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: 10 November 2023

STATISTICAL ANALYSIS PLAN

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 Yupelri® Inhalation Solution Delivered via Standard Jet Nebulizer or Tiotropium Delivered via a Dry Powder Inhaler (Spiriva® HandiHaler®)
Protocol Number:	0180
Compound Number:	Revefenacin (YUPELRI®)
Short Title	PIFR-2 Study
Sponsor Name:	Theravance Biopharma Ireland Limited
Legal Registered Address:	Ten Earlsfort Terrace Dublin 2 D02 T380 Ireland

This study will be conducted in compliance with Good Clinical Practice.

CONFIDENTIAL

SIGNATURE PAGE

Compound YUPELRI® (revefenacin)

Protocol Number 0180

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LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Description
ANCOVA	analysis of covariance
ATS	American Thoracic Society
BID	twice daily
BDI	Baseline Dyspnea Index
CAT	Chronic Obstructive Pulmonary Disease Assessment Test
CI	confidence interval
CompEx	composite endpoint for severe exacerbations of chronic obstructive pulmonary disease
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
DPI	dry powder inhaler
eDiary	electronic diary
E-RS: COPD	Evaluating Respiratory Symptoms in COPD
EXACT	EXAcerbations of Chronic Pulmonary Disease Tool
FEV_1	forced expiratory volume in 1 second
FRC	functional residual capacity
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IC	inspiratory capacity
ICS	inhaled corticosteroid
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
PEF	peak expiratory flow
PIFR	peak inspiratory flow rate

Abbreviation	Description
QD	once daily
RTSM	Randomization and Trial Supply Management
SAP	Statistical Analysis Plan
TDI	Transitional Dyspnea Index
TEAE	treatment-emergent adverse event
TLC	total lung capacity
US	United States

VERSION HISTORY

This statistical analysis plan for Study 0180 is based on protocol Amendment 4 dated 27 February 2023.

Table 2: Version History

SAP Version and Approval Date	Protocol Version and Approval Date	Changes	Rationale
1.0, 14 July 2022	Amendment 3, 09 February 2022	Not applicable	Original version
2.0, 27 March 2023	Amendment 4, 27 February 2023	Revise Section 1.2, Study Design: No. of centers changed from approximately 40 to approximately 70 Minimum postipratropium FEV_1 at screening changed from > 700 mL to > 500 mL for subjects with postipratropium % predicted normal $FEV_1 \geq 30\%$	Reflect protocol Amendment 4 changes
		Minor editorial changes	Remove ambiguities, increase consistency of usage, omit unnecessary information, add clarifying information
		Revise Section 2, Analysis Sets, to add a rescue analysis set	Because analyses of rescue medication use are based on reported uses of the study-supplied albuterol MDI inhaler, exclude subjects who are using non-study-supplied rescue medication during the treatment period and subjects on maintenance regimens that will limit/confound their rescue medication use, such as albuterol QID

SAP Version and Approval Date	Protocol Version and Approval Date	Changes	Rationale
		Revise Section 3.1.3, Variables, to mention that not only predicted normal FEV_1 but also predicted normal FVC is included in spirometry data transfers; same revision to Section 3.1.8.9, FVC, with addition of NHANES III Normal FVC Prediction Equations	Completeness: both screening (pre-ipratropium) FEV_1 as a fraction of predicted normal FEV_1 and screening (pre-ipratropium) FVC as a fraction of predicted normal FVC are included in summaries of baseline characteristics
		Add Section 3.1.8.5, COPD Maintenance Therapy at Baseline, to provide a Yes/No indicator of whether subjects entered the treatment period on COPD maintenance therapy	Subjects may enter the treatment period on a non-LABA or LABA/ICS regimen, e.g., ICS only, albuterol QID
		Revise Section 3.2.3, Demographic and Baseline Characteristics, to add FVC summaries corresponding to each FEV_1 summary	Provide a fuller picture of baseline spirometry values, since FVC is a secondary endpoint
		Revise Section 3.2.7, Prior and Concomitant Medications, to add a summary of COPD maintenance therapy at baseline	Subjects may enter the treatment period on a non-LABA or LABA/ICS regimen, e.g., ICS only, albuterol QID
		Revise Section 3.4.3, Main Analysis Methods, to say the treatment policy estimand is considered primary, rather than the hypothetical estimand as in SAP v1.0	Respond to regulatory comments
		Revise Section 3.4.4 to change the title from “Supplementary Analyses” to “Sensitivity Analysis” and to describe the tipping point analysis that will be provided to assess the sensitivity of the primary analysis result to the assumption that missing Day 85 FEV_1 measurements are missing at random (in the technical sense); add reference	Respond to regulatory comments

SAP Version and Approval Date	Protocol Version and Approval Date	Changes	Rationale
		Revise Section 3.7.2, Rescue-free Days, to change "If the eDiary was completed for the day" to "If there are eDiary data for the day"	The original text was unclear because what it means to "complete" the eDiary for a given day was not defined. It is assumed that if the subject was able to report other data using the eDiary data, the subject could and would have reported any uses of rescue medication.
		[redacted]	[redacted]
		Revise Section 3.8.1, Extent of Exposure, to add that if the date of last dose is not reported it will be imputed as the date of study completion or discontinuation	Some PIs may not wish to record an approximate last dose date when the actual last dose date is unknown
		Revise Section 3.8.1.1, Treatment Compliance, to state that compliance will be calculated only for subjects who return at least 1 study drug kit	Blinded data reviews have indicated that imputing all doses as taken when kits are not returned does not give credible compliance estimates for subjects who returned no kits.
		[redacted]	[redacted]
		Revise Appendix 5.1, Changes to Protocol-Planned Analyses, to list changes to analyses described in protocol Amendment 4	SAP v2.0 is based on Amendment 4

SAP Version and Approval Date	Protocol Version and Approval Date	Changes	Rationale
3.0, 10 November 2023	Amendment 4, 27 February 2023	Correct predicted FVC units in Table 8 footnote from mL to L	Correct typo; the coefficients given in the reference are for FVC in liters
		Update MedDRA and WHODrug coding versions	Bring text up to date; MedDRA® 26.1 Q3 2023 and WHODrug Q3 2023 C3 will be the versions in use at database lock
		Include the pre-ipratropium value as an additional baseline predictor in the models for FEV_1 and FVC endpoints	Increase precision of estimation and power by reducing residual variability
		Change the description of the calculation of predicted normal FEV_1 (mL) in Section 3.1.8.7 to state that calculated values will be truncated to 1 decimal place rather than to an integer; same change for predicted normal FVC, Section 3.1.8.9	Bring text up to date; the spirometry vendor changed the data transfer specification to add a decimal place
		Revise Section 2 analysis set definitions for all analysis sets except the enrolled and randomized sets to exclude subjects from sites [redacted]	Maintain reliability of inference by excluding data collected at sites where misconduct is suspected
		Change Section 3.6 endpoint testing sequence; move D85 FVC below D30 FEV_1 and D60 FEV_1	Increase expected number of endpoints met
		Added Section 3.4.5	Analysis to assess the impact of site exclusion

1. INTRODUCTION

This document presents the plan for the summarization and analysis of clinical data collected in Study 0180. The study purpose is to assess whether COPD patients with severe to very severe disease (GOLD airflow category 3 or 4) and low inspiratory flow rates have greater improvements in trough FEV_1 over an 84-day treatment period with revefenacin administered via nebulizer than with tiotropium administered via dry powder inhaler. Study 0180 is the successor to Study 0149, a study comparing the same 2 treatments over a shorter treatment period (28 days) in patients with low inspiratory flow rates and moderate to very severe disease (GOLD airflow category 2, 3, or 4).

1.1. Objectives and Endpoints

1.1.1. Primary Objectives and Endpoints

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 peak inspiratory flow rate (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 primary study endpoint is change from baseline in trough FEV_1 on Day 85 following 84 days of dosing.

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

1.1.2. Secondary Objectives and Endpoints

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 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 from baseline 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 deterioration based on objective measures of deterioration in peak expiratory flow (PEF), rescue medication use, COPD symptoms, and nocturnal awakening.

A moderate exacerbation is defined as an increase in symptoms that requires treatment with antibiotics and/or corticosteroids. 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 are defined in Section 5.4.3.

1.1.3. [redacted]

[redacted]

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

[redacted]

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

[redacted]

1.2. Study Design

This is a phase 4, randomized, double-blind, active-controlled parallel trial conducted to compare the effects of once daily nebulized revefenacin (Yupelri) and once daily tiotropium (Spiriva) delivered via the HandiHaler® on lung function in subjects with severe to very severe COPD and a low PIFR over an 84-day treatment period.

The study will be conducted at approximately 70 US centers. It is expected that approximately 366 male and female subjects 40 years of age or older will be randomized in a 1:1 ratio to one of the treatment regimens shown in Table 3, to be followed for up to 84 days. [redacted] the total number of subjects randomized may be increased to at most approximately 488 subjects.

Table 3: Blinded Treatment Regimens

Revefenacin	Tiotropium-matching placebo dry powder capsule administered by oral inhalation once every morning using the HandiHaler® device, followed by revefenacin solution (175 mcg in 3 mL) for oral inhalation by jet nebulizer
Tiotropium	Tiotropium dry powder capsule (Spiriva®, 18 mcg) administered by oral inhalation once every morning using the HandiHaler® device, followed by revefenacin-matching placebo solution (3 mL) for oral inhalation by jet nebulizer

During screening, subjects are required to "wash out" from certain medications or take a lower dose. Subjects required to wash out or take a lower dose will have their screening procedures conducted over 2 screening visits, 1A and 1B, where 1B is 2 to 9 days after 1A; others may complete all screening procedures during their first screening visit. Subjects will be assessed for suboptimal PIFR using the InCheck™ device set to DISKUS resistance, undergo ipratropium reversibility testing, receive rescue medication (albuterol MDI) for use as needed during the trial, receive an electronic diary (eDiary) device provided by the electronic clinical outcome assessment contract research organization (CRO), and have their adverse events and medications reviewed. Subjects will also undergo clinical laboratory testing if laboratory test results from within the previous 3 months are unavailable and physical examinations including vital sign, height, and weight measurements. Women of childbearing potential will have a local urine pregnancy test.

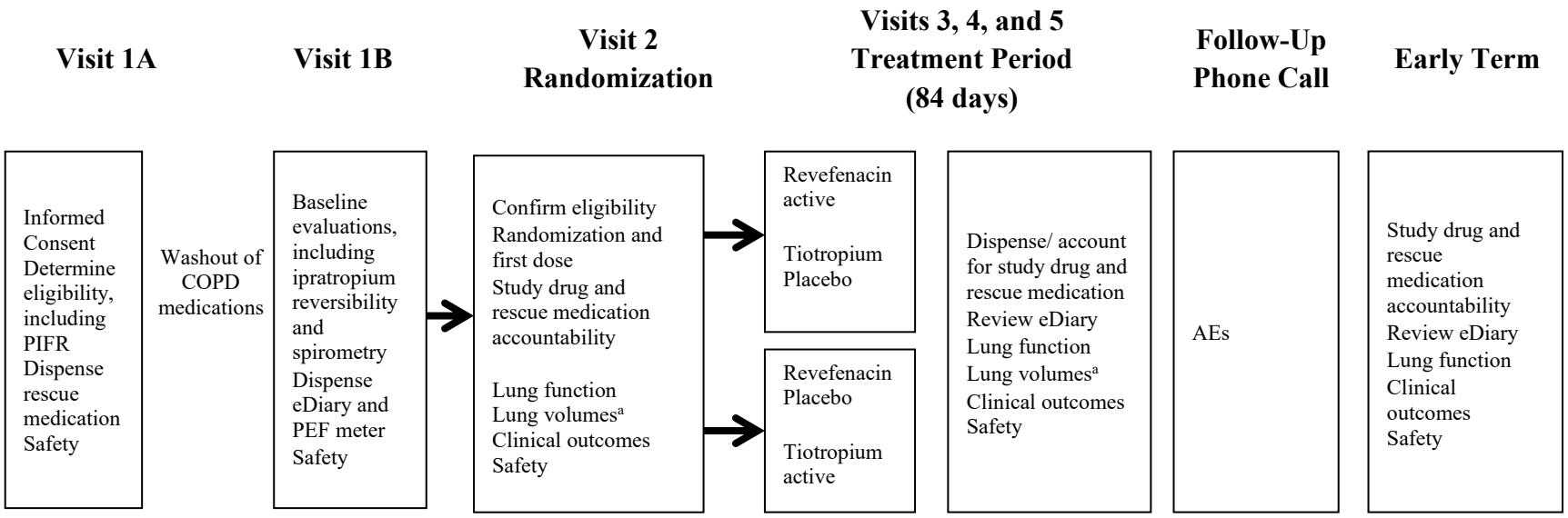
At the randomization visit on Day 1, subjects with PIFR < 55 L/min, with postipratropium FEV_1 < 50% of predicted normal (as calculated using NHANES III equations as described in Section 3.1.8.7) and > 500 mL (> 700 mL when postipratropium FEV_1 < 30% of predicted normal), and who meet all other eligibility criteria will be randomized to revefenacin (revefenacin 175 mcg/tiotropium placebo) or tiotropium (tiotropium 18 mcg/revefenacin placebo). Subjects will undergo baseline lung function tests and clinical outcome assessments and have their eDiaries, concomitant medications, and adverse events reviewed. [redacted] After in-clinic assessments are completed, subjects will take their morning long-acting beta-2 agonist (LABA) or LABA-combination dose if they are on LABA therapy, followed by their first HandiHaler® study drug dose, followed by their first nebulizer study drug dose.

Subjects will return to the clinic on Day 30 ± 7 days and Day 60 ± 7 days (Visits 3 and 4). eDiaries will be reviewed. Study drug and rescue medication will be accounted for, and new supplies will be dispensed. Adverse events and concomitant medications will be reviewed. Clinical outcomes and lung function will be assessed. [redacted]

Subjects will self-administer study medication once daily in the morning for 84 days, except on Days 30 and 60, when subjects will return to the study center for assessments prior to taking their study medication, and will record their HandiHaler® and nebulizer dosing times in their eDiary.

Subjects will return to the clinic on Day 85 ± 7 days (Visit 5) for final assessments. Study drug and rescue medication will be accounted for and eDiaries, concomitant medications, and adverse events will be reviewed. Subjects will undergo a physical examination including vital signs. Clinical outcomes and lung function will be assessed. [redacted]
Subjects who discontinue from the study prior to Visit 5 will undergo the same procedures at an early termination visit. At 7 ± 2 days after the last visit, subjects will be contacted by telephone for an assessment of their adverse events.

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

1.3. Treatment Assignment and Blinding

During the Day 1 visit, eligible subjects will be randomized in a 1:1 ratio to receive either revefenacin and dummy tiotropium or dummy revefenacin and tiotropium. The randomization will be stratified by ipratropium reversibility status (reversible/not reversible) and GOLD airflow category (3/4). Subjects in each of the 4 strata will be assigned to treatments using a sequence of randomly permuted blocks. Enrollment of GOLD 4 (FEV_1 < 30% of predicted normal) subjects will be capped at 30% to reflect what is expected in the population with severe to very severe COPD.

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. Matching placebo will be identically packaged and supplied as 3 mL of solution without the drug substance. Each kit will contain 35 vials. At the Day 1 visit, subjects will also be provided with a PARI LC Sprint® nebulizer with PARI Trek S® compressor and connector tubing.

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

Subjects will administer tiotropium or matching placebo using a HandiHaler® device before administering revefenacin or matching placebo using the PARI LC Sprint® nebulizer.

If they are taking a LABA, the sequence of drug administration will be LABA, followed immediately by tiotropium/placebo, followed by revefenacin/placebo. On in-clinic visit days, they will follow this sequence in the clinic; between visits, they will dose themselves every morning at approximately the same time within the window of 6:00 AM to 11:00 AM. The time will remain the same for the duration of the study. Subjects will record the time of administration (both HandiHaler® dosing time and nebulizer start time) in their eDiary. Only one pair of times can be recorded each day.

Before database lock, access to randomized treatment assignments will be limited to certain randomization and trial supply management (RTSM) system personnel, investigators, and certain sponsor drug safety personnel. Investigators may use the RTSM system to obtain a subject's randomized treatment assignment only in an emergency requiring the investigator to be unblinded. Drug safety personnel may use the RTSM system to obtain randomized treatment assignments for individual subjects only as needed to fulfill their reporting requirements. Any such individual-subject unblindings will be captured in the RTSM database. Any investigator-initiated unblindings will also be captured in the clinical database.

1.4. Schedule of Assessments

Table 4: 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

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
Plethysmography (IC, FRC, TLC) at 45 and 15 min predose[m]			X			X[j]			
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; FEV1, forced expiratory volume; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; INR; International Normalized Ratio; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; 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 protocol 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. INR and albumin collection to determine Child-Pugh score for exclusion is at the investigator's discretion.

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

i Reversibility testing pre- and postipratropium after withholding bronchodilators as specified in protocol 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

1.5. [redacted]

[redacted]

1.5.1. [redacted]

[redacted]

[redacted]

2. ANALYSIS SETS

Table 5: Analysis Sets

Analysis Set	Definition
Enrolled	All enrolled subjects. Subjects enroll by consenting to participate in the study.
Randomized	All randomized subjects
Interim	The first 100 randomized subjects who receive at least 1 dose of study drug (via HandiHaler® or nebulizer) (Section 5.2)
Safety*	All randomized subjects who receive at least 1 dose of study drug (via HandiHaler® or nebulizer)
Full*	All randomized subjects who receive at least 1 dose of study drug (via HandiHaler® or nebulizer) (same as safety analysis set)
Rescue*	A subset of the full analysis set which excludes subjects who are on a SABA maintenance regimen at baseline (e.g., albuterol QID) and subjects who use non-study-supplied rescue medication (e.g., nebulized albuterol) during the treatment period, to be used for analyses of rescue medication use and CompEx events
[redacted]	[redacted]

*Sites [redacted] were excluded from analysis on the grounds of potential misconduct, as described in:

PIFR-2 INDEPENDENT SPIROMETRY AND DATA ASSESSMENT FINAL INVESTIGATION REPORT

Unless otherwise specified, efficacy summaries will be based on the full analysis set [redacted]. SDTM and ADaM datasets will include data for site [redacted] and site [redacted] subjects and a listing of treatment-emergent adverse events reported for site [redacted] and site [redacted] subjects will be provided.

3. STATISTICAL ANALYSES

3.1. General Considerations

All data from both scheduled and unscheduled visits will be presented in data listings. However, unless noted otherwise, only data from visits (scheduled or unscheduled) that fall within analysis windows will be included in summaries, statistical analyses, and calculations of derived variables. The analysis windows are defined in Section 3.1.9.

Analyses will be performed and tabulations will be prepared using SAS®, version 9.4. The SAS/STAT version will be 15.1.

3.1.1. Table Columns

Summary tables will include the following columns:

- Tiotropium 18 mcg
- Revefenacin 175 mcg
- Total (required only for Section 3.2 summaries, exposure summaries, and compliance summaries)

3.1.2. Baseline

In general, "baseline" denotes the last measurement or assessment obtained before the start of study drug dosing. Both baseline and postbaseline FEV_1, FVC, and lung volume values are calculated by averaging 2 values collected approximately 30 minutes apart.

3.1.3. Change From Baseline

Change from baseline is calculated as postbaseline value – baseline value.

3.1.4. Use of the Term Trough

For a given dosing regimen (e.g., QD, BID), trough measurements are measurements made when drug concentrations are at their lowest. In this study, since both dosing regimens are QD, trough measurements are measurements made approximately 24 hours after the most recent study drug dosing. The operational definition of "approximately 24 hours" will be spirometry start time, defined as the time of the earliest 45 Minutes Predose/Time Point 1 effort within a testing session, within 24 ± 6 hours of HandiHaler® start time. If it is unclear whether this condition was met, e.g., because the subject did not complete the dosing diary the day before the spirometry visit, it will be assumed to have been met. [redacted]

3.1.5. Use of the Term "Evaluable N"

The term "Evaluable N" may be used in summaries presenting results of model-based analyses. The evaluable n is the number of subjects contributing information to the model-based treatment difference estimates, in the sense that excluding the subject's data could alter the estimate.

3.1.6. Evaluable Flags for Spirometry [redacted] Test Results

Spirometry [redacted] analysis variable values will be assigned the following flags as applicable (as many as apply):

- NT for non-trough (see Section 3.1.4)
- RM for protocol-disallowed rescue medication use (protocol definition: use of albuterol MDI within 6 hours of spirometry start time; operational definition: use of albuterol MDI within 5 hours of spirometry start time)
- CM for confounding use of systemic corticosteroids or any medication listed as prohibited except during exacerbations in protocol Table 2
- NS for evaluable but not selected for analysis, e.g., because there were multiple evaluable visits within the applicable analysis visit window

Except as indicated for treatment policy analyses, flagged analysis variable values will be excluded from analysis.

3.1.6.1. Spirometry Quality Grades

Screening Visit 1B ipratropium reversibility spirometry must receive a grade of A or B for FEV_1 and FVC for both pre- and postipratropium stages for the subject to be considered eligible for randomization. All other spirometry sessions must receive a grade of A, B, or C. The American Thoracic Society (ATS) quality standards (Standardization of Spirometry 2019 Update) applied are shown in Table 6:

Table 6: Spirometry Quality Grades for FEV_1 and FVC (Graded Separately)

Quality Grade	Description
A	2019 ATS/ERS criteria: At least 3 acceptable values with the highest 2 within 150 mL of each other
B	Only 2 acceptable values and they are within 150 mL of each other
C	At least 2 acceptable values with the highest 2 within 200 mL of each other
D	At least 2 acceptable values with the highest 2 within 250 mL of each other
E	Only 1 acceptable value
F	No acceptable values

3.1.7. Screening Visit

For measurements such as PIFR which are collected at both Visit 1A and Visit 1B (e.g., for subjects who need to complete a washout or dose-reduction period) the value selected for "Screening Visit" summaries will be the value from the second screening visit.

3.1.8. Variables

3.1.8.1. Study Day

Study Day 1 is defined as the day of the first dose of study drug (revefenacin, revefenacin placebo, tiotropium, or tiotropium placebo). Study Day -1 is the day before.

3.1.8.2. Age

The subject's full date of birth (year, month, and day) is captured in the spirometry database at Visit 1A and used to calculate the subject's predicted normal FEV_1 and FVC as a function of age, sex, height, and race/ethnicity. The subject's birth year as integrated from the RTSM database is used to populate the birth year field on the Demographics case report form, and age in years at Visit 1A is entered at the site. This site-reported age will be used in listings, summaries, and analyses.

3.1.8.3. Height

The subject's height in centimeters to 1 decimal place is captured in the spirometry database at Visit 1A and used in the calculation of the subject's predicted normal FEV_1 and FVC. The subject's height in centimeters to 1 decimal place is also captured in the Vital Signs - Screening eCRF at Visit 1B. For subjects whose 1A and 1B visits were not completed on the same day, the values may differ. The eCRF value will be used for vital signs listings and summaries and to calculate body mass index.

3.1.8.4. LABA or LABA/ICS Use

For summaries of LABA or LABA/ICS use at baseline, the following categories will be used:

- None
- LABA
- LABA/ICS

Subjects on a LABA or LABA/ICS regimen at baseline are expected to maintain their dosing regimen while on study drug and take their first or only LABA dose of the day immediately before the start of study drug dosing.

For model-based analyses, the LABA and LABA/ICS categories will be collapsed: LABA or LABA/ICS use will be treated as a Yes/No variable.

3.1.8.5. COPD Maintenance Therapy at Baseline

For baseline summaries and to facilitate exploratory analyses, a COPD maintenance therapy at baseline indicator variable (Yes/No) will be provided. Subjects will be counted as receiving background COPD maintenance therapy at baseline if the concomitant medications log has any entry with indication COPD and frequency other than PRN and a dosing period that includes Day 1.

3.1.8.6. PIFR

Subjects who at the time of screening are taking COPD medications requiring a washout or dose reduction will have 2 screening visits (1A and 1B) and will have PIFR measured at each visit. Subjects who do not require a washout or dose reduction may have their screening visits combined into one. On each screening occasion, subjects will perform 3 maneuvers using an In-Check® device set to match the airflow resistance of a Diskus® inhaler. The device measures peak flow as an integer ranging from 15 to 120 L/min. All 3 measurements will be captured and their maximum will be used for analysis. To be eligible, subjects requiring washout must have a maximum value of < 60 L/min at the 1A visit and < 55 L/min at the 1B visit; subjects who complete a single screening visit must have a maximum value < 55 L/min.

At Visit 2 (Day 1), subjects will perform 3 maneuvers using an In-Check® device set to match the airflow resistance of a Diskus® inhaler, followed by 3 more maneuvers with the device set to match the airflow resistance of a Spiriva HandiHaler®. To be eligible, subjects must have a maximum Diskus® resistance value < 55 L/min. The maximum Diskus® resistance value will be summarized, used for efficacy analyses as a covariate, and used to define baseline PIFR subgroups. The maximum Spiriva HandiHaler® value will be summarized (Section 3.2.3).

3.1.8.7. FEV_1 (Measured and Predicted Normal)

Forced expiratory volume in 1 second (FEV_1) (best effort) will be captured in mL to 0 decimal places. The time of the maneuver will also be captured. The spirometry CRO will derive predicted normal FEV_1 at Visit 1A using a prediction equation based on NHANES III survey data which is a function of sex (male or female), height in cm (136.0 to 202.0), race/ethnicity (African American, Asian, Caucasian, Mexican American, or Other [Caucasian Predictor applied]), and age at visit (integer) as calculated from visit date and birth date (Hankinson et al. 1999, Hankinson et al. 2010). The calculated FEV_1 in mL will be truncated to 1 decimal place. The prediction equation coefficients are shown in Table 7.

Table 7: NHANES III Normal FEV_1 Prediction Equations

Sex	Race	Intercept	Age	Age^2	$Height^2$
Male	Caucasian	553.60000	-13.03000	-0.17200	0.14098
Female	Caucasian	433.30000	-3.61000	-0.19400	0.11496
Male	African American	341.10000	-23.09000	0.00000	0.13194
Female	African American	343.30000	-12.83000	-0.09700	0.10846
Male	Mexican American	630.60000	-29.28000	0.00000	0.15104
Female	Mexican American	452.90000	-11.78000	-0.11300	0.12154

Age units: yr; height units: cm; predicted FEV_1 units: mL.
The prediction equations are based on samples of male subjects aged 20 to 80 and female subjects aged 18 to 80.
The Asian correction recommended in Hankinson et al. 2010 is applied by multiplying the Caucasian prediction by 0.88.

3.1.8.8. FEV_1 % Predicted

FEV_1 as a percentage of the predicted value will be derived by the spirometry CRO as FEV_1 divided by the predicted normal FEV_1 for the subject, converted to a percentage and truncated to 1 decimal place. (The calculation is performed before predicted normal FEV_1 is truncated.)

3.1.8.9. FVC (Measured and Predicted Normal)

Forced vital capacity (FVC) (best effort) will be captured in mL to 0 decimal places. The time of the best-effort maneuver may differ from the time of the best-effort FEV_1 maneuver. The spirometry CRO will derive predicted normal FVC at Visit 1A using a prediction equation based on NHANES III survey data which is a function of sex (male or female), height in cm (136.0 to 202.0), race/ethnicity (African American, Asian, Caucasian, Mexican American, or Other [Caucasian Predictor applied]), and age at visit (integer) as calculated from visit date and birth date (Hankinson et al. 1999, Hankinson et al. 2010). The calculated FVC in mL will be truncated to 1 decimal place. The prediction equation coefficients are shown in Table 8:

Table 8: NHANES III Normal FVC Prediction Equations

Sex	Race	Intercept	Age	Age^2	$Height^2$
Male	Caucasian	-0.1933	0.00064	-0.000269	0.00018642
Female	Caucasian	-0.3560	0.01870	-0.000382	0.00014815
Male	African American	-0.1517	-0.01821	0	0.00016643
Female	African American	-0.3039	0.00536	-0.000265	0.00013606
Male	Mexican American	0.2376	-0.00891	-0.000182	0.00017823
Female	Mexican American	0.1210	0.00307	-0.000237	0.00014246

Age units: yr; height units: cm; predicted FVC units: L.
The prediction equations are based on samples of male subjects aged 20 to 80 and female subjects aged 18 to 80.
The Asian correction recommended in Hankinson et al. 2010 is applied by multiplying the Caucasian prediction by 0.88.

3.1.8.10. FEV_1/FVC

The ratio of the best-effort FEV_1 to the best-effort FVC will be derived by the spirometry CRO as a decimal fraction, truncated to 3 decimal places.

3.1.8.11. MIP

MIP, which stands for maximal (or maximum) inspiratory pressure, will be measured using a handheld pressure meter, the MicroRPM meter, which has a digital display showing results in cmH_2O (water pressure units). MIP will be collected only at Visit 2 (Day 1), after PIFR assessment and immediately after completion of 45 minutes predose spirometry (Spirometry Reference Manual). To perform a MIP maneuver, subjects will insert and position the meter's mouthpiece, exhale completely, and then inhale as strongly as they can for as long as possible (a minimum of 2 seconds). Subjects will

perform 3 or more MIP maneuvers and the starting time and highest measurement (*nnn*) will be captured in the spirometry CRO database.

For summarization, values reported as 0, if any, will be treated as missing.

3.1.8.12. PEF

Peak expiratory flow (PEF) will be measured using a handheld flow meter, the Vitalograph® asthmaPLAN meter, which has a scale ranging from 50 to 800 L/min marked in 10-L/min increments from 50 to 700 L/min and in 20-L/min increments up to 800 L/min. Subjects enrolled under protocol versions earlier than Amendment 3 will be trained on the use of the PEF meter during the Day 1 visit, will record their highest of 3 peak flow measurements in the eDiary before taking their first study drug dose, and will repeat this procedure each day through the Day 85 or early termination visit before taking their study medication in the morning. On visit days, subjects will bring their flow meters to the study center and measure their peak flow in the presence of study center personnel. Reported PEF values as captured by the eDiary will be integers in the range 0 to 999.

Subjects enrolled under protocol Amendment 3 and later protocol versions will be trained on the use of the PEF meter at Visit 1B and will record their highest of 3 peak flow measurements in the eDiary during the visit and each subsequent morning through the Day 85 or early termination visit. Subjects will use their PEF meters following spirometry on spirometry visit days and before study drug dosing on study drug dosing days.

For summarization and analysis, reported PEF values > 0 and < 50 will be set to 49 and values > 800 will be set to 801. Values reported as 0, if any, will be treated as missing.

3.1.9. Analysis Windows

Endpoints assessed at in-clinic visits will be summarized using analysis windows. Except as otherwise specified, only data collected within analysis windows will be included in summaries, statistical analyses, and calculations of derived variables. Data collected outside analysis windows will be listed only.

The analysis windows shown in Table 9 will be used. The protocol windows for the Day 30, Day 60, and Day 85 visits are ± 7 days. The analysis windows are wider; they were chosen to ensure that no spirometry measurement obtained between Day 15 and Day 99 would be excluded from analysis as "out of window."

Table 9: Analysis Windows for In-Clinic Visit-Based Endpoints

Nominal Visit	**Start**	**Nominal Study** Day	**Stop**
Visit 2 (Day 1)	-1*	1	1
Visit 3 (Day 30)	2	30	45
Visit 4 (Day 60)	46	60	70
Visit 5 (Day 85)	71	85	99**

*Per protocol, subjects are randomized and begin study drug dosing during Visit 2. The analysis window is extended to Day -1 in case a subject cannot be randomized on the day of the visit and randomization and study drug dosing must be delayed until the following day. For spirometry variables, if no usable Visit 2 data were obtained, Visit 1B pre-ipratropium data will be substituted (if usable).
**For treatment policy analyses (Section 3.3.1.1), there is no upper limit to the Day 85 window.

If more than one visit falls within a visit window, the latest visit will be selected.

The analysis intervals shown in Table 10 will be used for endpoints collected daily, such as E-RS: COPD total scores and PEF measurements.

Table 10: Analysis Intervals for Diary Endpoints

Interval	Entry Time	First Day of Interval	Last Day of Interval
Month 1	PM	1	28
	AM	2	29
Month 2	PM	29	56
	AM	30	57
Month 3	PM	57	84
	AM	58	85

AM: Endpoints based on entries made in the morning before study drug dosing.
PM: Endpoints based on entries made in the evening before going to bed.

For instance, since PEF is measured in the morning before study drug dosing, the Month 1 PEF interval is Day 2 through Day 29.

For on-treatment summaries and analyses, AM data collected > 1 day after the date of last dose and PM data collected after the date of last dose are not included in the interval. For instance, for a subject who takes the last dose on Day 80, the Month 3 PEF interval is Day 58 to Day 81 or the last day for which a PEF measurement was reported, whichever is earlier. The corresponding Month 3 E-RS total score interval is Day 57 to Day 80 or the last day for which E-RS total score could be calculated, whichever is earlier.

Subjects are asked to record their study-supplied rescue medication (albuterol MDI inhaler) use in their eDiary device after each use. For analysis purposes, the Table 10 PM intervals will be used, e.g., the Month 1 rescue medication interval will be Day 1 through Day 28, the Month 3 interval will be Day 57 to Day 84 or the date of last dose, whichever is earlier.

3.2. General Analyses

3.2.1. Enrollment and Analysis Sets

Enrollment will be summarized by investigator, and a summary table will be provided showing the number of enrolled subjects included in each analysis set and the percentage of randomized subjects included in each subset of the randomized set.

3.2.2. Disposition

A disposition summary will be provided and will present numbers and percentages of subjects who:

- Were randomized
- Were treated with study drug
- Completed study treatment
- Discontinued study treatment, by reason for treatment discontinuation
- Completed the study
- Discontinued from the study, by reason for study discontinuation

A disposition listing will be provided and will include the date the informed consent form was signed, the date of the first dose of study drug, the date of the last dose of study drug, the study treatment completion or discontinuation date, a column showing study treatment status as "Completed" or the reason for treatment discontinuation, the study completion or discontinuation date, and a column showing study completion status as "Completed" or the reason for study discontinuation. The study completion or discontinuation date is the date of the last visit or assessment.

3.2.3. Demographic and Baseline Characteristics

The following summaries will be provided:

- A summary of demographic and baseline characteristics, including age, age group (< 65, ≥ 65), sex, ethnicity (Hispanic or Latino, not Hispanic or Latino), race, NHANES III race (i.e., the race category used to calculate predicted normal FEV_1 and FVC), weight (kg), height (cm), and body mass index (kg/m^2)
- Screening reversibility to ipratropium test results, including the following variables:
  - Pre-ipratropium FEV_1 (mL)
  - Postipratropium FEV_1 (mL)
  - Change in FEV_1 [post – pre] (mL)
  - Change in FEV_1 ≥ 200 mL (Yes/No)
  - FEV_1 ratio (post/pre)
  - FEV_1 ratio ≥ 1.12 (increase of ≥ 12%)
  - Reversibility criterion met (increase of ≥ 200 mL and ≥ 12%) (Yes/No)
  - Postipratropium FEV_1 % predicted normal
  - GOLD airflow category (3 = postipratropium FEV_1 % predicted ≥ 30% to < 50%, 4 = < 30%)
  - Time between tests (elapsed time between start of pre-ipratropium spirometry and start of postipratropium spirometry)
  - Time from ipratropium dosing stop time to start of postipratropium spirometry

- Screening (pre-ipratropium) and baseline lung function test results, including the following variables:
  - Predicted normal FEV_1 and FVC
  - Screening FEV_1 and FVC
  - Screening FEV_1/FVC ratio
  - Screening FEV_1 and FVC % predicted normal
  - Screening PIFR (as measured by In-Check™ device with resistance set to DISKUS®)
  - Baseline FEV_1 and FVC
  - Baseline FEV_1/FVC ratio
  - Baseline FEV_1 and FVC % predicted normal
  - Baseline PIFR as measured by In-Check™ device with resistance set to DISKUS®
  - Baseline PIFR as measured by In-Check™ device with resistance set to HandiHaler®
  - Baseline maximal inspiratory pressure (MIP)

Descriptive statistics for ratio variables (FEV_1/FVC ratio and FEV_1 and FVC % predicted normal) will include geometric means, calculated as the exponentiated mean of the log values, and standard deviation factors, calculated as the exponentiated standard deviation of the log values.

Also provided will be a summary of COPD clinical characteristics and history, including the following variables:

- Time since COPD diagnosis (years)
- Currently on supplemental oxygen (yes/no)
- Number of exacerbations in the past 12 months
- Number of exacerbations in the past 12 months that resulted in hospitalization

A summary of smoking status and history will be provided and will include the following variables:

- Smoking status: current, former (number, %)
- Number of years smoked
- Maximum number of packs per day (packs)
- Pack years (a cigarette smoking history or equivalent of at least 10 pack years is an inclusion criterion)

A pack year is 20 cigarettes per day for 1 year. Pack years as a history variable is an estimate of the total number of cigarettes a person has smoked, expressed in pack-year units (ignoring leap years, 1 pack year = 20 × 365 = 7300 cigarettes). Pack years will be calculated by multiplying the reported maximum number of packs per day by the reported number of years smoked.

3.2.4. COVID-19

A by-subject listing of visits affected by the COVID-19 pandemic will be provided. The COVID-19 Impacts to Visits form captures whether a visit was skipped, performed onsite but with one or more assessments skipped, performed outside the protocol-specified window, or affected in any other way because of COVID-19.

3.2.5. Protocol Deviations

A summary of major protocol deviations based on the file transferred to Theravance by the study monitoring CRO will be provided and will include numbers and percentages of subjects who have any important protocol deviations and numbers and percentages of subjects by important protocol deviation category. A by-subject listing of all protocol deviations, based on the same file, will be provided.

3.2.6. Medical History

Medical history entries will be coded to preferred terms using MedDRA® version 26.1 by the data management CRO, with Theravance review and approval of the mappings. A by-subject listing of medical history will be provided, and medical history entries will be summarized by MedDRA system organ class and preferred term. To characterize comorbidities, a similar summary restricted to entries mapped to system organ classes with an overall frequency > 5% will also be provided.

3.2.7. Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug (WHODrug) Global version Q3 2023 C3 by the data management CRO with Theravance review and approval of the mappings. Medications entered on the Prior and Concomitant Medications case report form will be assigned to a WHODrug Name and a primary Anatomic Therapeutic Classification (ATC) drug class. Each verbatim name will be classified by anatomical main group (ATC level 1), therapeutic subgroup (ATC level 2), pharmacological subgroup (ATC level 3), and chemical subgroup (ATC level 4). Medication use will be summarized by ATC class and preferred name. If available, ATC level 4 will be used as the ATC class. If ATC level 4 is not available, the next higher ATC level available (i.e., level 3 if available, otherwise level 2 if available, otherwise level 1) will be used. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and preferred name) will be counted only once.

Prior medications are medications taken before the date of the first dose of study drug and concomitant medications are medications taken on or after the date of the first dose,

including ongoing prior medications. The Prior and Concomitant Medications case report form includes the following question:

Did the subject take this medication at any time after first dose?

If the answer (Yes or No) is inconsistent with the other information recorded and the discrepancy is not resolved by querying, the answer will be used to classify the medication as concomitant or not concomitant.

The following medication summaries will be provided:

- Prior medications
- Baseline LABA and ICS COPD medications
- Baseline COPD medications
- Concomitant COPD medications
- Concomitant non-COPD medications
- Concomitant Corticosteroid Medications by Route of Administration

The summary of baseline LABA and ICS medication will include frequency (QD or BID). Medications will be classified as COPD if "Indication: COPD" is checked Yes and as non-COPD otherwise.

See Section 3.7.1 for the presentation of rescue albuterol MDI use.

3.3. General Considerations for Efficacy Analyses

All statistical tests will be tests of point null hypotheses vs. 2-sided alternatives and will be performed at the 0.05 significance level. P-values presented in tables will not be adjusted for multiple testing.

3.3.1. Estimand Types for Quantitative Spirometry Endpoints

Two estimand types are of interest:

- Treatment Policy
- Hypothetical

Both will be estimated for the quantitative spirometry endpoints (FEV_1 and FVC). The two are described in detail below. The population, analysis set, and population-level summary are the same:

Population: Patients with severe to very severe COPD and suboptimal PIFR

Analysis set: Full analysis set, i.e., subjects who are randomized and receive at least 1 dose of study drug

Population-level summary: Mean revefenacin vs. tiotropium difference

Table 11 shows the clinical objective each estimand type is intended to meet.

Table 11: Estimand Types

Estimand Type	Clinical Objective; Endpoints
Treatment Policy	Estimate differences in mean lung function measurements during specified intervals after start of dosing that would apply when patients start dosing on either the revefenacin or the tiotropium regimen and use albuterol MDI rescue medication as needed, whatever subsequent treatment changes occur. Trough measurements are selected if obtained; otherwise, measurements meeting ATS quality standards.
Hypothetical	Estimate revefenacin vs. tiotropium differences in mean lung function measurements during specified intervals after start of dosing that would apply when patients are on a stable background COPD regimen or taking revefenacin or tiotropium as monotherapy and use rescue medication as needed. It is expected that neither LAMA regimen is disease-modifying and consequently both can affect lung function only during treatment, to an extent varying with the time elapsed since the most recent dose; hence, trough measurements, unconfounded by other medication use, are selected as endpoints.

3.3.1.1. Treatment Policy Estimands

Treatments:

- Initiation of 175 mcg revefenacin daily (in the morning) via jet nebulizer, added to allowed background therapy or as monotherapy, with any subsequent changes to background therapy or revefenacin treatment including permanent discontinuation
- Initiation of 18 mcg tiotropium daily (in the morning) via DPI, with any subsequent changes to background therapy or tiotropium treatment including permanent discontinuation

Variables: Postbaseline FEV_1 and FVC: trough measurements if obtained, otherwise unconfounded follow-up measurements if obtained, otherwise confounded follow-up measurements, where "follow-up" means obtained > 1 day after study treatment discontinuation and "confounded" means flagged RM for use of albuterol MDI within 5 hours of spirometry start time as described in Section 3.1.1

Intercurrent events:

No measurements obtained will be excluded from analysis, regardless of the occurrence of an intercurrent event.

If no measurements are obtained for an analysis interval, they will be imputed, implicitly via MMRM modeling or explicitly via multiple imputation methods as specified in Section 3.4.4.

3.3.1.2. Hypothetical Estimands

Treatments:

- Administration of 175 mcg revefenacin daily (in the morning) via jet nebulizer, added to allowed stable background therapy or as monotherapy, with allowed dosing changes to background therapy as needed and with rescue medication (albuterol MDI) use as needed
- Administration of 18 mcg tiotropium daily (in the morning) via DPI, under the same conditions

Variables: Postbaseline trough FEV_1 and FVC measurements. The operational definition of trough will be "obtained within 24 ± 6 hours after the last study drug dosing."

Intercurrent events:

- Episodes of new COPD medication use, i.e., use of systemic corticosteroids or any medication listed as prohibited except during exacerbations in protocol Table 2. It is not expected that measurements will be obtained during such episodes, but if they are they will be excluded from analysis. Similarly, it is not expected that measurements affected by use of the study-supplied albuterol MDI for rescue within 5 hours of the spirometry start time (Section 3.1.6) will be obtained, but if they are they will be excluded from analysis.
- Study treatment discontinuation. Measurements obtained more than 1 day after treatment discontinuation will be excluded from analysis.

If no measurements are obtained for an analysis interval or all are excluded, they will be implicitly imputed via MMRM modeling.

3.3.1.3. Primary Endpoint Definitions

Because the population-level summary is the same for postbaseline values and changes from baseline, the Day 85 FEV_1 change from baseline endpoints for the 2 estimand types can also be described as follows:

- Treatment policy estimand: For subjects on study treatment, Day 85 trough FEV_1; for subjects not on study treatment, Day 85 FEV_1 at an unknown time relative to COPD maintenance therapy dosing
- Hypothetical estimand: Day 85 trough FEV_1

For the sake of brevity, the term "trough" will be used in treatment policy tables and figures even though it may not apply to all measurements.

3.4. Primary Endpoint Analyses

For the primary endpoint and other endpoints based on spirometry measurements, the treatment policy estimand is considered primary.

3.4.1. Definition of Primary Endpoint

At each time point (baseline, Day 30, Day 60, and Day 85), trough FEV_1 will be calculated as the average of the first-stage and second-stage best-effort measurements, i.e., the 2 best-effort measurements from the stages collected approximately 30 minutes apart. The quality grade for each baseline and postbaseline stage must be A, B, or C (Section 3.1.6.1). If only 1 of the 2 stages has a quality grade of at least C, only that stage's best-effort measurement will be used.

3.4.2. Statistical Hypotheses

The null hypothesis is that μ_R, the expected change from baseline in trough FEV_1 at Day 85 for subjects assigned to receive revefenacin at 175 mcg, is the same as μ_T, as the expected change for subjects assigned to receive tiotropium at 18 mcg. The alternative hypothesis is that the expected changes differ.

$$H_{0:}\, \mu_R = \mu_T$$

$$H_{1:}\, \mu_R \neq \mu_T$$

Because this is a randomized trial, the expected baseline FEV_1 for subjects receiving revefenacin is identical to the expected baseline FEV_1 for subjects receiving tiotropium. Hence, μ_R and μ_T may also be defined as expected trough FEV_1 at Day 85 for subjects assigned to receive revefenacin and for subjects assigned to receive tiotropium.

3.4.3. Main Analysis Methods

The primary efficacy analysis is a mixed model repeated measures (MMRM) analysis of trough FEV_1 (or equivalently change from baseline in trough FEV_1) on Days 30, 60, and 85, with the expected Day 85 revefenacin vs. tiotropium difference as the primary estimand. The Day 30 and Day 60 revefenacin vs. tiotropium expected differences and the average expected difference across the Day 30, Day 60, and Day 85 time points will also be estimated as secondary estimands. Point estimates, standard errors, and 95% CIs for the 4 revefenacin vs. tiotropium expected differences will be presented. (For this and all other MMRM analyses where a baseline value of the response is a covariate, revefenacin and tiotropium Day 30, Day 60, and Day 85 response and change from baseline least squares mean point estimates and standard errors will also be presented.)

The model has terms for treatment, reversibility to ipratropium status (reversible/not reversible), smoking status (current/former), concomitant LABA or LABA/ICS use (Yes/No), GOLD airflow category (3/4, i.e., postipratropium FEV_1 % predicted $< 30\%/\geq 30\%$), sex (woman/man), age group ($< 65/\geq 65$), baseline PIFR set to DISKUS® resistance, pre-ipratropium FEV_1, and baseline FEV_1. It also has terms for visit and its interactions with treatment and the continuous covariates, namely baseline PIFR, pre-ipratropium FEV_1, and baseline FEV_1. 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. Missing trough FEV_1 values are assumed to be missing at random (in the technical sense).

The analysis will be performed for both estimand types (treatment policy and hypothetical). For the treatment policy estimand analysis, postbaseline FEV_1 values flagged as NT (non-trough), RM (confounded by recent use of rescue medication), or CM (confounded by use of protocol-disallowed new COPD medication) will be handled as follows:

- Select the latest spirometry test within the analysis window with no exclusionary flags (NT, RM, or CM), if such a test was performed.
- Otherwise, select the latest spirometry test within the analysis window.

For the hypothetical estimand analysis, the latest spirometry test within the analysis window with no exclusionary flags (NT, RM, or CM) will be selected.

The primary endpoint will be considered to have been met if the 2-sided 95% CI for the Day 85 revefenacin vs. tiotropium treatment policy estimand difference lies above zero (equivalently, if the point estimate is above zero and the 2-sided t-test p-value from the SAS procedure MIXED analysis is < 0.05).

3.4.3.1. Figures

Figures will be provided showing the point estimate of and 95% CI for the revefenacin vs. tiotropium difference in trough FEV_1 (or equivalently change from baseline in trough FEV_1) on Days 30, 60, and 85. The figures will also show the point estimate of and 95% CI for the revefenacin vs. tiotropium average difference in trough FEV_1 across Days 30, 60, and 85.

Supporting figures will be provided showing model-based estimates of mean trough $FEV_1 \pm 1$ standard error vs. visit for each treatment, in a single panel.

3.4.3.2. Missing Data Handling

Subjects will not be excluded from spirometry analyses because they have a missing value for 1 or more of the baseline covariates. For all baseline covariates except smoking status and LABA or LABA/ICS status, missing values are not anticipated since a missing value would make it impossible for the IRT system to randomize the subject. Subjects with smoking status unclear will be assumed to be former rather than current smokers. LABA or LABA/ICS status at baseline, if unclear from information captured in the clinical database, will be confirmed prior to database lock. The information in the clinical database will be used for analysis purposes, if available; if not, the information in the IRT database will be substituted.

Missing postbaseline data for the primary analysis is assumed missing at random (MAR) and imputed implicitly via the MMRM modeling outlined in Section 3.4.3. An analysis for assessing the sensitivity of the primary analysis result to the MAR assumption is outlined in Section 3.4.4.

3.4.4. Sensitivity Analysis

If the primary endpoint is met, a tipping point analysis will be performed to assess the sensitivity of the primary analysis result to the assumption that missing Day 85 FEV_1 values are missing at random, in the technical sense that whether responses are missing may depend on observed responses and baseline covariates but not on unobserved responses. An overview is given below. SAS code adapted from a proc MIANALYZE example (SAS Institute Inc. 2013) will be used to perform the analysis, which will proceed as a sequence of multiple imputation ANCOVA analyses. In general, multiple imputation analysis proceeds as follows:

Step 1. Select the model to be used to fill in the missing observations (the "imputation model") and the algorithm that will be used to fill them in. Specify a random number seed and apply the algorithm *m* times to produce *m* randomly completed datasets.

Step 1 will be completed using SAS proc MI with random number seed 3293. For each analysis, *m* will be set to 25. The imputation model will be the same as the final ANCOVA model, with the addition of Day 30 and Day 60 FEV_1.

Step 2. Fit the final model to the *m* randomly completed datasets and save the *m* estimates of the parameter of interest and their estimated standard errors.

Step 2 will be carried out using SAS proc REG with a "`by _imputation_ ;`" statement. The final model will be the Day 85 FEV_1 ANCOVA model corresponding as closely as possible to the MMRM model, i.e., with the same categorical predictors and the following continuous predictors: baseline PIFR as measured with the In-Check™ device set to DISKUS® resistance and baseline FEV_1.

Step 3. Combine the *m* parameter and standard error estimates to obtain a multiple imputation point estimate of the parameter, an interval estimate (i.e., 95% CI), and a p-value for testing parameter = 0 vs. ≠ 0.

Step 3 will be carried out using SAS proc MIANALYZE.

The parameter of interest is the Day 85 revefenacin vs. tiotropium FEV_1 difference. To find the tipping point, the basic 3 steps are iterated as follows:

- For a range of shift pairs (s_j, t_k), hypothesize that the mean of the unobserved revefenacin group responses is lower than the missing at random model mean by s_i and the mean of the unobserved tiotropium group responses is lower than the missing at random model mean by t_k. For each of the shift pairs, generate *m* randomly completed datasets as in Step 1 and apply the shifts to the imputed responses.
- For each of the shift pairs, follow Steps 2 and 3 as above.

A table and figure will be provided showing, for a range of tiotropium group shifts on the y-axis and revefenacin group shifts on the x-axis, the difference estimates and estimated p-values corresponding to the shift pairs.

3.4.5. Supplementary Analysis

The primary analysis will be repeated including data from site [redacted] and site [redacted] to assess the impact of the exclusion of both sites on the primary endpoint.

3.5. Secondary Endpoint Analyses

3.5.1. Variable Definitions

The variables to be calculated for analysis are as follows:

- Trough FEV_1 on Days 30, 60, and 85 and FEV_1 at baseline
- Trough FVC on Days 30, 60, and 85 and FVC at baseline
- Increase from baseline in FEV_1 (at trough) of ≥ 80 mL on Day 85
- Time to first CompEx event

The baseline, Day 30, Day 60, and Day 85 FEV_1 variables are defined for analysis in Section 3.4. The baseline, Day 30, Day 60, and Day 85 FVC variables are defined for analysis in the same way, as the average of the 2 best-effort measurements obtained approximately 30 minutes apart, with the same minimum quality grade requirements. Average FEV_1 and average FVC across Days 30, 60, and 85 do not need to be calculated; an estimate of the average treatment difference across the 3 time points is obtained from the MMRM analysis. Time to first CompEx event is defined for analysis in Sections 3.7.3.1 and 5.4.

Day 85 trough FEV_1 responder/nonresponder status is a derived binary variable, scored as 1 (“responder”) or 0 (“nonresponder”). Response is defined as an increase of ≥ 80 mL over the baseline measurement: FU – BL ≥ 80 mL, where FU is a postbaseline measurement and BL is the baseline measurement. For subjects without a trough FEV_1 measurement obtained during the Day 85 analysis window because they discontinued from the study, scores will be either missing or 0 (“nonresponder”) according to the convention shown in Table 12:

Table 12: Study Discontinuation Reasons Classified As Treatment Failures

Discontinuation Reason	Counted As a Treatment Failure	Treatment Failure Status Set to Missing (Unknown)
Adverse Event	✔	
Death	✔	
Lost to Follow-up		✔
Physician Decision	✔	
Pregnancy		✔
Protocol Violation		✔
Study Terminated by Sponsor		✔
Withdrawal by Subject	✔	
Other		✔

The variable is a composite variable: observed changes FU – BL < 80 mL and changes not observed because the subject discontinued from the study, when the reported reason was adverse event, death, or physician or subject decision, are both assumed to be "bad" outcomes.

3.5.2. Main Analysis Methods

As specified in Section 3.4.3, the primary MMRM analysis of trough FEV_1 will also provide estimates of Day 30, Day 60, and overall (i.e., averaged across Day 30, Day 60, and Day 85) trough FEV_1 treatment differences.

Trough FVC will be analyzed in the same way as trough FEV_1, by fitting a model with the same terms, except that baseline FEV_1 is replaced by baseline FVC and pre-ipratropium FEV_1 is replaced by pre-ipratropium FVC. A similar summary table and pair of figures will be provided. The table and figure will include point and interval estimates of revefenacin vs. tiotropium trough FVC differences at Days 30, 60, and 85 and the average trough FVC difference across the 3 time points.

3.5.2.1. Increase From Baseline in Trough FEV_1 of ≥ 80 mL on Day 85

Revefenacin and tiotropium responder probabilities will be compared by fitting a logistic regression model with the same predictors as the primary efficacy analysis model (but not including visit or associated interaction terms). The model will include terms for pre-ipratropium FEV_1, baseline FEV_1, baseline PIFR, reversibility to ipratropium status (reversible/not reversible), smoking status (current/former), concomitant LABA or LABA/ICS use (Yes/No), GOLD airflow category (3/4), sex (woman/man), age group (< 65/≥ 65), and treatment. A summary of responder status by treatment group will show counts and percentages and a point estimate of and profile likelihood 95% CI for the revefenacin:tiotropium odds ratio.

As a sensitivity analysis, the analysis will be repeated for the composite variable defined by counting observed changes < 80 mL and changes not observed because the subject discontinued from the study for any reason as "bad" outcomes.

3.5.2.2. Time to First CompEx Event

A Cox proportional hazards model with the same covariates as used for the responder analysis will be fitted to time to first CompEx event, as described in Section 3.7.3.1.

3.6. Multiplicity Adjustment

To control the global (across families) familywise type 1 error rate at 0.05, the primary and secondary endpoint hypotheses will be tested in the following endpoint sequence:

- Trough FEV_1 on Day 85
- Average FEV_1 across Days 30, 60, and 85
- Trough FEV_1 on Day 30
- Trough FEV_1 on Day 60
- Trough FVC on Day 85
- Increase from baseline in trough FEV_1 of ≥ 80 mL on Day 85
- Time to first CompEx event

If the primary endpoint is met, i.e., the revefenacin 175 mcg vs. tiotropium 18 mcg trough FEV_1 difference treatment policy estimand point estimate is > 0 and the 2-sided t-test p-value from the SAS procedure MIXED analysis is < 0.05, multiplicity-controlled testing will proceed to the next test in the sequence, stopping after the first failure to reject the null hypothesis of no treatment difference (i.e., stopping when $p \geq 0.05$).

3.7. Exploratory Endpoint Analyses

3.7.1. Rescue Medication Use

Daily rescue medication use (number of puffs) is a count variable which will be calculated for days on which the eDiary was completed. If the eDiary was completed for the day and no [redacted] uses were recorded, the count will be assumed to be 0.

[redacted]

3.7.3. COPDCompEx Events and Moderate or Severe Exacerbations

COPDCompEx events are defined as any of the following events (see Appendix 5.4 for details). Event codes to be used in listings are shown in parentheses:

- Severe exacerbation in COPD (S)
- Moderate exacerbation in COPD (M)
- Clinically relevant deterioration in COPD (D)
- Premature termination from the study for any reason other than "Study Terminated by Sponsor" (T)

This composite-event endpoint is designed as a higher-frequency surrogate for moderate to severe exacerbations that may enable smaller, shorter trials to be used to explore possible treatment differences in the rate of moderate to severe exacerbations. For instance, the estimated COPDCompEx hazard ratio from studies like this one might be used to estimate the sample size needed for a study designed to show a difference in the rate of moderate to severe exacerbations. It is hoped that the COPDCompEx hazard ratio would be a more stable estimator than the direct estimator based on the observed rates of moderate to severe exacerbations, which are expected to be low in this 12-week study.

Event summaries will be summaries of treatment-emergent events as defined in Section 3.8.2 , i.e., events with onset on or after the date of first revefenacin/tiotropium dose through the date of last dose + 7 days, with the additional restriction that the date of onset for all clinical deterioration events must be Study Day 15 or later (see Appendix 5.4).

3.7.3.1. Time to First Event Summaries

For time to first event endpoints, time to first event will be calculated as follows:

date of onset – date of first dose + 1

For subjects without events with onset during the treatment period, censoring time will be calculated as follows:

date of last dose – date of first dose + 1

Times will be analyzed by fitting a Cox proportional hazards model with the same covariates as the primary efficacy analysis model. Analysis summary tables and Kaplan-Meier plots will be provided for the following times:

- Time to first CompEx event
- Time to first moderate or severe COPD exacerbation
- Time to first severe COPD exacerbation

The analysis summary tables will include descriptive statistics and point estimates of and 95% CIs for revefenacin vs. tiotropium hazard ratios.

[redacted]

3.7.4. Peak Expiratory Flow

[redacted]

[redacted]

[redacted]

3.7.7. Nighttime Awakenings

Subjects will be given the eDiary at screening Visit 1B (which may be combined with Visit 1A) and will answer the following question each day thereafter through the Day 85 or early termination visit:

How many times did you awaken last night due to breathing problems? _____

(For example: wheezing, cough, shortness of breath, etc.) (If none, enter zero)

[redacted]

[redacted]

3.7.8. Evaluation of Respiratory Symptoms in COPD

The Evaluation of Respiratory Symptoms in COPD (E-RS: COPD) assessment of daily breathlessness, cough/sputum, and chest symptoms is recorded in the eDiary. Subjects will complete the 14-question EXACT, which was developed to assess acute exacerbations of COPD, each evening just prior to bedtime, and the first 11 questions will be scored as shown in Appendix 5.3 (EXACT-Respiratory Symptoms [E-RS] User Manual).

The response to each question is scored either from 0 (best) to 4 (worst) or from 0 to 3; note the special coding of questions 3, 8, 9, 10, and 11. The total score is integer-valued and can range from 0 to 40. Subjects will be given the eDiary at screening Visit 1B (which may be combined with Visit 1A) and will record their question responses each day thereafter through the Day 85 or early termination visit. Subjects are not expected to complete the E-RS daily assessment while hospitalized.

[redacted]

[redacted]

[redacted]

[redacted]

3.8. Safety Analyses

Adverse events, vital signs (heart rate and blood pressure), and concomitant medication use will be summarized. Extent of study drug exposure and treatment compliance will also be summarized; laboratory test results will be listed.

3.8.1. Extent of Exposure

Duration of study drug exposure (days) will be summarized. Duration of exposure will be calculated as (date of last study drug nebulizer or DPI dose – date of first study drug nebulizer or DPI dose + 1). The summary table will include the columns specified in Section 3.1.1.

The date of last dose (Study Treatment Completion or Discontinuation Date) is collected on the Study Drug Discontinuation form. If no date is reported, it will be imputed for analysis purposes as the Study Completion or Discontinuation Date as reported on the End of Study form.

3.8.1.1. Treatment Compliance

Although treatment compliance for nebulizer treatment and for DPI treatment is expected to be identical for most subjects, it will be calculated for each route of administration. For subjects who return at least 1 study drug kit, treatment compliance as a percentage of the expected total dose will be calculated as follows from drug accountability data for nebulizer treatment and for DPI treatment:

100 × (number of doses dispensed – number of doses returned)/
(date of last dose – date of first dose + 1), rounded to the nearest 0.1%

Treatment compliance over the interval from first to last study drug dose will be summarized as a continuous variable and using the following categories:

- > 120%
- ≥ 105% – ≤ 120%
- ≥ 95% — < 105%
- ≥ 90% — < 95%
- ≥ 80% — < 90%
- < 80%

The summary table will include the following columns: TIO, DPI, REV, and Nebulizer.

Study drug accountability data will be listed, and CRF and dosing eDiary study drug administration data listings will be provided. An abbreviated combined listing of study drug administration data will also be provided and will present the following information for the 2 days preceding and the day of each postbaseline visit during which spirometry test results were obtained:

- Spirometry Visit Date (Study Day)
- Spirometry Start Time (Earliest)
- Date (Study Day)
- Was Tiotropium/Placebo Administered? (source In-Clinic Study Drug Administration form)

- Time of Tiotropium/Placebo Administration (source In-Clinic Study Drug Administration form)
- Was Revefenacin/Placebo Administered? (source In-Clinic Study Drug Administration form)
- Start Time of Revefenacin/Placebo Administration (source In-Clinic Study Drug Administration form)
- End Time of Revefenacin/Placebo Administration (source In-Clinic Study Drug Administration form)
- Dosing Diary Entry Start and End Date/Time
- When did you administer 1 capsule of study drug from the HandiHaler? (hh:mm) (source eDiary)
- After your HandiHaler dose, when did you nebulize your vial of study drug? (hh:mm) (source eDiary)

3.8.2. Adverse Events

A treatment-emergent adverse event (TEAE) will be defined as any adverse event that begins on or after the date of the first study drug dose up through 7 days after the date of the last study drug dose. COPD exacerbations are adverse events and will be included in all summaries of adverse events. Separate forms, "COPD Exacerbation" and "Adverse Event," were developed to capture exacerbation and non-exacerbation adverse events, in order to collect additional information about the exacerbation events. Hence, although COPD exacerbations will be included in all adverse event listings except the listing of adverse events of special interest, a listing of COPD exacerbations based on the "COPD Exacerbation" form will also be provided.

Adverse events are collected from the signing of the informed consent form through the end of follow-up. Site personnel are to telephone subjects 7 ± 2 days after their last visit to review their adverse events; in addition, they are to telephone subjects who discontinue from the study early because of an adverse event approximately 30 days after discontinuation to review their adverse events and medications. Follow-up may be further extended as described in protocol Amendment 3 Section 7.4.

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA® 26.1 Q3 2023) by the data management CRO with Theravance review and approval of the mappings. The following adverse event summaries will be provided:

- TEAE overall summary
- TEAEs by preferred term
- TEAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term, and LABA or LABA/ICS use
- Severe TEAEs by system organ class and preferred term
- TEAEs by preferred term with frequency > 3% of safety analysis set subjects
- TEAEs by system organ class, preferred term, and severity
- Drug-related TEAEs by system organ class and preferred term
- Drug-related TEAEs by system organ class, preferred term, and LABA or LABA/ICS use
- Drug-related TEAEs by system organ class, preferred term, and severity
- Drug-related severe TEAEs by system organ class and preferred term
- Serious TEAEs by system organ class and preferred term
- Drug-related serious TEAEs by system organ class and preferred term
- Adverse events with fatal outcome by system organ class and preferred term
- TEAEs leading to premature study drug discontinuation by system organ class and preferred term
- TEAEs of special interest by preferred term

The TEAE overall summary will show the number and percentage of subjects for whom at least 1 adverse event in each of the following categories was reported:

- Any TEAE
- Any moderate or severe TEAE
- Any severe TEAE
- Any drug-related TEAE
- Any moderate or severe drug-related TEAE
- Any severe drug-related TEAE
- Any serious TEAE
- Any drug-related serious TEAE
- Any TEAE leading to permanent study drug discontinuation
- Any TEAE leading to temporary interruption of study drug
- Any adverse event with fatal outcome, including adverse events that were not treatment-emergent

If no adverse events meeting a specific table definition are reported, the body of the table will contain only a statement that no adverse events met the table definition.

The following adverse event listings will be provided:

- TEAEs
- COPD exacerbations
- Adverse events leading to premature discontinuation of study drug
- Adverse events resulting in temporary interruption of study drug
- Serious adverse events
- Adverse events with fatal outcome
- Adverse events of special interest
- Non-treatment-emergent adverse events

3.8.2.1. Adverse Events of Special Interest

Since revefenacin and tiotropium are long-acting muscarinic antagonists, antimuscarinic TEAEs are of special interest. Any TEAE coded to one of the following preferred terms will be included in the summary of TEAEs of special interest:

- Constipation
- Dry mouth
- Dysuria
- Bronchospasm, paradoxical
- Glaucoma, Angle closure glaucoma
- Urinary retention

3.8.3. Additional Safety Assessments

3.8.3.1. Clinical Laboratory Test Results

The following local laboratory test results collected at screening will be listed:

- Creatinine
- Hematocrit
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Bilirubin
- Alkaline phosphatase
- International normalized ratio (INR)
- Albumin

Collection of INR and albumin to calculate Child-Pugh score (since a score of B or C is an exclusion criterion) is at the investigator's discretion.

3.8.3.2. Vital Signs

Blood pressure and heart rate are collected at screening, on Day 1 before dosing, and at the Day 85 or early termination visit. They are to be collected after the subject has been resting in a semi-recumbent position for approximately 5 minutes. All measurements obtained will be listed, and measurements outside the ranges shown in Table 13 will be flagged in the listing.

Table 13: Heart Rate and Blood Pressure Ranges

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

Summaries of baseline measurements and of measurements and changes from baseline at Day 85 will be provided. Also provided will be a summary showing numbers and percentages of subjects with measurements outside the ranges shown in Table 13 at baseline and on Day 85.

3.9. Other Analyses

3.9.1. Subgroup Analyses

To assess consistency of treatment differences across subgroups, the analysis of the primary endpoint will be repeated for each of the subgroups shown in Table 14:

Table 14: Subgroups

Subgroup Variable	Subgroups
Baseline PIFR*	< 40 L/min, ≥ 40 L/min
Baseline smoking status	Current Smoker, Former Smoker
Age	< 65, ≥ 65
Sex	Female, Male
Current LABA or LABA/ICS use (at baseline)	Yes, No
Baseline reversibility to ipratropium status (a randomization stratification variable)	Yes, No, where reversibility to ipratropium is defined as a postipratropium increase of at least 12% and at least 200 mL in FEV_1
Baseline GOLD airflow category (a randomization stratification variable)**	3, 4, where category 3 = postipratropium FEV_1 as percentage of predicted normal ≥ 30% to < 50% and category 4 = < 30%

*PIFR as measured by In-Check™ device with resistance set to DISKUS®.
**If there are any subjects with postipratropium FEV_1 as percentage of predicted normal ≥ 50%, they will be included in the GOLD 3 subgroup for analysis purposes.

The model will be adjusted as needed to remove single-valued covariates, e.g., by omitting sex for analyses by sex. Point estimates, standard errors, and 95% CIs for the revefenacin vs. tiotropium difference at each visit will be presented. For each visit (Day 30, Day 60,

and Day 85), a forest plot showing point estimates of and 95% CIs for revefenacin vs. tiotropium differences by subgroup will be provided.

3.10. [redacted]

[redacted]

3.10.1. Data Monitoring Committee

No independent data monitoring committee is planned for this study.

The sponsor will monitor trial data to ensure the safety of subjects via periodic review and discussion of safety data collected during the trial.

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13. PIFR-2 INDEPENDENT SPIROMETRY AND DATA ASSESSMENT FINAL INVESTIGATION REPORT

5. APPENDICES

5.1. Changes to Protocol-Planned Analyses

5.1.1. Changes to Protocol-Planned Analyses of Primary and Secondary Efficacy Endpoints

Protocol Amendment 4 lists defines a CompEx event as the occurrence of a moderate or severe exacerbation or clinically relevant deterioration based on objective measures of deterioration in peak expiratory flow (PEF), rescue medication use, COPD symptoms, and nocturnal awakening. Although all 4 types of eDiary data are collected, only PEF measurements, rescue medication use, and E-RS: COPD total symptom scores are used to identify clinically relevant deterioration events. See Section 5.4.3 for details.

5.2. [redacted]

5.3. Evaluation of Respiratory Symptoms in COPD

The scoring of EXACT questionnaire responses for the E-RS: COPD and the EXACT is shown below:

Table 15: E-RS: COPD Scoring

Question	Responses
1. Did your chest feel congested today?	0. Not at all 1. Slightly 2. Moderately 3. Severely 4. Extremely
2. How often did you cough today?	0. Not at all 1. Rarely 2. Occasionally 3. Frequently 4. Almost constantly
3. How much mucus (phlegm) did you bring up when coughing today?	0. None at all 1. A little 1. Some 2. A great deal 3. A very great deal "A little" and "Some" are scored the same.
4. How difficult was it to bring up mucus (phlegm) today?	0. Not at all 1. Slightly 2. Moderately 3. Quite a bit 4. Extremely
5. Did you have chest discomfort today?	0. Not at all 1. Slight 2. Moderate 3. Severe 4. Extreme
6. Did your chest feel tight today?	0. Not at all 1. Slightly 2. Moderately 3. Severely 4. Extremely

Question	Responses
7. Were you breathless today?	0. Not at all 1. Slightly 2. Moderately 3. Severely 4. Extremely
8. Describe how breathless you were today:	0. Unaware of breathlessness 1. Breathless during strenuous activity 2. Breathless during light activity 3. Breathless when washing or dressing 3. Present when resting "Breathless when washing or dressing" and "Present when resting" are scored the same.
9. Were you short of breath today while performing your usual personal care activities like washing or dressing?	0. Not at all 1. Slightly 2. Moderately 3. Severely 3. Extremely 4. Too breathless to do these "Severely" and "Extremely" are scored the same.
10. Were you short of breath today while performing your usual indoor activities like cleaning or household work?	0. Not at all 1. Slightly 2. Moderately 3. Severely 3. Extremely 3. Too breathless to do these "Severely," "Extremely," and "Too breathless to do these" are scored the same.
11. Were you short of breath today while performing your usual activities outside the home such as yard work or errands?	0. Not at all 1. Slightly 2. Moderately 3. Severely 3. Extremely 3. Too breathless to do these "Severely," "Extremely," and "Too breathless to do these" are scored the same.

Question	Responses
Questions 12, 13, and 14 are scored for the EXACT but not the E-RS: COPD.	
12. Were you tired or weak today?	0. Not at all 1. Slightly 2. Moderately 3. Severely 4. Extremely
13. Last night, was your sleep disturbed?	0. Not at all 1. Slightly 2. Moderately 3. Severely 4. Extremely
14. How scared or worried were you about your lung problems today?	0. Not at all 1. Slightly 2. Moderately 3. Severely 3. Extremely "Severely" and "Extremely" are scored the same.

Source: The Exacerbations of Chronic Pulmonary Disease Tool (EXACT©) Patient-Reported Outcome (PRO) User Manual (Version 7.0), October 2014. EXACT© 2013, Evidera, Inc.

For the E-RS: COPD, the response to each of the first 11 questions is scored either from 0 (best) to 4 (worst) or from 0 to 3; note the special coding of questions 3, 8, 9, 10, and 11. The total score is integer-valued and can range from 0 to 40. The EXACT total score is the sum of all 14 question scores and can range from 0 to 51. EXACT total scores will be included in the listing of E-RS: COPD total scores but will not be summarized.

Internally inconsistent answers, e.g., "Were you breathless today?" answered "Not at all" but "Describe how breathless you were today" answered "Breathless during strenuous activity," will be summarized as collected. Monthly average E-RS total scores will be calculated only if the assessment was completed on at least 14 days during the interval. The eDiary does not let users skip questions; hence, it is expected that either all questions will be answered or none. If the questions are answered more than once during the same eDiary availability interval (this is not expected to occur), the latest set of answers will be used.

Externally inconsistent answers, e.g., all 11 answers scored 0 but rescue medication was used, will also be summarized as collected.

5.4. CompEx Events

5.4.1. Moderate or Severe Exacerbations

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. Criteria for classifying exacerbations of COPD as severe, moderate, or mild are given in protocol Section 6.8.

A moderate exacerbation is defined as any increase in COPD symptoms that does not meet the criteria for a severe exacerbation but leads to treatment with antibiotics or systemic corticosteroids. This may include emergency treatment in a hospital setting of the COPD for < 1 day.

For consistency with adverse event summaries, for CompEx analysis purposes, the date of onset and severity will be as captured in the COPD Exacerbation CRF.

5.4.2. Combination Rule for Exacerbations

To avoid over-counting moderate and severe exacerbations, if there are < 7 days between the stop date of the previous exacerbation and the start date of the next one (i.e., start date – stop date ≤ 7 days), they will be treated as a single exacerbation with severity moderate if both were moderate, and severe otherwise. This rule will be applied for CompEx analyses but not for adverse event summaries.

5.4.3. Clinically Relevant Deterioration

A clinically relevant deterioration is defined as any increase in COPD symptoms that meets specified PEF, rescue medication use, and E-RS total score threshold and slope criteria. As shown in Table 16, either all 3 slope conditions and at least 1 of the threshold conditions must be met or the symptom score threshold condition and at least 1 of the other 2 threshold conditions must be met concurrently.

Table 16: Threshold and Slope Criteria for Diary Variables

Threshold conditions must be met concurrently on consecutive days			**Slope conditions must be met for all 3 diary variables over 5 consecutive days**
AM PEF: ≥ 12% decrease from baseline	Increase in total albuterol MDI puffs/day of ≥ 1.75 × baseline average	E-RS total score increase from baseline of ≥ 8	
✔			✔
	✔		✔
		✔	✔
✔		✔	
	✔	✔	

A checkmark indicates that the condition is met. If there is no checkmark, the condition may or may not be met.

To obtain baseline averages defined over the same interval relative to first dose for all subjects for testing the threshold conditions, the 10-day interval beginning on Day -3 and ending on Day 7 will be used, since all subjects are expected to have diary data for at least the 3 days preceding Day 1. If one treatment reaches its full effect on the diary variables more quickly than the other, this choice of interval may tend to handicap that treatment.

Since at least 1 threshold condition must be met to fulfill the criteria for a clinical deterioration event, the date of onset will be defined as the earlier of the 2 days on which it was met (or they were met). Labeling the date of onset as Day 0, Table 17 shows the required relationship of slope and threshold intervals:

Table 17: Threshold and Slope Intervals

Condition	**Day -4**	**Day -3**	**Day -2**	**Day -1**	**Day 0**	**Day 1**
Threshold					✔	✔
Slope	✔	✔	✔	✔	✔	

The slope criteria are specified in Table 18:

Table 18: Clinical Deterioration Slope Criteria for PEF, Rescue Medication Use, and Symptom Score

Diary Variable	Slope Definition
PEF	Rate of decrease of ≥ 3%/day
Rescue Medication Use	Rate of increase of ≥ 0.4 puffs/day
E-RS Total Score	Rate of increase of ≥ 2 points/day

The date of onset for all clinical deterioration events must be Study Day 15 or later and at least 7 days later than the onset date of any previous clinical deterioration event. It must also be at least 7 days later than the stop date of any previous moderate or severe exacerbation. For the conditions for a clinical deterioration event to be fulfilled by meeting all 3 slope conditions and at least 1 of the threshold conditions, data for the applicable slope interval must be obtained for at least 4 of the 5 days for all 3 diary variables.

To determine whether the slope criterion is met for a particular diary variable, assuming data were obtained for at least 4 of the 5 days, fit a simple linear regression model. For PEF, calculate the absolute rate of change per day (L/min), R, and compare it to baseline PEF, B. If $R < 0$ and $|R|/B$ rounded to 3 decimal places is ≥ 0.03, count the slope criterion as met for PEF. For rescue medication use and E-RS total score, compare the calculated slope to the cutpoint shown in Table 18 after rounding the slope estimate to 1 more decimal place than shown for the cutpoint, i.e., to 2 decimal places for rescue medication use and to 1 decimal place for E-RS total score.

5.5. Missing Data Imputation Rules

5.5.1. Adverse Events Severity and Relationship

In adverse event summaries, adverse events with severity not reported are counted as "Severe" and adverse events with relationship to study drug not reported are counted as "Related."

5.5.2. Missing Start and Stop Dates and Times for Adverse Events

Missing start dates and times will be handled as follows:

- Onset date completely missing:
  - If event is not ongoing and onset date missing and end date missing, then impute onset as date/time of first dose.
  - Else if event is not ongoing and onset date missing and end date not missing and date/time of first dose ≤ end date, then impute onset as date/time of first dose of study drug.
  - Else if event is not ongoing and onset date missing and end date not missing and end date is BEFORE first dose of study drug, then impute onset as end date YEAR and MONTH with 01 as the day and 00:00 as time.
  - Else if event is ongoing and onset date missing, then impute onset as date/time of first study drug dose.
- Onset date has year and month only:
  - If onset date has year and month only and they are the year and month of first dose of study drug, then impute onset as date/time of first dose:
  - Else if onset date has year and month only and date/time of first dose is not missing, then impute onset as onset year and month with 01 as the date and 00:00 as the time.
- Onset date has year only:
  - If onset date has year only and it is year of first dose of study drug, then impute onset as date/time of first dose of study drug.
  - Else if onset date has year only and date of first study drug dose is not missing and year of onset is NOT the year of first dose of study drug, then impute onset as Jan. 1 of the onset year and 00:00 as the time.
- Onset missing (where it was not handled by the above cases):
  - If onset date is missing, then impute onset as date/time of first study drug dose.
- Onset has complete date but missing time:
  - If onset date is a date only and is same as date of first study drug dose, then impute onset as date/time of first study drug dose.
  - Else if onset date is a date only and is NOT = date of first study drug dose, then impute onset as onset date with 00:00 as the time.

Missing end date and times will be handled as follows:

- End date - completely missing:
  - If event is not ongoing and both onset and end dates are missing, then impute end date as date/time of last study drug dose.
  - Else if event is not ongoing and onset date not missing and end date missing AND onset date ≤ date/time of last dose, then impute end date as date/time of last study drug dose.
  - Else if event is not ongoing and onset date is not missing and end date is missing and date of last dose is not missing and onset is AFTER date of last dose, then impute end date as the last day of the month of onset date, with 23:59 as time.
- End date = year and month only:
  - If event is NOT ongoing and end date consists of year and month only, then impute end date as the last day of the month of end date month and year, with 23:59 as time.
- End date = year only:
  - If event is NOT ongoing and end date consists of a year only, and year = year of onset and onset date ≤ date of last study drug dose, then impute end date as the date of last study drug dose.
  - Else if event is NOT ongoing and end date consists of a year only, and year = year of onset and onset date > date of last study drug dose, then impute end date as the year and month of onset, with the last day of the month as the day, and 23:59 as the time.
- End date = complete date but no time:
  - If event is NOT ongoing and end date consists of a complete date but no time, then impute end date = trim (end date) || "T23:59".

5.5.3. Missing Start and Stop Dates for Prior and Concomitant Medications

To determine whether medications were used prior to initiation of dosing and whether they were used after initiation of dosing, missing or partial dates for medications will be imputed according to the following rule:

Missing medication start date:

- If only have a YEAR, impute as January 1
- Else if only have YEAR and MONTH, impute as Day 1 of month
- Else if completely missing, and (end date is present and ≥ date of first dose) or (end date is missing and is marked as "ONGOING"), impute as date and time of first dose. If missing and end date is present and prior to date of first dose, then leave as missing.

Missing medication end date:

- If only have a YEAR and it is same as year of study completion, impute as date of study completion
- Else if only have a YEAR, impute as December 31
- Else if only have YEAR and MONTH, impute as last day of the month
- Else if end date is completely missing and not flagged as Ongoing, impute as date of study completion
- Otherwise, no imputation