology of revefenacin, when administered into the lungs, is consistent with that of a long-acting muscarinic antagonist and demonstrates good selectivity for lung versus systemic effects.

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

1.2.2. Toxicology

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

1.3. Clinical Experience

Revefenacin was evaluated in a single-dose first-in-human clinical study using a DPI formulation in 21 healthy adults. Study AC5108696 investigated the safety, tolerability, pharmacodynamic effect, and pharmacokinetics of single doses of revefenacin of up to 500 mcg DPI. Subsequently, revefenacin inhalation solution delivered using a standard jet nebulizer was evaluated in 3 single-dose studies in a total of 80 healthy adults (Studies 0134, 0135, and 0136), and in 9 repeat-dose studies in a total of 3125 adults with COPD (Studies 0059, 0091, 0116, 0117, 0126, 0127, 0128, 0149 and 0167). An additional 9 healthy adults received a single dose of either an IV formulation or an oral solution formulation of [^{14}C]-labeled revefenacin (Study 0130). To date, revefenacin has been evaluated in 14 clinical studies, all of which are described in the IB, and has been an effective bronchodilator in participants with moderate to very severe COPD, with a duration of action consistent with its FDA approval as a once-daily agent.

Revefenacin demonstrated a consistent and favorable safety and tolerability profile during its development. Of the 14 completed clinical studies, the primary safety data sets that supported approval in the US are from the pooled double-blind, placebo-controlled replicate Phase 3 studies (Studies 0126 and 0127) and from the long-term (52-week) active-controlled safety study (Study 0128).

The safety profile for revefenacin inhalation solution in participants with moderate to very severe COPD was similar to placebo, and favorable when evaluated in Study 0128 with active control tiotropium (Spiriva® HandiHaler®). Furthermore, in the Phase 3 program, the adverse event (AE) profile of revefenacin inhalation solution was consistent with that of other clinical programs developing LABA therapies, particularly long-acting muscarinic antagonist (LAMA) products.

Worsening/exacerbation of COPD (Medical Dictionary for Regulatory Activities [MedDRA] preferred term, chronic obstructive pulmonary disease) was the most common AE reported in the Phase 3 program, but the incidence of this AE was numerically lower in the revefenacin arms than in the placebo arm in the 12-week studies (Studies 0126 and 0127). In the long-term safety study (Study 0128), the incidence of this AE compared favorably to that of the clinically established LAMA, tiotropium, which served as the active control in the study. So, while a common AE in the revefenacin clinical program, chronic obstructive pulmonary disease (as the MedDRA preferred term) did not appear to be an adverse drug reaction.

Other than worsening/exacerbation of COPD, the most common adverse drug reaction, defined as any AE where the event rate was higher than that of placebo and occurred in more than 1% of the population in the 12-week trials, was cough. The difference in rates between placebo and revefenacin, however, was very small (4.1% vs. 4.3% respectively).

For patients who need more than 1 medication to manage their COPD, the safety profile supports the use of revefenacin 175 mcg. For patients taking LABA and/or inhaled corticosteroid (LABA or ICS/LABA), there was no apparent increase in AEs or tolerability with the higher dose, neither in absolute incidence nor in exposure adjusted incidence.

Subsequent to the Phase 3 studies cited earlier, revefenacin inhalation solution (175 mcg once daily) was evaluated against tiotropium dry powder (18 mcg once daily) in participants with COPD and suboptimal PIFR (<60 L/min). Adverse events were reported less frequently during

treatment with revefenacin (11.7%) compared to tiotropium (37.5%). An AE of COPD (i.e., worsening of COPD) only occurred in the tiotropium group (1 participant). The most frequently reported AEs differed between treatment groups and are described later in this section.

Safety was also evaluated when revefenacin inhalation solution (175 mcg once daily) or matching placebo was administered sequentially (i.e., immediately before), or in combination with, formoterol fumarate inhalation solution (20 mcg). The overall incidence of AEs was higher in the control group (placebo and formoterol; 11% to 12% depending on timing of administration) compared to the revefenacin and formoterol group (5% to 8%), but the incidence was comparable between sequential and combination administration. COPD (worsening) was among the most frequently reported AEs (2 participants), and occurred more frequently in the placebo and formoterol group compared to the revefenacin and formoterol group.

In the revefenacin clinical program to date, 6 on-study deaths have been reported: 1 in the Phase 2 Study 0116 and 5 in the Phase 3 Studies 0126, 0127, and 0128; an additional 7 deaths were reported at least 7 days after the last dose in Study 0128. None of the reported on-study or off-study deaths were considered by the investigator to be related to the study drug, and there was no apparent signal related to cause of death suggesting any pattern or dose response relationship.

Efficacy of revefenacin was demonstrated in the Phase 3 studies (Studies 0126 and 0127), with marked improvements in FEV_1 (i.e., trough, peak, weighted mean, trough overall treatment effect) for participants treated with revefenacin when evaluated as within-group change from baseline measurements and as compared with placebo. Improvements in FEV_1 were similar in subgroups of participants taking concurrent LABAs and those not taking concurrent LABAs.

Efficacy was also characterized in the Phase 3 long-term safety study (Study 0128) through exploratory analyses. In Study 0128, revefenacin and tiotropium resulted in improved lung function (trough FEV_1) throughout the study compared to baseline.

Additional efficacy information is available from a Phase 3b study in participants with COPD and suboptimal PIFR comparing revefenacin to tiotropium (Study 0149). Efficacy in Study 0149 was characterized by change from baseline in trough FEV_1 as the primary endpoint, and changes from baseline in trough FVC and inspiratory capacity, and peak FEV_1 and FVC as secondary endpoints. Within the ITT population, primary and secondary efficacy endpoints did not demonstrate statistically significant improvements in lung function relative to tiotropium. However for the combined GOLD 3 and GOLD 4 population, nominally statistically significant differences from tiotropium were observed for both trough FEV_1 and FVC.

In Study 0167, a 6-week study of revefenacin and formoterol, revefenacin administered either immediately before or in combination with formoterol resulted in a greater response for FEV_1 and FVC compared to formoterol alone (i.e., placebo and formoterol).

The clinical pharmacokinetics of revefenacin inhalation solution in participants with moderate to severe COPD have been evaluated after single- and/or repeat-dose administration in Studies 0059, 0091, and 0117. Plasma concentrations of revefenacin and its major metabolite, THRX-195518, were low after inhaled administration, declined in a bi-exponential fashion with an initial rapid decline and a slower terminal elimination phase, and resulted in limited

accumulation for both revefenacin and THRX-195518 in plasma after repeated administration. No significant renal excretion of revefenacin and THRX-195518 was observed.

1.4. Risks and Benefits

Participants 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.

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

Clinically significant bronchodilation has been observed in each of the COPD study populations. Two replicate phase 3 efficacy studies (0126 and 0127) with a 3-month treatment period have demonstrated that a 175-mcg dose of revefenacin was generally well tolerated, with comparable rates of AEs and serious adverse events for revefenacin and placebo. The most commonly reported AEs, across both trials were COPD exacerbation, nasopharyngitis, cough, dyspnea and headache. There were no reports of blurred vision, narrow-angle glaucoma or worsening of urinary retention, all of which are commonly reported AEs for this class of medication. In addition, reports of dry mouth were < 0.5% for revefenacin. A long term safety study (0128) with a 1-year treatment period revealed a similar safety profile to what was observed to the efficacy studies.

2. OBJECTIVES

The primary objectives of the study are as follows:

- To characterize the relative efficacy on change from baseline in trough FEV_1 on Day 85 of revefenacin inhalation solution administered once daily via nebulization (YUPELRI ®) compared to tiotropium powder for inhalation administered once daily (Spiriva® HandiHaler®) in adults with severe to very severe COPD who have impaired expiratory flow (i.e., FEV_1 < 50% of predicted normal) and suboptimal PIFR (i.e., PIFR < 55 L/min via In-Check™ device set to DISKUS resistance) following 84 days of dosing.
- To evaluate the safety and tolerability of revefenacin inhalation solution administered in adults with severe to very severe COPD, impaired expiratory flow, and suboptimal PIFR

The secondary objectives of the study are as follows:

- To evaluate the relative efficacy of once-daily revefenacin via nebulization compared to tiotropium administered once daily via HandiHaler® on average FEV_1 across Days 30, 60, and 85
- To evaluate the relative efficacy of once-daily revefenacin via nebulization compared to tiotropium administered once daily via HandiHaler® on trough FVC on Day 85
- To evaluate the relative efficacy of once-daily revefenacin via nebulization compared to tiotropium administered once daily via HandiHaler® on trough FEV_1 on Day 30
- To evaluate the relative efficacy of once-daily revefenacin via nebulization compared to tiotropium administered once daily via HandiHaler® on trough FEV_1 on Day 60
- To evaluate the relative efficacy of once-daily revefenacin via nebulization to tiotropium administered once daily via HandiHaler® in achieving improvements in lung function of ≥80 mL, as measured by trough FEV_1 on Day 85
- To evaluate time to first CompEx (composite endpoint for moderate or severe exacerbations of COPD) event

The exploratory objectives of the study are as follows:

- [redacted]
- [redacted]

- [redacted]
- [redacted]

3. STUDY DESIGN

3.1. Overview

This is a randomized, double-blind, double-dummy, parallel-group study evaluating efficacy and safety of revefenacin vs. tiotropium in adults with severe to very severe COPD and suboptimal PIFR. Participants will visit the clinic for up to 2 screening visits and eligible participants will visit the clinic for a randomization visit, up to 2 intermediate on-treatment visits, and a final or early termination visit. Unscheduled visits may also be required.

During screening, participants are required to "wash out" from certain medications, or to take a different dose. Such medications include, but are not limited to, long-acting muscarinic antagonists (LAMA), LABA, LAMA/LABA, LABA/inhaled corticosteroids (ICS), and LAMA/LABA/ICS (see complete list in Table 2). Participants will be assessed for suboptimal PIFR using the In-Check™ device set to DISKUS resistance in addition to other inclusion and exclusion criteria, undergo ipratropium reversibility testing, receive rescue medication, receive an electronic diary (eDiary) device, receive a PEF meter and be trained on its use, have their adverse events and other concomitant medications reviewed. Participants will also undergo physical examinations (including vital signs, height, and weight measurements). Participants will also undergo clinical laboratory testing if results from the previous 3 months are unavailable. Women of childbearing potential will have a urine pregnancy test. Participants who are required to wash out from medications will have these procedures conducted over 2 screening visits 5 to 9 days apart; participants not required to wash out will have these procedures conducted in a single visit.

At the randomization visit on Day 1 (3 to 7 days after screening), eligible participants with PIFR < 55 L/min, post ipratropium 30% $\leq$ FEV_1 < 50% of predicted normal (using National Health and Nutritional Examination Survey-predicted equations) and absolute FEV_1 > 500 mL, or FEV_1 < 30% predicted normal and absolute FEV_1 > 700 mL, and who meet all other inclusion criteria will be randomized to revefenacin (revefenacin 175mcg/tiotropium placebo) or tiotropium (tiotropium 18 mcg/revefenacin placebo) in a 1:1 ratio. Enrollment of participants with Global Initiative for the Treatment of Obstructive Lung Disease airflow category 4 (GOLD 4; FEV_1 <30% of predicted normal) will be capped at 30% to reflect what is expected in the population with severe to very severe COPD. Participants will be trained on the use of the DPI device and nebulizer prior to receiving their first dose of study medication. Participants will undergo baseline lung function tests, clinical outcomes assessments, and have their diaries, concomitant medications, and adverse events reviewed. [redacted]

Participants will return to the clinic on Days 30 and 60 ± 7 days each (Visits 3 and 4 respectively). Diaries will be reviewed to assess compliance with regard to their completion. Study drug and rescue medication will be accounted for and new supplies will be dispensed. Adverse events and concomitant medications will be reviewed, and women of childbearing potential will undergo urine pregnancy testing. Clinical outcomes will be measured, and lung function will be assessed. [redacted] Participants will administer their study medication in the presence of study center personnel not involved in the measurement of efficacy parameters.

Participants will self-administer study medication once daily in the morning for 84 days, except on Days 30 and 60, when participants will return to the study center for assessments prior to taking their study medication.

Participants will return to the clinic on Day 85 ± 7 days (Visit 5) for final assessments. Study drug and rescue medication will be accounted for; diaries, concomitant medications, and adverse events will be reviewed. Participants will undergo a physical examination including vital signs. Clinical outcomes will be measured, and lung function will be assessed. [redacted] Women of childbearing potential will undergo urine pregnancy testing. Participants who discontinue from the study prior to this visit will undergo the same procedures at an early termination visit.

At 7 ± 2 days after the last visit, participants will be contacted by telephone for an assessment of their adverse events.

Revefenacin (or matching placebo) will be administered as a 3-mL inhalation solution using the PARI LC Sprint® jet nebulizer and using a mouthpiece. Tiotropium (or matching placebo) will be administered as a dry powder using the HandiHaler® device. Participants will take study drug via DPI first, and then via nebulizer.

A supply of rescue medication (albuterol MDI) for use in the study and a supply of study medication will be provided for each participant at each visit, except at Visit 1B for participants requiring 2 screening visits, and at Visit 5 or at early termination.

The primary efficacy assessment is FEV_1 as measured by spirometry.

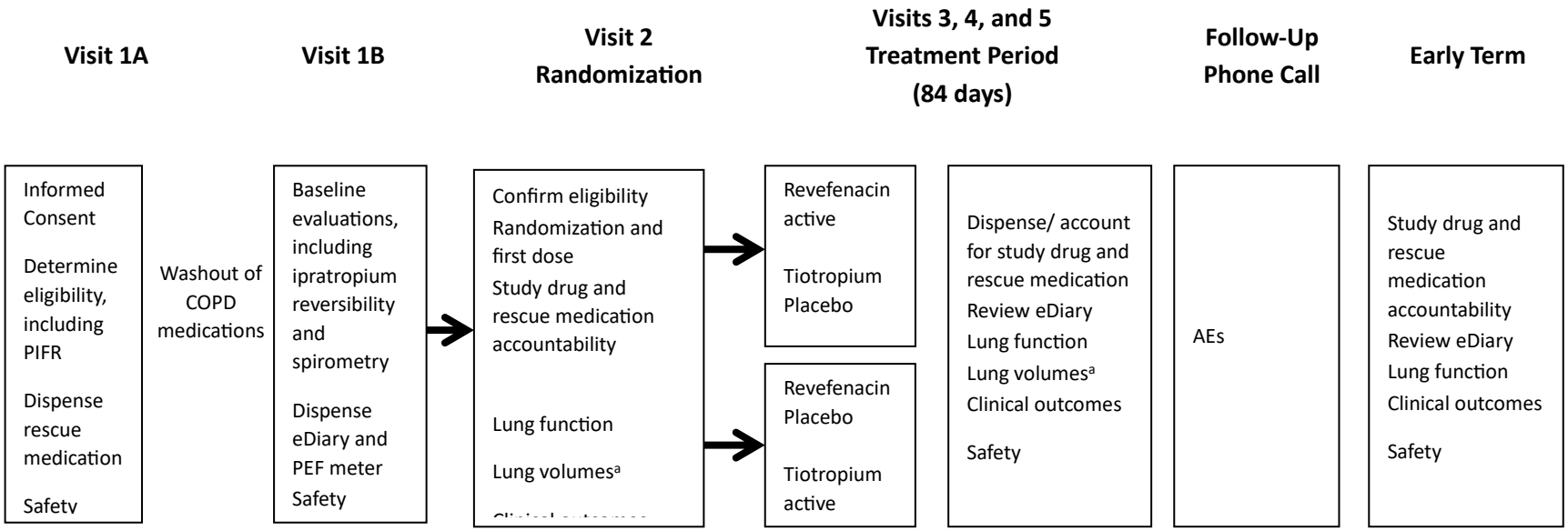
Secondary efficacy assessments are FVC, also measured by spirometry, and use of rescue medication as measured by daily participant diaries.

Safety assessments, including collection of AEs, measurement of vital signs (heart rate and blood pressure), urine pregnancy testing for women of childbearing potential, and review of concomitant medications, will be performed at every visit.

Exploratory assessments are events associated with a composite endpoint for severe exacerbations of COPD (CompEx) [redacted].

The study design is depicted in Figure 1.

Figure 1: Study Design Schema



AEs, adverse events; eDiary, electronic diary; PEF, peak expiratory flow, PIFR, peak inspiratory flow rate;
[a] Measured at Visits 2 and 5 in participants enrolled at selected study centers capable of performing these assessments

3.2. Rationale for Study Design

This is a Phase 4 study to assess revefenacin at a dose of 175 mcg administered once daily for 84 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 severe to very severe COPD who have suboptimal PIFR, where nebulized delivery of revefenacin could provide more benefit, as measured by spirometry and dyspnea symptoms, than a DPI (HandiHaler®), which would support the use in this demographic as a bronchodilator for the treatment of adults with COPD. The 175-mcg dose is approved by the US FDA for the maintenance treatment of COPD, and is considered to have an optimal benefit:risk ratio to further characterize its use in this population.

The study is designed as a double-blinded, double-dummy, parallel-group study, with 183 evaluable participants randomized to each treatment group with the intention of obtaining data from at least 146 evaluable participants per group on Day 85 for the primary analysis. Randomization allows for an unbiased assessment of treatment effects across revefenacin and tiotropium. The duration of treatment is limited, and all participants will have study-specific rescue medication (albuterol MDI) provided for the full duration of the study, including during the screening and follow-up periods.

Participants will be required to meet the standard spirometry definitions for severe to very severe COPD (postbronchodilator FEV_1/FVC ratio of <0.7 and a postbronchodilator FEV_1 < 50% of predicted normal based on the third National Health and Nutrition Examination Survey). Participants should meet a PIFR of < 55 L/min as measured by In-Check™ device with resistance set to DISKUS® at screening.

3.3. Selection of Doses and Duration of Treatment

The selection of the 175-mcg dose of revefenacin for this study is based on approval by the US FDA and the results of a previous study in adults with moderate to very severe COPD and PIFR <60 mL/min as measured by In-Check™ device with resistance set to DISKUS. Revefenacin, administered once daily via a standard jet nebulizer at a dose of 175 mcg, demonstrated clinically important and nominally statistically significant improvements in trough FEV_1 over the entire treatment period for participants with severe or very severe COPD (i.e., GOLD 3 and 4 airflow categories), which represented the majority (78%) of the ITT population. Revefenacin was well tolerated with rates of AEs less than those for tiotropium. The most common AEs were headache and dyspnea, with higher percentages of both in the tiotropium group. The AE profile did not differ from the expected safety/tolerability profile to date for revefenacin or other LAMAs.

3.4. Study Endpoints

The primary study endpoint is change from baseline in trough FEV_1 on Day 85 following 84 days of dosing.

The secondary endpoints are as follows:

- Trough overall treatment effect (OTE) on FEV_1 over 85 days
- Change from baseline in Trough FVC on Day 85
- Change from baseline in Trough FEV_1 on Day 30
- Change from baseline in Trough FEV_1 on Day 60
- 80 mL response, defined as at least an 80 mL improvement in trough FEV_1 on Day 85
- Time to first CompEx (composite endpoint for exacerbations of COPD) event

  A CompEx event is defined as the first occurrence of a moderate or severe exacerbation or clinically relevant deteriorations based on objective measures of deterioration in peak expiratory flow (PEF), rescue medication use, COPD symptoms and nocturnal awakening.[5, 6]

  A moderate exacerbation is defined as an increase in symptoms that requires treatment with antibiotics and/or oral corticosteroids and a severe exacerbation is defined as a deterioration of COPD symptoms that results in hospitalization for emergency treatment of the COPD and the duration of the visit is ≥1 day, as recorded via CRF.

  Clinically relevant deteriorations will be defined in the statistical analysis plan (SAP).

Exploratory endpoints are:

- [redacted]

[redacted]

The safety endpoints are the incidence of AEs (including exacerbations of COPD), and vital signs (heart rate and blood pressure).

3.5. Minimization of Bias

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

3.5.1. Blinding

All study participants, 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. Participants 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 participant's treatment assignment using the Randomization and Trial Supply Management (RTSM) system. The blind should be broken only if knowledge of the participant's study medication would affect subsequent treatment and such knowledge is required for the clinical management of the participant. Any investigator unblinding will be documented within the appropriate section of the participant's case report from (CRF) and will be captured in the RTSM system.

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

3.5.2. Treatment Assignment

After a participant is screened and the investigator determines that the participant is eligible for enrollment, the participant will be randomized to one of the two treatment groups using the RTSM system (Day 1 visit). The randomization will be stratified by ipratropium reversibility (reversible/not reversible) and GOLD airflow category (3/4). Enrollment of GOLD 4 (FEV1 <30% of predicted normal) participants will be capped at 30% to reflect what is expected in the population with severe to very severe COPD.

4. STUDY POPULATION

4.1. Inclusion Criteria

Unless otherwise noted, all participants must meet the following criteria:

1. Participant is a male or female 40 years of age or older
2. Participant is female and is nonpregnant and nonlactating. A woman of childbearing potential must have a documented negative urine pregnancy test at screening.

   Women are considered not to be 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.
3. During the study and for 30 days after receiving the last dose of study drug, women of childbearing potential and men capable of fathering children must agree to use highly effective birth control measures or agree to abstain from sexual intercourse.

   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.
4. Participant has a diagnosis of COPD, specifically, a post-ipratropium FEV_1/FVC ratio < 0.7
5. Participant has a post ipratropium $30\% \leq FEV_1 < 50\%$ of predicted normal (using National Health and Nutrition Examination Survey-predicted equations) and absolute $FEV_1 > 500$ mL, or $FEV_1 < 30\%$ predicted normal and absolute $FEV_1 > 700$ mL.
6. Participant has a PIFR <60 L/min as measured by an In-Check™ device with resistance set to DISKUS at Visit 1A (if not combined with Visit 1B) and <55 L/min as measured by an In-Check™ device with resistance set to DISKUS at Visit 1B and Visit 2 prior to randomization
7. Participant is capable of performing reproducible spirometry maneuvers [redacted] as described by current American Thoracic Society (ATS) Guidelines.
8. Participant is an active or former smoker with a cigarette smoking history (or equivalent for cigar or pipe smoking history) of at least 10 pack-years.
9. Participant or legal guardian is willing and able to provide signed and dated informed consent to participate prior to initiation of any study related procedures.
10. Participant is willing and able to adhere to all study assessments/procedures. Care partner assistance is acceptable.

11. Participant is willing and able to adhere to all restrictions during their study participation as follows:
    - 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)
12. Participant (or care partner) based on the investigator's assessment is able to properly prepare and administer study medication administered either from both nebulizer and HandiHaler® according to their respective Instructions for Use.

4.2. Exclusion Criteria

Participants who satisfy any of the following criteria are not eligible for study enrollment:

1. Participant 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. Participant has a history of reactions or hypersensitivity to inhaled or nebulized anticholinergics
3. Participant 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. Participant has Moderate to Severe Hepatic impairment (Child-Pugh B or C) or Severe Renal Insufficiency (i.e., a glomerular filtration rate <30 mL/min/1.72m^2).
5. Participant has been hospitalized for COPD or pneumonia within 8 weeks prior to Visit 1.
6. Participant is receiving a LABA or LABA/inhaled corticosteroid (ICS; either QD or BID) at a dose that has been stable for ≤ 30 days prior to screening
7. Participant has used systemic corticosteroids within 8 weeks of Visit 1.
8. Participant has used antibiotics for respiratory tract infections within 8 weeks of Visit 1, or is using antibiotics prophylactically.
9. Participant received COVID-19 vaccine within 2 weeks of Visit 1.

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 participants to one of the treatment groups will be accomplished by randomizing the participant through the RTSM system. Each drug kit will contain a unique kit number which will be provided by the RTSM system on Day 1 to identify the study drug kits to dispense to particular participants.

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 597.76. It is a white to off-white crystalline powder and is slightly soluble in water.

Revefenacin will be supplied as 3 mL of solution packaged in a unit-dose low-density polyethylene vial with a twist-off top overwrapped in a foil pouch. Each vial contains 175 mcg of revefenacin in 3 mL of isotonic, sterile aqueous solution containing sodium chloride, citric acid, sodium citrate, and water for injection, at pH 5.0.

Matching placebo will be identically packaged and supplied as 3 mL of solution without the drug substance.

Revefenacin and its placebo must be stored at temperatures stated in the Pharmacy Manual.

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

5.1.2. Tiotropium

Tiotropium will be supplied as kits containing 1 HandiHaler® device and 4 blister cards with 10 capsules each, containing either 18mcg Spiriva® dry powder or matching placebo.

Tiotropium and its placebo should be stored at room temperature (68°F to 77°F [20°C to 25°C]; excursions permitted from 59°F to 86°F [15°C to 30°C]).

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

5.2. Dosage and Administration

Participant will administer tiotropium or matching placebo using a HandiHaler® device before administering revefenacin or matching placebo using a jet nebulizer. For participants who are taking a LABA, the sequence of drug administration will be LABA, followed immediately by tiotropium/placebo, followed by revefenacin/placebo.

5.2.1. Revefenacin

Revefenacin will be administered immediately after tiotropium placebo each day. Revefenacin placebo will be administered immediately after tiotropium each day.

Participant will be trained on the use of nebulizer on Day 1 after randomization during the administration of their first dose while at the study center. Participants 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. Additional information on the training of the participant on home nebulization is contained in the Pharmacy Manual.

Upon leaving the study center, the participant will take the jet nebulizer, compressor and study drug home. Participants will self-administer revefenacin (or placebo) every morning at approximately the same time within the window of 6:00 am and 11:00 am; the time will be chosen based on convenience for the participant and will remain the same for the duration of the study. Participants will record the time of administration in their eDiary.

Participants will refrain from taking their dose at home on Days 30 and 60, when dosing will occur during their required visit to the study center. Participants will bring their nebulizer and unused revefenacin vials to the study center on these days. Prior to leaving the study center, participants will be dispensed sufficient revefenacin (or placebo) for home dosing until the time the participant returns for their next study visit. Participants may receive additional training at these visits at the discretion of the investigator.

5.2.2. Tiotropium

Tiotropium will be administered immediately prior to revefenacin placebo on each day. Tiotropium placebo will be administered immediately prior to revefenacin each day.

Participants will be trained on the use of the HandiHaler® device on Day 1 after randomization during their first dose of tiotropium (or matching placebo) while at the study center. Additional information on the training of the participant on the use of the HandiHaler® device is contained in the Package Insert.

Upon leaving the study center, the participant will take the HandiHaler® device and the tiotropium dry powder capsules home. Participants will self-administer tiotropium (or placebo) every morning at approximately the same time within the window of 6:00 am and 11:00 am; the time will be chosen based on convenience for the participant and will remain the same for the duration of the study. Participants will record the time of administration in their eDiary.

Participants will refrain from taking their dose at home on Days 30 and 60, when dosing will occur during their required visit to the study center. Participants will bring their HandiHaler® device and unused tiotropium capsules to the study center on these days. Prior to leaving the study center, participants will be dispensed sufficient tiotropium (or placebo) capsules for home dosing until the time the participant returns for their next study visit. Participants may receive additional training at these visits at the discretion of the investigator.

5.3. Treatment Compliance

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

Compliance outside the 80% to 120% range for each method of administration will be documented in the electronic case report form (eCRF) as to reasons why, the number of doses that were outside this range, and whether any AE occurred as a result of the non-compliance.

5.4. Drug Accountability and Reconciliation

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

Study drug accountability will be performed at Visits 3, 4, and 5 (Days 30, 60 and 85, respectively) to document compliance with the dosing regimen. Participants will be instructed to bring back all remaining used and unused study drug at each study visit for drug accountability. Treatment compliance will be assessed by subtracting the number of unused returned foil pouches from the number of foil pouches that were supplied to the participant (for revefenacin) and by counting the number of used and unused blister cards (for tiotropium). If a participant does not return the unused foil pouches or blister cards, it will be assumed that the participant administered the study drug. Discrepancies between the participant's eDiary and the count of returned study drug should be documented in the source documents.

Albuterol (MDI) use will be captured from the rescue medication section of the eDiary. For accountability purposes, participants will be instructed to bring their albuterol inhaler to each study visit for drug accountability. Discrepancies between the participant's eDiary and the count of returned study drug should be documented in the source documents. Additional guidance may be found in the Pharmacy Manual.

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, tests not done, or procedures that are not conducted must be reported as such on the eCRFs.

The research site will follow institutional and government guidelines/precautions regarding Coronavirus Disease 2019 (COVID-19) to reduce the risk of infection for study participants and study staff. Any adaptations to study conduct will be documented appropriately and will take into considering the FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency (updated January 2021)

The scheduling of Visits 3, 4, and 5 (Day 30, Day 60, and Day 85, respectively; ± 7 days each) is based on the date of Visit 2 (Day 1 of the treatment period when the participant is randomized). The follow-up phone call should be scheduled 7 days after Visit 5, with a window of ±2 days.

6.2. In-Clinic Procedures by Visit

6.2.1. Screening

Screening assessments and study procedures outlined in this section will be performed after obtaining informed consent. Importantly, this includes any washout of a participant's current medication for the purpose of participation in the study or changing a participant's combination medication containing a LAMA to LABA or ICS/LABA (see Table 2 for specific washout periods required).

Prior medical history should be obtained for the previous 2 years as part of screening the participant 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 (Spiriva®), glycopyrronium bromide, aclidinium (Tudorza®), umeclidinium (Incruze®)) or any other approved LAMA; combination LAMA/LABA products (ANORO®, olodaterol/tiotropium or any other approved combination LAMA/LABA); combination LAMA/ICS/LABA products (TRELEGY® or any other approved combination LAMA/ICS/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 9 days. As part of the screening visit, the investigator should review participants' most recent lab work (within the previous 3 months) to ensure that participants are stable and to confirm that creatinine, hematocrit, and liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin [bili], alkaline phosphatase [alk phos]) 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. Collection of International Normalized Ratio (INR) and albumin for exclusion based on hepatic impairment (Section 4.2) is at the discretion of the investigator.

Participants not taking the long-acting bronchodilators described above, and participants on LABAs (e.g. salmeterol, indacaterol, vilanterol, formoterol, arformoterol, olodaterol) either alone or in combination with an ICS (e.g. fluticasone propionate, fluticasone furoate, budesonide, ciclesonide, beclomethasone), will not need to undergo a washout of these medications before enrolling in the study; these participants can be randomized 3 to 7 days after screening.

The first visit will be Screening Visit 1A. Informed consent will be obtained and the participant's existing COPD medication will be assessed to decide whether any adjustments are required to comply with the requirements of the protocol. If required, participants will start a washout period only after signing the informed consent form. After completing the necessary washout period (if required) participants will return for Screening Visit 1B within the next 5 to 9 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 the screening visit (Visit 1A if only one visit is required; from Visit 1B if two visits are required) to randomization at Visit 2 will be 3 to 7 days. Review of the spirometry results collected at the screening visit (either Visit 1A or Visit 1B) will take approximately 2 business days and must be completed to determine if the spirometry meets the eligibility criteria before the participant can be randomized.

If a participant 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 this should be considered screen failure. This includes spirometry such that if a participant fails to meet any spirometry-related criteria after the first attempt, this will be considered a screen failure. Repeat screening of spirometry will only be considered if there is a technical issue with the spirometer or with the software, or if the spirometry was not performed properly due to study center error.

6.2.1.1. Visit 1A

Participants 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, participants should not have taken albuterol (MDI) or any other short acting bronchodilator for approximately 6 hours prior to the PIFR measurements. If participants have not refrained from taking these medications in the specified time windows, this visit will be rescheduled.

The following procedures will be performed at this visit:

- 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 participant's COPD medication
- If required, based on the washout periods specified in Table 2, the participant will begin their washout. If the participant is receiving a combination COPD medication containing a LAMA, this may include changing this medication to an inhaled LABA or ICS/LABA product.

Participants who do not require washout of their COPD medications can have all of these procedures combined with those for Visit 1B.

- Review of inclusion and exclusion criteria
- Urine pregnancy test for women of childbearing potential
- Participant will be dispensed one albuterol MDI as a rescue bronchodilator.
- Review of AEs
- Local lab tests for creatinine, hematocrit, ALT, AST, bili, and alk phos, if historical local labs within 3 months of Visit 1A are not available; fasting values will not be required. Collection of INR and albumin for exclusion based on hepatic impairment (Section 4.2) is at the discretion of the investigator.
- PIFR (as measured by In-Check™ device with resistance set to DISKUS®)
  - participants requiring a washout of a LAMA with PIFR ≥60 L/min will be considered a screen failure at Visit 1A
  - participants not requiring a washout of a LAMA with PIFR ≥55 L/min will be considered a screen failure at Visit 1A

6.2.1.2. Visit 1B

This visit is required for participants who began washout of their COPD medications at Visit 1A. Participants who did not require washout can have these procedures in combination with those for Visit 1A.

Ipratropium reversibility testing will be described in the study manual. Participants 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, participants should have refrained from taking their study supplied albuterol MDI for 6 hours prior to spirometry assessments. They should further refrain from using albuterol MDI throughout the study visit. If participants have not refrained from taking these medications in the specified time windows, this visit will be rescheduled.

The following procedures will be performed at this visit:

- Prior to administration of ipratropium
  - Complete physical examination
  - Height and weight
  - Vital signs (blood pressure [BP] and heart rate [HR]) - participants need to be resting in a semirecumbent position approximately 5 minutes prior to assessment of vital signs
- PIFR – (before spirometry) as measured by In-Check™ device with resistance set to DISKUS® participants who required a washout of a LAMA with ≥55 L/min of PIFR will be considered a screen failure at Visit 1B

- 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).
- PEF (after spirometry)
- Dispense diaries (after spirometry) and record:
  - Daily breathlessness, cough/sputum, and chest symptoms via the Evaluating Respiratory Symptoms in COPD (E-RS:COPD) assessment in the evening prior to bedtime
  - Nocturnal awakenings (after spirometry)
  - Rescue albuterol use (captured throughout the day)
- Dispense PEF Meter for at-home collection by the participants. Training will be provided during the PEF collection.
- Review of concomitant medications
- Review of AEs
- Review of inclusion and exclusion criteria

6.2.2. Treatment and Follow-up Period

The timing of predose procedures is relative to the start of study drug administration (using the HandiHaler®).

The sequence of events for the participant to follow at home will be as follows: recording the start time of study drug (i.e., use of HandiHaler®) in the eDiary, then using the HandiHaler® first, then using the nebulizer.

At study visits, the trough FEV_1 will be assessed before administration of study drug (and before taking LABA if applicable). If the participant is taking a LABA this must be taken immediately before the study drug. For participants that are taking a LABA, the sequence will be LABA, followed immediately by tiotropium/placebo (HandiHaler®), and followed by nebulized revefenacin/placebo.

6.2.2.1. Day 1 (Visit 2) Randomization

Participants 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 at the study center. Additionally, participants will refrain from taking their short-acting bronchodilators (study-supplied albuterol MDI) for 6 hours prior to spirometry assessments. They will further refrain from using albuterol MDI throughout the study visit. If participants have not refrained from taking these medications in the specified time windows, this visit will be rescheduled to the following day.

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 participant is taking a LABA this must be taken immediately before the study drug.

The following procedures will be performed at this visit:

- Vital signs (BP and HR prior to dosing and after resting in a semirecumbent position for approximately 5 minutes)
- Confirm eligibility via review of inclusion and exclusion criteria
- Randomization (participant eligibility must be confirmed by investigator before randomizing participant)
- Urine pregnancy test for women of childbearing potential if visit is > 7 days after visit 1A
- Review eDiary
- Dispense study drug (RTSM system will assign 1 kit of each drug)
- Dispense/perform accountability of rescue albuterol MDI
- Review of concomitant medications
- Review of AEs
- BDI assessment
- PIFR assessment - participants will complete PIFR measured by In-Check™ device with resistance set to DISKUS® followed by PIFR set at the HandiHaler® resistance
- Measure maximal inspiratory pressure
- Completion of CAT
- Predose FEV_1, FVC via spirometry to be done 45 minutes and 15 minutes prior to the start of study drug dosing
- PEF (after predose spirometry)
- Complete nocturnal awakenings assessment
- [redacted]
- If appropriate, administer LABA containing product (for those on existing LABA-containing therapy)
- Study drug dosing via HandiHaler® (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.
- Complete E-RS:COPD in the evening before bedtime.

6.2.2.2. Day 30 (Visit 3)

Participants 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 at the study center. Additionally,

participants will refrain from taking their short-acting bronchodilators (study-supplied albuterol MDI) for 6 hours prior to spirometry assessments. They will further refrain from using albuterol MDI 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 participant is taking a LABA this must be taken immediately before the study drug.

The following procedures will be performed at this visit:

- Urine pregnancy test for women of childbearing potential
- Review eDiary
- Dispense study drug (RTSM system will assign 1 kit of each drug)
- Dispense rescue albuterol MDI
- Study drug/rescue medication accountability
- Review of concomitant medications
- Review of AEs
- TDI assessment
- Completion of CAT
- Predose FEV_1, FVC via spirometry to be done 45 minutes and 15 minutes prior to the start of study drug dosing
- PEF (after predose spirometry)
- Complete nocturnal awakenings assessments
- If appropriate, administer LABA containing product (for those on existing LABA-containing therapy)
- Study drug dosing via HandiHaler® (tiotropium or placebo) followed immediately by study drug dosing via nebulizer (revefenacin or placebo)
- Complete E-RS:COPD in the evening before bedtime.

6.2.2.3. Day 60 (Visit 4)

Participants 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 at the study center. Additionally, participants will refrain from taking their short-acting bronchodilators (study-supplied albuterol MDI) for 6 hours prior to spirometry assessments. They will further refrain from using albuterol MDI 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 participant is taking a LABA this must be taken immediately before the study drug.

The following procedures will be performed at this visit:

- Urine pregnancy test for women of childbearing potential
- Review eDiary
- Dispense study drug (RTSM system will assign 1 kit of each drug)
- Dispense rescue albuterol MDI
- Study drug/rescue medication accountability
- Review of concomitant medications
- Review of AEs
- TDI assessment
- Completion of CAT
- Predose FEV_1, FVC via spirometry to be done 45 minutes and 15 minutes prior to the start of study drug dosing
- PEF (after predose spirometry)
- Complete nocturnal awakenings assessments
- If appropriate, administer LABA containing product (for those on existing LABA -containing therapy)
- Study drug dosing via HandiHaler® (tiotropium or placebo) followed immediately by study drug dosing via nebulizer (revefenacin or placebo).
- Complete E-RS:COPD in the evening before bedtime

6.2.2.4. Day 85 (Visit 5)

Participants 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 at the study center. Additionally, participants will refrain from taking their short-acting bronchodilators (study-supplied albuterol MDI) for 6 hours prior to spirometry assessments. They will further refrain from using albuterol MDI throughout the study visit.

It is important at the Day 85 study visit that the trough FEV1 is done before taking COPD medications in the morning (e.g., LABA if applicable).

The following procedures will be performed at this visit:

- Physical examination
- Vital signs (BP and HR after resting in a semi-recumbent position for approximately 5 minutes)
- Urine pregnancy test for women of childbearing potential
- Review eDiary

  Participants will return the eDiary device to study staff by the conclusion of this visit.

- Study drug/rescue medication accountability
- Review of concomitant medications
- Review of AEs
- TDI assessment
- Completion of CAT
- FEV_1, FVC via spirometry at two time points 30 minutes apart
- PEF (after spirometry)
- Complete nocturnal awakenings assessments
- [redacted]
- If appropriate, administer LABA-containing product (for those on existing LABA-containing therapy)

6.2.2.5. Follow-up Phone Call

The follow-up phone call is required for all randomized subjects, whether they complete or early terminate from the study. At 7 ± 2 days after visit 5 (or early termination), study center personnel will contact participants by telephone to review their AEs.

6.2.3. Early Termination/Withdrawal Visit

The following procedures will be performed at the Early Termination Visit:

- Physical exam
- Vital signs (BP and HR after resting in a semi-recumbent position for approximately 5 minutes)
- Urine pregnancy test for women of childbearing potential
- Review of eDiary

  Participants will return the eDiary device to study staff by the conclusion of this visit.
- Study drug/rescue medication accountability
- Review concomitant medications
- Review AEs
- TDI assessment
- Completion of CAT
- Spirometry (FEV_1, FVC) at two time points 30 minutes apart
- PEF (after spirometry)
- Complete nocturnal awakenings assessment

If a participant discontinues from the study prematurely due to an AE, study center personnel will contact the participant by telephone approximately 30 days later to review concomitant medications and AEs. This is in addition to the 7-day follow-up telephone call.

Refer to the Case Report Form Completion Guidelines (CCGs) for further guidance.

6.2.4. At-Home Procedures

The following procedures will be performed by the participant prior to a scheduled visit and at home when not scheduled to visit the study center, unless otherwise noted:

After completing Visit 1B:

- PEF
  - On visit day: measurement will be performed at the study center prior to dosing
  - Other times: daily prior to dosing
- Complete eDiary for
  - Daily breathlessness, cough/sputum, and chest symptoms via E-RS:COPD assessment in the evening prior to bedtime
  - Nocturnal awakenings
  - Rescue albuterol use throughout the day

After completing Visit 2:

- If taking a LABA containing product (for those on existing LABA-containing therapy), take this prior to study drug dosing.
- Study drug dosing via HandiHaler® (tiotropium or placebo) followed immediately by study drug dosing via nebulizer (revefenacin or placebo).

6.2.5. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on AEs, at the participant'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, and results will be recorded in the appropriate CRF unless otherwise noted:

- Medical/medication history update
- Physical exam
- Vital signs (BP and HR after resting in a semi-recumbent position for approximately 5 minutes)
- Review concomitant medications
- Review AEs
- PEF (before first spirometry assessment; record result in eDiary)

- Spirometry (FEV_1, FVC) at two time points 30 minutes apart
- Complete eDiary for nocturnal awakenings assessments

6.3. Description of Study Assessments

6.3.1. Demographic and Baseline Assessments

After obtaining informed consent, each participant will be asked to provide a relevant medical history for the previous 2 years (with the aid of medical records if available) including medication history, concomitant medications, and demographic information including year of birth, sex, race, and ethnicity. The participant will also undergo a physical examination including vital signs, height, and weight and also will have the following assessments measured; BDI, PIFR, CAT, FEV_1, FVC (as part of spirometry for ipratropium reversibility), and a urine pregnancy test for women of childbearing potential.

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. Changes in medical history will be recorded at any unscheduled visit.

6.3.2. Pulmonary Function 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.[7]

- At Visit 1B (as part of ipratropium reversibility)
- At Visits 2, 3, 4, prior to dosing of study drug
- At Visit 5 prior to dosing of LABA (if applicable)
- At early termination (if possible)
- At any unscheduled visit (if possible)

The time window for the 45 and 15 minute predose spirometry will be ± 10 minutes, which applies to the end time of the session. At Visit 5, early termination, and any unscheduled visit, spirometry assessments will be performed at 2 time points 30 minutes apart.

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

6.3.2.2. Peak Inspiratory Flow Rate

PIFR will be measured at time points shown in the schedule of study procedures (Table 1) 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 study center will be asked to verify the reading and this verification will be noted in the source documents.[8]

6.3.2.3. Maximal Inspiratory Pressure

Maximal inspiratory pressure will be measured at Visit 2 (randomization).

6.3.2.4. Peak Expiratory Flow

Peak expiratory flow will be measured using a portable meter that will be given to participants at study entry. Participants will be trained on the use of the meter at Visit 1B and will begin measuring PEF each day thereafter before taking COPD medications or study medication (beginning Day 1) in the morning. On visit days, participants will bring this meter with them to the study center and perform the measurements in the presence of study center personnel.

For each study-specified assessment, participants will take 3 measurements and record the highest value in the eDiary.

6.3.3. Safety Assessments

6.3.3.1. Adverse Events

Adverse events will be reviewed and recorded beginning at screening (i.e., after signing the Informed Consent Form [ICF]) up to and including the telephone contact occurring 7 days after the last dose of study drug; AEs will also be reviewed and recorded at the early termination visit, at any unscheduled visits, and, for participants who discontinue due to an AE, 30 days after the date of discontinuation (Section 6.2.3). Adverse events may be observed by the study center personnel or spontaneously reported by the participant. Participants will be reminded to call the study center to report AEs that occur between visits.

6.3.3.2. 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.

6.3.3.3. Vital Signs

Vital signs will be collected after the participant has been resting in a semirecumbent position for approximately 5 minutes.

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.

6.3.3.4. Pregnancy

Urine pregnancy tests will be performed per the study center's testing procedure in women of childbearing potential. A positive urine pregnancy test result will be confirmed with a second urine test. If the second test result is positive, blood will be collected for a serum pregnancy test assessed by the study center's local lab. If the participant is an early termination or withdrawal, a urine pregnancy test will also be performed at the early termination visit.

Refer to Section 6.7 for additional information on reporting pregnancy during the study.

6.3.4. Clinical Outcome Assessments

All clinical outcome assessments (Section 6.3.4.1 through Section 6.3.4.5) will be collected electronically. Paper diaries for albuterol use data collection will be available ad hoc only in instances where the electronic devices are not available.

6.3.4.1. Baseline/Transitional Dyspnea Index

The BDI has a scale of 5 grades, scored 0 to 4, for each of the following categories: functional impairment, magnitude of task, and magnitude of effort. The ratings for each of the 3 categories are added to give the total score (range, 0 to 12).

For the TDI, using the scores of the BDI as a reference point after reminding the participant about the comments and choices made during the initial interview, the interviewer can choose a score of 0 (no change), improvements (1 to 3), or worsening (-1 to -3) for each of the 3 categories leading to a total score of between -9 and +9.

The BDI will be completed at randomization prior to dosing (Visit 2) using the site-based eDiary device. The TDI will be completed prior to dosing on Day 30 and Day 60 (Visits 3 and 4), and on Day 85 (Visit 5, or at early termination/withdrawal) using the site-based eDiary device.

6.3.4.2. Chronic Obstructive Pulmonary Disease Assessment Test

The CAT is a participant-completed instrument that complements existing approaches to assessing COPD, such as FEV_1 measurement. Scores on the CAT range from 0 to 40 with higher scores indicating worse health status.

The CAT will be completed prior to dosing at randomization, Day 30, and Day 60 (Visits 2, 3. and 4), and on Day 85 (Visit 5, or at early termination/withdrawal) using the eDiary device.

6.3.4.3. Evaluation of Respiratory Symptoms in Chronic Obstructive Pulmonary Disease

The E-RS:COPD is used to assess the severity of respiratory symptoms and the effect of treatment in patients with stable COPD. It includes 14 items based on breathlessness, sputum and cough, and chest symptoms. Participants will score all 14 items, of which only the first 11 items will be used to calculate the overall score. Most items are scored on a 5-point scale, although some are based on a 4-point scale.

Participants will complete one E-RS:COPD assessment daily in the evening prior to bedtime using the eDiary device, including scheduled visit days.

6.3.4.4. Nocturnal Awakenings

Each day before dosing, participants will answer a single question using their eDiary device about the number of awakenings due to COPD symptoms during the previous night. On visit days, participants will answer this question using their eDiary device before visiting the study center.

6.3.4.5. Rescue Albuterol Use

Participants will be dispensed albuterol MDI for use as rescue medication at each study visit (except Visit 1B for participants requiring two screening visits, Visit 5, or early termination visit). Starting at Visit 1B, participants will record the use of albuterol MDI in their eDiary (i.e., number of inhalations, time of day) which will be reviewed at each visit. Albuterol MDI use will be reviewed as part of drug accountability.

6.3.5. [redacted]

[redacted]

6.4. Concomitant Medications

Inhaled maintenance steroid therapy will be continued at the allowed maintenance dose throughout the treatment and washout periods. Albuterol MDI will be allowed as required (or "PRN") during the study. Albuterol MDI 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 MDI should be used during the participant's participation in the study.

If participants have used albuterol MDI within 6 hours of the spirometry measurement the visit must be rescheduled. Use of albuterol MDI as a rescue inhaler will be documented in the eDiary and checked in the eCRF.

Participants who are receiving a LABA or LABA/ICS (either QD or BID) may be enrolled into the study provided that the dose of the LABA and/or ICS component 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 participant's LABA or LABA/ICS together with the study drug. These participants 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 participants should be instructed to follow the same procedure while at home between study visits. If participants 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 participant 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 maintenance treatment for COPD during this study is strictly prohibited; new treatments for the duration of COPD exacerbations are permitted. Table 2 lists the medications that require washout prior to Randomization. These medications are also prohibited throughout the study (except for exacerbations). Participants will be permitted to restart their routine medications after the completion of Visit 5.

Any concomitant medication taken within 60 days prior to signing of informed consent should be reported on the case report form for all randomized subjects. For subjects who sign informed consent but who screen fail prior to randomization, the concomitant medication case report form is only required for subjects who report adverse events.

Table 2: List of Medications Requiring Washout (or Modification) Prior to Visit 1B and Prohibited During the Study

Medication	Washout Required (or Modification) and Prohibited Time Period
• Any ICS at a dose of >1000 mcg/day fluticasone propionate or equivalent	Participants on a dose >1000 mcg/day fluticasone propionate or equivalent are excluded. No modification of ICS dose will be allowed for those participants taking doses above this level.
• LAMA - tiotropium (Spiriva®), glycopyrronium bromide, aclidinium, umeclidinium, revefenacin • roflumilast • LAMA/LABA combination product e.g. umeclidinium/vilanterol (Anoro®) • LAMA/ICS/LABA combination products, e.g., umeclidinium/vilanterol/fluticasone furoate (Trelegy®).	Participants on a LAMA or roflumilast need to wash out **48 hours** prior to the Ipratropium Reversibility test at screening and prohibited during the course of the study through to Day 85. Participants on a LAMA/LABA combination need to be switched to the LABA only product at least **48 hours** prior to the Ipratropium Reversibility test at screening and maintained during the course of the study through to Day 85. Participants on a LAMA/ICS/LABA combination need to be switched to the ICS/LABA product at least **48 hours** prior to the Ipratropium Reversibility test at screening and maintained during the course of the study through to Day 85.
• LABA - salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol, vilanterol, olodaterol. • LABA/ICS products	Participants on a LABA or LABA/ICS product do not need to be washed out provided they have been on a stable dose for at least **30 days** prior to the Ipratropium Reversibility test at screening and this is continued through to Day 85. The steroid component should be ≤1000 mcg fluticasone propionate or equivalent.
• Oral theophyllines • Oral leukotriene inhibitors • Other antimuscarinic medications (e.g. atropine, cyclopentolate, homatropine, hyoscine, tolterodine, oxybutynin and/or tropicamide)	**48 hours** prior to the Ipratropium Reversibility test at screening and prohibited during the course of the study through to Day 85.
• Sodium cromoglycate • Nedocromil sodium	**24 hours** prior to the Ipratropium Reversibility test at screening and prohibited during the course of the study through to Day 85.
• Short acting beta-agonists • Short acting anti-muscarinics (e.g. ipratropium)	**6 hours** prior to the Ipratropium Reversibility test at screening. Participants will be provided with albuterol MDI to be used as rescue medication during screening and throughout the course of the study. Albuterol MDI must be withheld at least 6 hours prior to any spirometry performed during the study. Short acting antimuscarinics must be washed out prior to the Ipratropium Reversibility test and are prohibited during the course of the study through to Day 85.
• Antibiotics	**Any prophylactic use of antibiotics**
• OATP1B1 and OATP1B3 inhibitors (e.g., rifampicin, cyclosporine, etc.)	**Any concomitant use of these medications is prohibited.**

Medication	Washout Required (or Modification) and Prohibited Time Period

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist

Acetaminophen is the preferred drug for pain relief or to reduce fever.

Prophylactic use of antibiotics, and concomitant use of OATP1B1 and OATP1B3 inhibitors are not permitted.

Participants on Long Term Oxygen Therapy at 2 L/min or less will be permitted to enter the study.

Participants will be provided with study-specific albuterol MDI for use as rescue medication in the study.

In addition to the prohibited concomitant medications listed in Table 2, participants should not be taking any other prescription medications that are not part of a stable regimen. Prior to randomization, participants should not be considered eligible for the study if they have a known hypersensitivity to a similar drug class as revefenacin and/or a history of hypersensitivity to drugs with a clinically significant reaction. Any medications including PRN medications for conditions other than COPD must be reviewed with the investigator.

All concomitant medications, including name of medication, date started and stopped, route of administration, indication, and dose will be recorded in the source documentation and on the CRF. The Sponsor must be notified in advance (or as soon as possible thereafter) of any administration of a prohibited medication. Administration of a prohibited medication may result in the participant being discontinued from the study.

6.5. Restrictions

Participants are to observe the following restrictions from Screening through Day 85:

- 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 participant is at the study center), smoking, exercise, or caffeine intake or large meals should be restricted (further details are provided in the study manual).

6.6. Discontinuation

6.6.1. Participant Discontinuation

Any participant (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 participant who requests to be withdrawn. A participant'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 early termination visit should be carried out. All efforts should be made however to minimize discontinuations from the study. If a participant withdraws before completing the study, the reason for withdrawal is to be documented on the CRF and the Sponsor retains the right to use the participant's data through to the date the participant withdraws consent.

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

- AE
- Participant choice (i.e., withdrawal of consent)
- Major deviation from the protocol
- Lost to follow-up
- Termination of the study by the Sponsor
- Other

Participants 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 approximately 30 days after discontinuation to review concomitant medications and AEs if the discontinuation was due to an AE, in addition to the 7-day Follow-up Telephone Contact. If a participant 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 participant.

6.6.2. Participant Replacement

The assumption is that the dropout rate will be approximately 20%. The target is at least 146 participants completing 84 days (12 weeks) of therapy in each treatment group. Participants who withdraw will not be replaced in this study.

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.

6.7. Pregnancy

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

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

If not all information requested on the **Pregnancy Reporting Form** is available at the time of the initial report, the Investigator is required to follow up on the pregnancy until it has completed. Follow-up information regarding the outcome of the pregnancy, status of the newborn (if applicable), and any postnatal sequelae in the newborn will be required and must be submitted within 24 hours of the Investigator's becoming aware of any new information using the **Pregnancy Reporting Form**.

6.8. Exacerbation of Chronic Obstructive Pulmonary Disease

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

Table 3: Severity Criteria for COPD Exacerbations

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

Participants will be questioned regarding having experienced moderate or severe exacerbations. Information on all exacerbations will be collected using a separate CRF.

7. ADVERSE EVENTS

7.1. Definitions

The definitions below are based on International Conference on Harmonization (ICH) guideline E2A, "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting", and guideline E6, "Good Clinical Practice."

7.1.1. Adverse Events (AEs)

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

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

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

An AE does not include the following:

- Medical or surgical procedures (such as surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an AE
- Preexisting diseases or conditions present or detected before signing an informed consent form that do not worsen
- Situations where an untoward medical occurrence has not occurred (such as hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of either study drug or concomitant medication without any signs or symptoms, unless the participant is hospitalized for observation

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

Pregnancy is not an AE; however, if a female participant becomes pregnant during the conduct of the study, Theravance Biopharma, Inc. (TBPH) will be notified according to the procedures for SAE reporting as outlined in Section 7.5.3. Follow-up information regarding the outcome of the pregnancy and any fetal or neonatal sequelae will be obtained and documented.

Exacerbations of COPD (Section 6.8) will be collected as AEs. Details of the exacerbation event (e.g., symptoms, concomitant medication) will be recorded on a separate CRF.

7.1.2. Serious Adverse Event (SAE)

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

- Death
- Life-threatening situation. "Life-threatening" refers to a situation in which the participant was at risk of death at the time of the event; it does not refer to an event which might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization

  Note: "Inpatient hospitalization" means the participant has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure, scheduled treatments, or routine check-ups do not meet this criterion. Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- Disability- 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 participant who received study drug
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant 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
- Severe exacerbations of COPD, as described in Section 6.8

7.1.3. Additional Considerations for Serious Adverse Events

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

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

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

Abnormal laboratory findings (such as clinical chemistry, hematology, or urinalysis) or other abnormal assessments (such as electrocardiograms, X-rays, or 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 AE (or SAE), as described in Section 7.1.1 (Adverse Events) and Section 7.1.2 (Serious Adverse Events).

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

7.3. Assessment of Adverse Events

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

7.3.1. Severity

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

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

7.3.2. Causal Relationship to Study Medication

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

- Possible alternative causes of the AE, including the disease under treatment, co-morbid conditions, other drugs, and environmental factors.
- The temporal association between drug exposure and onset of the AE.
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study medication.

- Whether the AE resolved or improved with decreasing the dose or stopping the study medication ("dechallenge") or recurred or worsened upon re-exposure to the study medication ("rechallenge").

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

- **Not Related:** Evidence exists that the AE has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the participant'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 AE reporting.

7.4. AE Reporting and Recording

7.4.1. AE Reporting

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

7.4.2. AE and SAE Recording

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

Description of event:

- Signs and symptoms due to a common etiology should be reported as a single diagnosis; for example, cough, runny nose, sneezing, sore throat, and head congestion would be reported as "upper respiratory infection".
- A diagnosis or description must be as specific and as complete as possible (e.g., "lower extremity edema" instead of "edema").

- Hospitalization or surgical procedures should not be used as AE terms (e.g., if a participant was hospitalized for cholecystectomy due to cholecystitis, the AE term should be recorded as cholecystitis, and not as the procedure, cholecystectomy).
- "Death" should not be used as an AE term unless the cause of death is unknown. For events with a fatal outcome, the cause of death should be the AE term (e.g., if a participant died of an acute myocardial infarction, the AE term should be recorded as "Myocardial Infarction" and the event outcome as fatal).

Relationship to study medication: The Investigator will make an assessment of the causal relationship of the study medication to the AE using the guidelines in Section 7.3.2.

Severity: The severity of the AE will be assessed using the guidelines in Section 7.3.1.

Outcome: The outcome of AEs will be recorded.

Therapeutic measures: Measures taken for the treatment or management of the AEs will be recorded.

7.4.3. SAE Reporting Timeline

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

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

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

Theravance Biopharma Clinical Safety

Fax: [redacted]

Email: [redacted]

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

Sponsor Medical Monitor Contact Information:

[redacted]

Telephone: [redacted]

Email: [redacted]

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

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the study drug and is unexpected/unlisted based on the current revefenacin 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.

7.5. Adverse Event Follow-up

A participant 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 AEs 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) 9.4 or higher.

Continuous data will be summarized using n, mean, standard deviation, and other descriptive statistics as appropriate.

Categorical data will be summarized using the frequency of events and percentage of total events.

Any changes to the protocol-specified analyses will be pre-specified in the Statistical Analysis Plan (SAP) prior to data lock/unblinding.

8.2. Sample Size and Power

[redacted]

8.2.1. [redacted]

[redacted] The total number of participants will be capped up to a maximum sample size of 488 participants. [redacted]

8.3. Analysis Sets

The full analysis set (FAS) will include all randomized participants who:

- Receive at least one dose of study drug (revefenacin or tiotropium)

The FAS will be the primary analysis set for general and efficacy analyses. Participants will be analyzed according to their randomized treatment group.

The safety analysis set is the primary analysis set for safety analyses and will include all participants who are randomized and receive at least one dose of study drug. Participants will be analyzed according to their treatment actually received.

8.3.1. Examination of Subgroups

The following subgroups are pre-defined for the purposes of analyses:

- Baseline PIFR: [a] < 40 L/min, [b] ≥ 40 L/min
- Baseline smoking status: [a] current smoker, [b] former smoker
- Age: [a] < 65, [b] ≥ 65
- Gender: [a] woman, [b] man
- Current LABA or ICS/LABA use: [a] yes, [b] no
- Reversibility to a short-acting bronchodilator: [a] not reversible to ipratropium, [b] reversible to ipratropium
- Baseline GOLD airflow category: [a] 3 (30% to < 50% of predicted normal FEV_1), [b] 4 (< 30% of predicted normal FEV_1)

Additional subgroups may be specified in the SAP.

8.3.2. 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.

- Participant did not meet efficacy-defined inclusion criteria (Inclusion criteria 4, 5, 6)
- Participant drug compliance < 80% or > 120% separately for DPI and nebulizer
- Participant was taking a concomitant LAMA

Additional criteria may be specified in the SAP. Major protocol deviations will be summarized but will not be used to exclude subjects from analyses.

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 FAS.

8.4.2. Screening and Baseline Spirometry

A summary of lung function at screening, including reversibility, and at baseline using the FAS will be provided.

8.4.3. COPD Clinical History and Smoking History

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

8.4.4. Medical History

A summary of selected medical history/characteristics using the safety analysis set will be provided characterizing co-morbidities and disease severity. A summary of medical history by system organ class and preferred term will also be provided.

8.4.5. Reversibility

Reversibility to ipratropium is defined as a postbronchodilator increase of ≥ 12% and at least a 200-mL increase in FEV_1 relative to the prebronchodilator response. A summary will be provided for the FAS.

8.5. Analysis of Efficacy

For efficacy analyses, the FAS will be used unless otherwise specified. For the primary efficacy endpoint, subgroup analyses for the subgroups listed in Section 8.3.1 will be performed.

8.5.1. Efficacy Endpoints

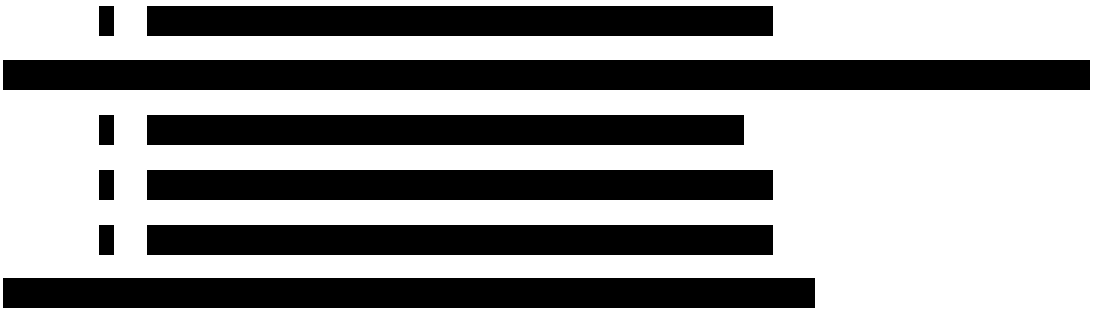
The primary study endpoint is change from baseline in trough FEV_1 on Day 85 following 84 days of dosing.

The secondary endpoints are as follows:

- Trough overall treatment effect (OTE) on FEV_1 over 85 days
- Change from baseline in Trough FVC on Day 85
- Change from baseline in Trough FEV_1 on Day 30
- Change from baseline in Trough FEV_1 on Day 60
- 80-mL response, defined as at least an 80-mL improvement in trough FEV_1 on Day 85
- Time to first CompEx event

Exploratory endpoints are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]



8.5.1.1. Primary Efficacy Evaluation

The primary estimate of interest, change from baseline in trough FEV_1 on Day 85 after 84 days of dosing, is used to evaluate the effectiveness of revefenacin therapy relative to the active comparator of tiotropium.

The null hypothesis for the treatment comparison will be that there is no difference between revefenacin and tiotropium in change from baseline in trough FEV_1 on Day 85. The alternative hypothesis will be that there is a difference.

For the primary endpoint, a repeated measures mixed effects model (RMMM) model will be used to estimate treatment differences. The model will include fixed class terms for randomized treatment group, ipratropium reversibility (reversible/not reversible), smoking status (current/former smoker), concomitant LABA or ICS/LABA use (Yes/No), GOLD (3/4), sex (woman/man), age (<65/≥65), and continuous covariates for baseline PIFR set to DISKUS® resistance and baseline FEV_1, as well as a time effect (visit) and its interaction terms with treatment and the baseline values of the covariates. Within-subject correlation will be modelled using an unstructured variance-covariance matrix. The Kenward and Roger method for approximating the denominator degrees of freedom will be used. Least-squares (LS) means and 95% confidence intervals (CIs) for LS mean differences between revefenacin and tiotropium will be calculated and presented in tabular and graphical format. Nominal p-values and CIs will be reported.

For the primary and secondary endpoints, both treatment policy and efficacy estimands will be estimated, as detailed in the SAP. Treatment policy analyses will not exclude data collected following permanent discontinuation of study drug or initiation of new maintenance treatment for therapy. If the 2-sided 95% CI for the Day 85 revefenacin vs. tiotropium treatment policy estimand difference lies above zero, the primary endpoint will be considered to have been met and a tipping point analysis systematically varying assumptions about unobserved responses.

8.5.2. Secondary [redacted] Efficacy Evaluations

The following endpoints can all be estimated from the same model outlined for the primary analysis:

- Change from baseline in Trough FEV_1 on Day 30
- Change from baseline in Trough FEV_1 on Day 60
- Trough overall treatment effect (OTE) on FEV_1 over 85 days

Change from baseline in trough FVC on Day 85 will be analyzed using similar methodology as the primary endpoint.

A responder analysis based on Day 85 trough FEV_1 will be conducted using a logistic regression model with a similar set of covariates as the primary efficacy endpoint. A summary of responders will be presented with frequency distributions (counts and percentages), observed LS percentages and revefenacin:tiotropium odds ratios.

A Cox proportional hazards model with the same covariates as the primary efficacy analysis model will be used to derive hazard ratios and analyze time to first event for CompEx COPD.

A statistical hierarchy will be used to test the hypotheses of the primary and secondary endpoints to control the family-wise type 1 error rate at 5%. Details will be provided in the SAP.

All efficacy endpoints will also be reported with nominal p-values, unless specified otherwise.

[redacted]

8.5.3. Multiplicity Adjustment

Multiplicity adjustment of p-values for the primary and secondary hypotheses will be conducted in a stepwise manner; full details of the testing procedure will be provided in the SAP.

8.6. Safety Analyses

The safety endpoints are the incidence of AEs (including exacerbations of COPD), and vital signs. For all safety analyses, the safety analysis set will be used.

8.6.1. Extent of Exposure

A participant's data for the extent of exposure to study drug will be generated from the study drug administration page of the CRF. Dosing information for individual participants will be listed. Using drug administration data, estimates of exposure to revefenacin and tiotropium will

be summarized. Dose discontinuations and reasons for study drug discontinuation will be listed and summarized.

8.6.2. Adverse Event Data

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

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

A TEAE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 7 days. AEs observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from TEAEs.

All AEs and all TEAEs will be listed by participant. The frequency of participants 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 participants who experience an SAE. Data listings will also be provided for participants who discontinued the study due to any AE, as well as for an SAE.

8.6.3. Concomitant Medications

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

8.6.4. Vital Signs Data

Vital signs data (heart rate and blood pressure) will be summarized in terms of observed values (by time point), changes from baseline (by time point), and counts and percentages based on clinically important thresholds (Table 4).

Table 4: Clinically Important Thresholds for Vital Signs

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

8.7. Missing Data Handling

Missing values for the primary and secondary spirometry efficacy endpoints will not be imputed except for the responder analysis, and any additional sensitivity analyses specified in the SAP. The responder analysis will impute missing data with a negative outcome of non-response.

Details on sensitivity and supplementary analyses will be outlined in the SAP.

8.8. Data Monitoring Committee

No data monitoring committee is planned for this study.

The Sponsor will monitor trial data to ensure the safety of participants via periodic review and discussion of safety data collected during the trial. These discussions 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 study center must provide to the Sponsor or its designee a fully executed and signed Form FDA 1572 and, if applicable, a financial disclosure form. For applicable studies, financial disclosure forms must also be completed for all subinvestigators who will be directly involved in the treatment or evaluation of research participants in this study. (A subinvestigator is defined in ICH E6 as any individual member of the clinical study team designated and supervised by the investigator at a study center 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 participants.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential participants, 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 Code of Federal Regulations Title 21 (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 Part 312.62 and to make those records available for inspection in accordance with 21 CFR Part 312.68.
- He or she will ensure that the Institutional Review Board/Independent Ethics Committee (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 participants 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 participants.

- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

9.2. Institutional Review Board/Independent Ethics Committee

Before beginning study-specific research, the investigator will obtain written confirmation that the IRB, IEC, or Research Ethics Board (REB) is properly constituted and compliant with ICH and Good Clinical Practice (GCP) requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to the Sponsor or its designee. The protocol, ICF, IB, and any other appropriate written information provided to the participants 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 participant 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 study center, 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 executed ICF, in compliance with ICH E6 (GCP Guideline, Section 4.8), 21 CFR Part 50, and other applicable local regulations, will be obtained for each participant before enrollment of the participant 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 participant (or the participant's legally authorized representative) and will maintain the original in the participant'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 or electronic form 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. Examples of other methods include, but are not limited to, eDiary, electronic clinical outcomes assessment (eCOA), eConsent, and electronic laboratory data transfer. Study center personnel will enter (in English) study data into the CRFs

for each participant. Training on the EDC application, as well as any other system used for the capture of clinical data, will be completed and documented before access 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 study center 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 participant. The investigator is also responsible for ensuring the availability of any original source documentation related to the study (including any films, tracings, digital media, and worksheets). In most cases the source is the participant'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 study center and clearly identify those data that will be recorded in the CRF and for which the CRF will stand as the source document. In addition, any data entered directly by participants (e.g., eDiary data) will be considered source documentation.

9.5. Document Retention

Until otherwise notified by the Sponsor, an investigative study center must retain in a controlled manner all study documents required by the Sponsor and by the applicable regulations. The investigative study center 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., participant 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 participant, before enrollment into the study, that, for evaluation of study results, the participant's confidential medical information obtained during the study may be shared with the study sponsor, the study sponsor's affiliated companies, the study sponsor's designated service providers, regulatory agencies, and the IRB/IEC/REB. The investigator (or designee) is responsible for obtaining written or electronic consent 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 participant or, if appropriate, the participant'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 participant will be collected.

Participant 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 participant information will only be identified by the participant identification number, year of birth, and study number, and not by the participant's full name, except the participant consent form, which is archived at the study center only. The participant's name will not be used in any public report of the study.

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

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 participant'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 participant 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 from the medical records should be attributable (signed and dated), consistent with local medical practice. The investigator must therefore agree to allow direct access to all source data. Participants (or their legally authorized representatives) must also allow access to their medical records, and participants 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 study center visits conducted by the Sponsor or its designees. Access to clinical data may occur remotely based on site and local requirements if deemed necessary.

Members of the Sponsor's GCP Quality Assurance Department or designees may conduct an on-site or remote audit of a clinical study center 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/REB 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 center 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

1. Mahler DA, Waterman LA, Ward J, Gifford AH. Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate. J Aerosol Med Pulm Drug Deliv. 2014;27:103–109.
2. Mahler DA, Ohar JA, Barnes CN, Moran EJ, Pendyala S, Crater GD. Nebulized Versus Dry Powder Long-Acting Muscarinic Antagonist Bronchodilators in Patients With COPD and Suboptimal Peak Inspiratory Flow Rate. Chronic Obstr Pulm Dis. 2019 Oct 23;6(4):321-31.
3. Loh CH, Peters SP, Lovings TM, Ohar JA. Suboptimal Inspiratory Flow Rates Are Associated with Chronic Obstructive Pulmonary Disease and All-Cause Readmissions. Ann Am Thorac Soc. 2017;14:1305–1311.
4. [redacted]
5. Fuhlbrigge AL, Bengtsson T, Peterson S, Jauhiainen A, Erickson G, Da Silva CA, et al. A novel endpoint for exacerbations in asthma to accelerate clinical development: a posthoc analysis of randomized clinical trials. Lancet Respir Med. 2017;5:577-90.
6. Da Silva CA, Bengtsson T, Peterson S, Karlsson N, Fageras M, Jauhiainen A. COPDCompEx: A Novel Composite Endpoint to Accelerate Early Clinical Development of New Agents for Treatment of COPD. Am J Respir Crit Care Med. 2018;197:A7428.
7. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019 Oct 15;200(8):e70-e88.
8. Barnes CN, Mahler DA, Ohar JA, Lombardi DA, Crater GD. Defining Repeatability Limits for Measuring Peak Inspiratory Flow Rates (unpublished).

APPENDIX 1. PROTOCOL SIGNATURE FORM

Protocol Signature Form

Protocol #:	0180
Protocol Title:	A Phase 4, Randomized, Double-Blind, Double-Dummy, Parallel-Group Study Comparing Improvements in Lung Function in Adults With Severe to Very Severe Chronic Obstructive Pulmonary Disease and Suboptimal Inspiratory Flow Rate Following Once-Daily Treatment Over 12 Weeks With Either Revefenacin Inhalation Solution Delivered via Standard Jet Nebulizer or Tiotropium Delivered via a Dry Powder Inhaler (Spiriva® HandiHaler®)
Version:	Amendment 4
Version Date:	27 Feb 2023 (FINAL) Supersedes 9 Feb 2022

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

Investigator's Name (print)

Investigator's Signature

Date