Mylan

REV-3001 CLINICAL STUDY PROTOCOL

Protocol Title	A Randomized, Double Blind, Placebo-Controlled, Parallel Group Study of Nebulized Revefenacin Inhalation Solution in Chinese Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD).		
Product	Revefenacin Inhalation Solution		
Study Type	Phase 3		
Version	2.0 (Global Protocol Amendment 1)		
Protocol Date	03 December 2019	**Revision Date**	15 July 2020
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Legal/Filing Sponsor	Mylan Pharma UK Ltd. Registered office: 20 Station Close, Potters Bar, Hertfordshire, EN6 1TL, UK. UK Business address: Mylan Global Respiratory Group, Ramsgate Road, Sandwich, Kent, CT13 9ND, UK.		
Background and Rationale	COPD is a respiratory disease characterized by airflow obstruction that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response in the airways and the lung to noxious particles or gases (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2019 [1]). In 2012, it was estimated that more than 3 million people died prematurely due to COPD and it is projected to be the third leading cause of death worldwide by 2020 (GOLD 2019 [1]). In the People's Republic of China, the prevalence rate of COPD was reported to be between 1.20% and 8.87% depending on the provinces/cities surveyed (Zhu et al., 2018 [2]), and in 2013 there were 910,809 deaths due to COPD, which represented 31% of total deaths due to COPD in the world (Yin et al., 2016 [3]). In addition to the high prevalence of COPD in China, a separate survey across 7 provinces found that only 7.9% of patients had regular medical treatment for COPD, highlighting the need, in some regions of China at least, for improvement in the management of COPD (Zhu et al., 2018 [2]). Pharmacologic treatment of COPD with bronchodilators is central to the management of both the symptoms and the long-term risks of the condition. Long-acting inhaled bronchodilators are convenient and are more effective for long-term symptom relief than short-acting bronchodilators; accordingly, widely accepted treatment guidelines such as those produced by GOLD recommend the use of a long-acting muscarinic antagonist (LAMA) bronchodilator as first-line therapy for patients with persistent COPD symptoms (GOLD 2019 [1]).		

	For some COPD patients, nebulization may be the optimal method for delivering bronchodilator therapy. Revefenacin is a potent LAMA that was designed as a lung selective, once-daily agent and formulated as an inhalation solution to be administered using a standard jet nebulizer via a mouthpiece. Revefenacin inhalation solution (175 mcg in 3 mL) was approved by the United States Food and Drug Administration (US FDA) in November 2018 with the tradename Yupelri® for the maintenance treatment of patients with COPD [4]. In support of the US FDA approval, the efficacy and safety of revefenacin inhalation solution were evaluated in two replicate 12-week, Phase 3 clinical trials examining efficacy and safety (studies 0126 and 0127), and a 52-week long-term safety trial (study 0128), in moderate to very severe COPD patients. Although the data from studies 0126, 0127 and 0128 were derived from clinical trials with patients of predominantly Caucasian ethnicity, based on metabolism of the drug, it is unlikely to exhibit different exposure in Chinese patients, making these studies highly relevant for extrapolating safety and efficacy. Clinical trials on other LAMAs conducted in East Asian COPD patients have demonstrated comparable efficacy and safety compared to large global registration trials conducted primarily in Caucasian patients. For example, Wang et al. (2015) [5] reported that the efficacy and safety results of the GLOW7 trial on glycopyrronium in predominantly East Asian patients with moderate to severe COPD were similar to previous trials conducted in predominantly Caucasian patients. Likewise, a comparison of the efficacy data for East Asian patients compared to the overall study population of the TONADO trial on tiotropium/olodaterol versus its mono-components concluded that the lung function responses were consistent and there were no significant differences in safety outcomes between the two populations (Bai et al., 2017 [6]). The objectives of this study are therefore to confirm the efficacy and safety of revefenacin inhalation solution (175 mcg once daily) for the treatment of Chinese patients with moderate to very severe COPD, in order to provide a bridge for this population to the existing body of data derived from clinical trials with patients of predominantly Caucasian ethnicity.
Primary Objective	To confirm the efficacy of revefenacin inhalation solution 175 mcg administered once daily via nebulization for 12 weeks compared to placebo in a population of Chinese subjects with moderate to very severe COPD.
Study Endpoints	The primary endpoint is: • Trough Forced Expiratory Volume in 1 second (FEV_1) on Day 85 (mean of measurements at -45 and -15 minutes pre-dose) The secondary efficacy endpoints are: • Peak FEV_1 (0-2h) on Day 1 • St. George's Respiratory Questionnaire (SGRQ) responders (total score ≥4 units) on Day 85 • Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) on Day 85 • Average count of salbutamol puffs per day (Days 1-85) • Percentage of salbutamol rescue free 24h periods (Days 1-85)

	• Trough FEV_1 on Days 29 and 57 • BDI/TDI on Day 29 and 57 • Weighted Mean FEV_1 (0-2h) on Day 1 and Day 85 • Peak FEV_1 (0-2h) on Day 85 • Trough forced vital capacity (FVC) on Days 29, 57 and 85 • SGRQ on Day 85 (continuous endpoint) • TDI responders (focal score ≥1) on Days 29, 57 and 85 The secondary safety endpoints are: • Adverse Events (AE) • Acute Exacerbations of COPD (AECOPD) • Laboratory Tests • Vital Signs (blood pressure and pulse rate) • 12-lead ECG Pharmacokinetic (PK) endpoints are: • Population PK parameters for revefenacin inhalation solution (C_{max}, C_{trough})
Methodology and Treatments	This will be a multi-center, randomized, double blind, placebo-controlled, parallel group study, randomizing approximately 320 male or female moderate-very severe COPD subjects. Subjects will receive study drug for 12 weeks. Treatments to be received during the study will include one of the following, administered using a centrally-provided, standard jet nebulizer and compressor via a mouthpiece: A. Revefenacin inhalation solution 175 mcg QD. B. Placebo inhalation solution QD. Subjects will be randomly assigned via Interactive Voice/Web Response System (IVRS/IWRS) to receive either revefenacin or placebo in a 1:1 ratio stratified by concomitant long-acting β_2 agonists (LABA) use and reversibility to ipratropium. They will be permitted to remain on stable doses of LABA, inhaled corticosteroids (ICS), or combinations containing LABA/ICS provided the ICS component is equivalent to fluticasone propionate ≤1000 mcg/day. Rescue medication (salbutamol) will be provided to all subjects. Subjects will have approximately 6 clinic visits (encompassing a screening period of up to 30 days and a treatment period of 12 weeks), and a follow-up telephone call 1-2 weeks after the End of Treatment (EoT) visit: V1: Screening Visit 1 (14 days prior to V3 [permitted window: 30-4 days prior to V3]) V2: Screening Visit 2 (7 (± 3) days prior to V3) V3: Day 1, Randomization V4: Day 29 (±7 days) V5: Day 57 (±7 days) V6: Day 85 (±7 days), EoT Follow-up (7-14 days after V6; by telephone)

	Subjects will commence screening procedures within 30 days prior to randomization to confirm that they meet the selection criteria for the study. At Screening V1, assessments will include informed consent, a review of demography, medical history (including COPD, smoking, and COPD exacerbation history) and concomitant medication, a physical examination, supine or semi-recumbent vital signs, supine or semi-recumbent 12-lead ECG, laboratory safety tests, pregnancy test (if required), and a chest X-ray (unless obtained within the previous 12 months). Subjects who are on a LAMA-containing treatment for their COPD will be required to have a washout of at least 7 days prior to undergoing an ipratropium reversibility test at Visit 2. However, for subjects who are not on LAMAs and who have observed the appropriate washout for other concomitant medications (e.g., 48 hours for oral leukotriene antagonists and systemic anti-muscarinics, 6 hours for short-acting beta-agonists and anti-muscarinics), V2 procedures (i.e., pre- and post-bronchodilator spirometry for FEV_1/FVC measured as part of an ipratropium reversibility test) may be conducted on the same day as Visit 1. After completion of V2 procedures, subjects will be discharged from the clinic with salbutamol as rescue medication and a diary card to record rescue medication use and return 7 (± 3) days later for V3. Subjects who are eligible to be randomized to the study will undergo the procedures below during the 12-week treatment period (V3-V6). <u>Admission procedures for each visit:</u> On admission at V3 to V6 the Investigator should check if the appropriate washout period has been met for use of rescue medication or other restricted concomitant medications. If not, then the visit should be rescheduled within the protocol-specified timeframe. Subjects should first complete the patient reported outcomes questionnaires (PRO) - BDI/TDI, Modified Medical Research Council Dyspnea Scale (mMRC), SGRQ (in that order) - at the following visits: BDI/TDI: BDI at V3 and TDI at V4, V5, and V6 mMRC: at V3 SGRQ: at V3 and V6 After completion of PROs, AEs, concomitant medication use, and rescue medication use since the previous visit should be reviewed. <u>Rescue medication:</u> Salbutamol (100 mcg) pressurized metered dose inhalers (pMDI) will be provided as rescue medication to all subjects. Subjects will record the use of salbutamol rescue medication (number of puffs daily) in a diary card which will be reviewed by the Investigator and recorded in the CRF. If a subject has used rescue medication on the same day as the clinic visit, prior to spirometry assessments, then both the number of puffs and the time of administration will be documented to allow evaluation of impact, if any, on spirometry measurements. Please note that if subjects have used rescue medication within 6 hours prior to spirometry, then the visit should be rescheduled. <u>Vital signs and 12-lead ECG:</u> Supine or semi-recumbent blood pressure, pulse rate, and 12-lead ECG (single measurement) will be measured pre-dose and approximately 1 hour post-dose at

	V3-V6. Where ECG and spirometry are scheduled at the same timepoint, ECG must be performed before spirometry. PK sampling: Pre- and post-dose PK samples will be collected at all visits between V3 and V6. A pre-dose PK sample will be collected within 30 minutes prior to dosing and a post-dose PK sample will be collected at any time between 1 to 30 minutes post-dose. At V6 only, an additional PK sample will be collected at any time between 1-4 hours post-dose. Care will be taken to ensure that PK samples are not contaminated by the study drug dosing procedure (i.e., by performing PK sampling and sample processing in a different room to study drug administration). Safety laboratory tests: Urine or serum pregnancy tests will be performed at all visits between V3 and V6 for female subjects of child-bearing potential. At V6 only, blood and urine samples will be taken for routine laboratory safety tests (hematology, clinical chemistry, urinalysis). Spirometry: Spirometry measurements of FEV_1 and FVC will be performed in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Graham et al., 2019 [7]) using standardized, centralized spirometry equipment that have been calibrated according to manufacturer's guidelines. Investigators must check that subjects have not taken salbutamol rescue medication within 6 hours prior to spirometry. If the washout period for rescue medication or other restricted medications have not been met, the visit should be rescheduled within the visit window. Pre-dose measurements will be performed at -45 and -15 minutes pre-dose at all visits between V3 and V6. Post-dose measurements will be performed at V3 and V6 only at the following timepoints after dosing: 5, 15, and 30 minutes, and 1, 1.5, and 2 hours. Study drug administration: Study drug will be administered using a centrally-provided, standard jet nebulizer (PARI LC Sprint) and compressor (PARI TurboBOY) via a mouthpiece. Prior to the first dose on Day 1, subjects (and their caregiver, if applicable) will be trained on the use and maintenance of the nebulizer and compressor. Study drug administration will be performed at the Investigator site at V3, V4, V5 and V6. It will take up to approximately 10 minutes and completion will be evidenced by spluttering of the nebulizer. Dosing time will be recorded in date, hours, and minutes corresponding to the start and completion of nebulization. Pre-dose assessment time is defined relative to the start of nebulization. Post-dose assessment time is defined relative to the completion of nebulization. Subjects who are on concomitant LABA or ICS/LABA should take their regular morning dose after pre-dose spirometry and immediately prior to study drug administration (if a subject takes their LABA or ICS/LABA prior to the pre-dose spirometry, the visit should be rescheduled). Between visits, study drug will be self-administered at home every morning at approximately the same time within the window of 06:00 and 11:00. The time of home administration will be recorded by the subjects in their diary. Study drug compliance will be checked by counting used and unused vials returned to the site at each visit to ensure that it is within 80-120%. Study drug administration must be performed in a different room from that used for PK blood sampling and processing to avoid contamination of PK samples.

	Discharge procedures for each visit: Prior to discharge from the clinic at V3 to V5, subjects will be dispensed sufficient rescue medication, study drug supplies, and diary cards (for recording rescue medication and study drug administration). At V6 only, a general physical examination will be performed prior to discharge. Follow-up: A follow-up telephone call will be conducted 7-14 days after V6 to review adverse events and concomitant medication.
Inclusion/ Exclusion Criteria	**Inclusion criteria** 1. Males and females of Chinese ethnicity, at least 40 years of age. Females may be of either childbearing or non-childbearing potential. All females of childbearing potential must be using an acceptable, highly effective method of contraception and have a negative pregnancy test at screening. 2. A clinical diagnosis for at least 6 months prior to screening of COPD according to GOLD guidelines (GOLD, 2019 [1]). 3. Subject is capable of performing reproducible spirometry maneuvers as described by current American Thoracic Society/European Respiratory Society (ATS/ERS) Guidelines (Graham et al., 2019 [7]) and has a post-ipratropium (500 mcg nebulized) FEV_1/FVC ratio <0.7 at Visit 2. 4. Subject has moderate to very severe COPD with a post-ipratropium (500 mcg nebulized) FEV_1 less than 80% of predicted normal (using the Global Lung Function Initiative reference range; Quanjer et al., 2012 [8]) and an absolute FEV_1 >700 mL at Visit 2. 5. Current smoker or ex-smoker, with a history of at least 10 pack-years of tobacco smoking. Ex-smokers must have stopped smoking >6 months prior to Visit 1. Formulae for pack-years: • Average number of cigarettes per day x 1/20 x years of smoking Or • Ounces of tobacco per week x 2/7 x years of smoking Or • Grams of tobacco per week x 2/175 x years of smoking 6. Capable of self-administering (or with the help of a caregiver) study medication, assessed at training at Visit 1 and Visit 3. 7. Able to understand and complete the study requirements (including literacy, to enable diary and questionnaire completion), provide written informed consent, and agree to abide by the study protocol and its restrictions. **Exclusion Criteria** 1. Previously dosed with revefenacin. 2. Current diagnosis of asthma. 3. Alpha-1 anti-trypsin deficiency. 4. Other chronic or active respiratory disorder (e.g., clinically significant [as determined by the Investigator] bronchiectasis, pulmonary fibrosis, sarcoidosis, pneumoconiosis, active tuberculosis).

	5. Symptoms of, or treatment for an AECOPD requiring antibiotics and/or oral/systemic corticosteroids or in-patient hospitalization during the 28 days preceding screening or during the screening period between Visit 1 and Visit 3. An AECOPD is defined as an acute event in the natural course of the disease warranting a change in the subject's regular medication specifically to address the exacerbation event, characterized by: Worsening, beyond normal day-to-day variation, of two or more of the following major symptoms for at least two consecutive days: • Dyspnea • Sputum volume • Sputum purulence or Worsening, beyond normal day-to-day variation, of any one major symptom outlined above plus any one of the following minor symptoms for at least two consecutive days: • Sore throat • Colds (nasal discharge and/or nasal congestions) • Fever without other cause • Increased cough • Increased wheeze 6. Pneumonia requiring hospitalization within 28 days prior to screening or during the screening period between Visit 1 and Visit 3. 7. Lower respiratory tract infection requiring treatment with antibiotics during the 28 days preceding screening or during the screening period between Visit 1 and Visit 3. 8. History or presence of pulmonary hypertension, respiratory failure, cor pulmonale or right ventricular failure which may impact the safety of the subject in the clinical judgement of the Investigator. 9. History of pulmonary lobectomy, lung volume reduction surgery, or lung transplantation. 10. Use of supplemental oxygen therapy for more than 15 hours per day (includes night-time use). 11. Subjects participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the trial (maintenance program is permitted). 12. Clinically significant, abnormal chest X-ray at screening indicating an active/significant disease process other than COPD. If a prior chest X-ray or thoracic high-resolution CT scan within 12 months prior to screening is available this will be acceptable. 13. History of long QT syndrome or screening ECG with QTcF greater than 500 milliseconds (0.500 seconds). 14. History within past 5 years of paroxysmal atrial fibrillation. Subjects with continuous atrial fibrillation controlled with a rate control strategy (i.e., cardioselective β-blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be

	included if the ventricular rate is below 100 bpm. 15. Any other clinically significant abnormality on the 12-lead ECG at screening which in the judgment of the Investigator would put the subject at potential risk if enrolled into the trial (these subjects should not be re-screened). Clinically significant abnormalities may include but are not limited to the following: left bundle branch block, Wolff-Parkinson-White syndrome, clinically significant arrhythmias (e.g., ventricular tachycardia). 16. Current evidence of, or history within the 6 months prior to screening of unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, or myocardial infarction. 17. Subjects with hepatic impairment. A history of hepatitis B or hepatitis C may be permitted at the discretion of the Investigator, provided the subject has no signs of hepatic impairment, is asymptomatic, and liver transaminases (ALT/AST) are ≤1.5 times the upper limit of normal (ULN) at Screening. 18. History of malignancy of any organ system treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases. The only exceptions are previous in situ carcinoma of the cervix, localized basal cell carcinoma of the skin or localized squamous carcinoma of the skin if the subject has been treated and is considered cured. 19. Subject suffers from any medical condition that would preclude the use of inhaled anticholinergics, including narrow-angle glaucoma, symptomatic benign prostatic hyperplasia, bladder neck obstruction, or urinary retention. 20. Use of any investigational drug within 28 days, or 5 half-lives, prior to screening whichever is longer. 21. Use of medications with the potential to interact with revefenacin, salbutamol or ipratropium bromide (as indicated in respective Investigator Brochure (IB) or product labels), or medications with the potential to affect or confound COPD disease status. Drugs should be washed out prior to screening (further details of washout periods prior to screening are in Table 5-1) and not taken thereafter during the study until after the final dose of study drug: 1. Oral anticholinergics. 2. Oral or “systemic” (parenteral; intravenous or intra-articular, intramuscular, spinal) corticosteroids. 3. OATP1B1 and OATP1B3 inhibitors (e.g., rifampicin, cyclosporine) 4. Strong CYP3A4 inhibitors. 5. Use of marijuana. 6. Herbal medications and Traditional Chinese Medications. 22. History of reactions/hypersensitivity to any of the following inhaled drugs or drugs of a similar class: short- or long- acting β2 agonists (e.g., salbutamol, formoterol), anticholinergic agents (e.g., tiotropium, ipratropium bromide), corticosteroids, sympathomimetic amines. Subjects with previous reaction to inhaled agents due to lactose

	sensitivity alone will be permissible for this study. 23. Subjects who are unable to stop any of the following medications, and refrain from their use throughout the study until the final dose of study drug (further details in Table 5-1): • Short-acting β2 agonists (except study-supplied salbutamol). • Short-acting anticholinergic agents (except those used for reversibility testing). • Long-acting anticholinergics (except study supplied medication). • Combination β2 agonists/anticholinergic agents. • Combination β2 agonists/inhaled corticosteroids/anticholinergic agents. • Phosphodiesterase 4 inhibitors. • Theophyllines. • Leukotriene inhibitors. • Orally inhaled nedocromil or cromolyn sodium. • Oral or parenteral corticosteroids. 24. Pregnant or nursing females or females intending to become pregnant during the course of the study. 25. Clinically significant abnormal laboratory test(s) at screening deemed exclusionary by the Investigator. 26. History of illegal or recreational drug or alcohol abuse within the past 5 years. 27. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.
Planned Number of Subjects	Approximately N=320 subjects will be randomized in a 1:1 ratio to revefenacin or matching placebo (N=160 on revefenacin and N=160 for placebo).
Statistical Methods	**Sample size estimation** The null hypothesis is that there is no difference in the mean change from baseline trough FEV_1 on Day 85 between revefenacin and placebo. The alternative hypothesis is that there is a difference. A sample size of 256 evaluable subjects (128:128; a 1:1 ratio of revefenacin to placebo) is required to provide at least 90% power to detect a difference between revefenacin and placebo of 100 mL in the analysis of the change from baseline trough FEV_1 at Day 85 assuming a standard deviation of 245 mL and a two-sided 5% significance level. To allow for a 20% dropout rate, approximately 320 subjects in total will be randomized. In the event of a public health emergency such as COVID-19, the Sponsor may consider increasing enrollment to overcome any additional loss of

information for the primary endpoint due to the inability of subjects to attend for scheduled clinic visits. The maximum number of subjects to be randomized under such circumstances will be limited to 428 (an additional 20% increase in enrollment).

Analysis Populations

The following 4 analysis populations are planned for this study:

- Full Analysis Set (FAS): all randomized subjects who received at least one dose of study drug and have at least one recorded post-baseline efficacy assessment.
- Safety Analysis Set (SS): all subjects who received at least one dose of study drug.
- Per Protocol Set (PP): all subjects in the FAS who had no major protocol violation that would impact significantly on the primary efficacy endpoints.
- Population Pharmacokinetic Analysis Set (PPK): all randomized subjects who receive at least one dose of study drug and who provide at least one evaluable post dose concentration sample for the PPK analysis.

Statistical Analyses

Primary Efficacy Endpoint

The primary endpoint is trough FEV_1 on Day 85. Trough FEV_1 will also be measured on Days 29 and 57.

The analysis of the primary endpoint will be based on a mixed model repeated measures (MMRM) analysis including changes from baseline trough FEV_1 measurements on Days 29, 57 and 85 as the dependent variable. The model will include independent fixed-effect terms for concomitant LABA use, reversibility to ipratropium, smoking status, age, sex, concomitant LABA, reversibility, treatment and baseline FEV_1 as a covariate. A time effect (visit) and its interaction terms with treatment and baseline FEV_1 will be included. The variance estimation will be based on an unstructured covariance matrix. The Kenward-Roger method for approximating the denominator degrees of freedom will be used.

Primary Efficacy Analysis

The primary analysis of the primary efficacy endpoint will be based on the FAS population. Available data for a subject prior to discontinuing study treatment will be used in the MMRM analysis. Missing data is assumed as missing at random (MAR). The difference between revefenacin and placebo on Day 85 will be estimated from the least squares means (LSmeans) along with the 95% confidence interval (CI) and associated 2-sided p-values.

Primary Efficacy Sensitivity Analyses

The primary efficacy analysis will be repeated for pre-defined subgroups and in the PP population.

	Missing data in the primary efficacy analysis is assumed as missing at random (MAR). The following missing data imputation methods will be used in sensitivity analyses to test the robustness of the conclusions to this assumption: • A two-dimensional tipping point multiple imputation method will be applied to the MMRM analysis (FAS population). • A Last-Observation-Carried-Forward (LOCF) single imputation method for the changes from baseline trough FEV_1 at Day 85 will be used and analyzed using an Analysis of Covariance (ANCOVA) model. Secondary Efficacy Analyses In all the secondary efficacy analyses, missing data will not be imputed and will be assumed to be missing at random (MAR). Secondary efficacy analyses will be performed using the FAS population and include, but is not limited to, the following comparisons: • Peak FEV_1 (0-2h) on Day 1: Analysis of Covariance (ANCOVA) will be used to assess the difference between treatment groups for change from baseline Peak FEV_1 after the first dose on Day 1. The ANCOVA model will include fixed-effect terms for concomitant LABA use, reversibility to ipratropium, smoking status, age, sex, treatment and baseline FEV_1 as a covariate. The difference between revefenacin and placebo on Day 1 will be estimated from the LSmeans along with the 95% CI and associated 2-sided p-values. • SGRQ responders (total score >=4 units) on Day 85: The number and percentage of responders on Day 85 in each treatment group will be summarized. A comparison between revefenacin and placebo will be evaluated with the odds ratio (OR) and corresponding 95% confidence interval from a logistic regression model. The model will include fixed-effect terms for concomitant LABA use, reversibility to ipratropium, smoking status, age, sex, treatment and baseline SGRQ total score as a covariate. For subjects who discontinue study treatment, the SGRQ completed at the Early Termination (ET) visit will be carried forward and used in the analysis. • BDI/TDI on Day 85: The TDI focal score will be analyzed using the same MMRM analysis described for the primary analysis of the primary endpoint. The baseline FEV_1 covariate will be replaced with the BDI focal score. Estimates for TDI on Day 85 will be derived from the model. The difference between revefenacin and placebo on Day 85 will be estimated from the LSmeans along with the 95% CI and associated 2-sided p-values • Average Count of Salbutamol Puffs Per Day (Days 1-85): The average count of salbutamol puffs per day will be analyzed using the same MMRM analysis described for the primary analysis of the primary endpoint with the time variable Month (1, 2, 3) replacing Visit. The average count of salbutamol puffs per day for the study (Days 1-85) will be estimated from the model-derived average of each of the 3 months using an appropriate contrast statement along LSmean differences, 95% CI and associated 2-sided p-values. • Percentage of salbutamol rescue free 24h periods (Days 1-85): The percentage of salbutamol rescue free 24h periods will be analyzed using the same MMRM analysis described for the primary analysis of the

	primary endpoint with the time variable Month (1, 2, 3) replacing Visit. The average percentage of salbutamol rescue free 24h periods for the study (Days 1-85) will be estimated from the model-derived average of each of the 3 months using an appropriate contrast statement with LSmean differences, 95% CI and associated 2-sided p-values. Safety Analyses All safety data will be presented in listings. Descriptive summary tables will be provided for treatment-emergent adverse events (TEAE), laboratory evaluations, vital signs, 12-lead ECG parameters, and concomitant medications. Safety data will be presented using the SS population. A summary of acute exacerbations of COPD (AECOPD) reported with an AE preferred term of COPD will be descriptively summarized by severity. Exacerbation data will be summarized (N, %) for all exacerbations; moderate and severe exacerbations; and severe only exacerbations. PK Analyses Plasma concentration data for revefenacin and THRX-195518 will be listed, summarized on the basis of time intervals, and plotted using a scatter plot with time relative to the preceding revefenacin dosing time. Summary statistics (mean, standard deviation, minimum, maximum, number of subjects, and coefficient of variation) will be calculated for plasma concentrations for each time interval and by treatment group. All analyses using the PPK set will group subjects according to treatment actually received. Full details of the PPK analysis, including methods for handling data (missing values, outliers), etc., will be documented in a PPK analysis plan and will be conducted and reported separately.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AECOPD	Acute Exacerbation of COPD
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
ATS	American Thoracic Society
AUC	Area Under the Curve
BDI	Baseline Dyspnea Index
BDR	Blinded Data Review
BID	Bis in die (two times a day)
BP	Blood Pressure
bpm	beats per minute
CI	Confidence Interval
C_{max}	Maximum observed plasma concentration
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRP	C-reactive Protein
C_{trough}	Trough plasma concentration
CYP	Cytochrome P450
CT	Computed Tomography
ECG	Electrocardiogram
EoT	End of Treatment
ERS	European Respiratory Society
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second

IUD	Intrauterine Device
IUS	Intrauterine System
IVRS/ IWRS	Interactive Voice Response System/ Interactive Web Response System
LABA	Long-acting beta-adrenoceptor agonist
LAMA	Long-acting muscarinic receptor antagonist
LOCF	Last Observation Carried Forward
LSmean	Least Squares Mean
MAR	Missing At Random
Max/Min	Maximum/Minimum
mcg	Microgram
MCID	Minimally Clinically Important Difference
mL	Milliliter
mM	Millimolar
mmHg	Millimeter of Mercury
mMRC	Modified Medical Research Council Dyspnea Scale
MMRM	Mixed Model Repeated Measures
ms	Millisecond
NYHA	New York Heart Association
OR	Odds Ratio
PI	Principal Investigator
pMDI	Pressurized Metered Dose Inhaler
PP	Per Protocol
PPK	Population Pharmacokinetics
PRN	pro re nata
PRO	Patient Reported Outcome
QD	Quaque die (once a day)
QTc	QT corrected

FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
hCG	Human Chorionic Gonadotropin
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid
ID	Identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent To Treat

QTcF	QT corrected (Fridericia's correction)
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGRQ	St. George's Respiratory Questionnaire
SID	Subject Identification
SS	Safety Analysis Set
SOP	Standard Operating Procedure
TDI	Transition Dyspnea Index
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WM	Weighted-Mean

1 STUDY DIAGRAM AND STUDY SCHEDULE OF ACTIVITIES

The Schedule of Activities table (Table 1-1) provides an overview of the protocol visits and procedures. Refer to the Study Conduct (Section 6) for detailed information on each procedure and assessment required for compliance with the protocol.

Figure 1-1: Study Diagram

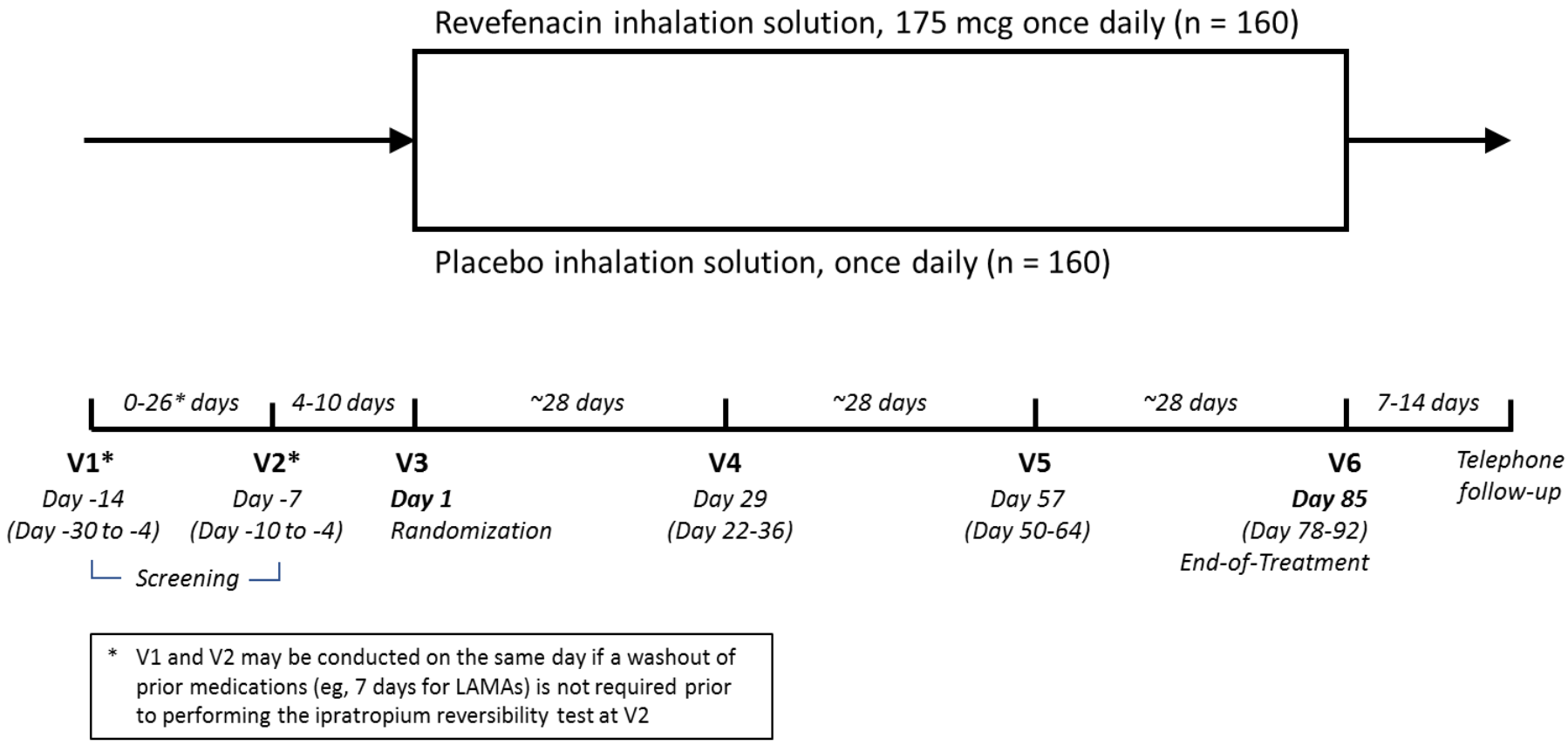

Table 1-1: Study Schedule

VISIT	1 (Screen 1)	2 (Screen 2)[1]	3 Randomization	4	5	6 (EoT)	Early term (ET)	Follow up (Telephone)
NOMINAL DAY (ALLOWABLE WINDOW)	-14 (-30 to -4)	-7 (-10 to -4)	1	29 (22-36)	57 (50-64)	85 (78-92)		7-14 days after V6/ET
NOMINAL WEEK	-2	-1	0	4	8	12		
Written informed consent	x							
IVRS/IWRS transaction	x		x	x	x	x	x	x
Demography and medical history (incl. COPD, smoking, and exacerbation history)	x							
Review concomitant medications	x	x	x	x	x	x	x	x
Physical examination	x					x	x	
Chest X-ray (if not done in past 12 months)	x							
Height and weight	x							
Vital Signs (supine or semi-recumbent blood pressure, pulse rate)	x		x[2]			x[2]	x	
12-lead ECG (supine or semi-recumbent)	x		x[2]			x[2]	x	
Spirometry (FEV_1, FVC) pre-bronchodilator		x						
Spirometry (FEV_1, FVC) 45 min post-ipratropium (500 mcg nebulized)		x						
Laboratory Safety – Blood and Urinalysis	x					x	x	
Pregnancy Test	x		x	x	x	x	x	
Dispense Rescue Medication (salbutamol pMDI)	x		x	x	x			
Dispense Daily Diary	x		x	x	x			
Record Adverse Events	x	x	x	x	x	x	x	x

VISIT	1 (Screen 1)	2 (Screen 2)[1]	3 Randomization	4	5	6 (EoT)	Early term (ET)	Follow up (Telephone)
NOMINAL DAY (ALLOWABLE WINDOW)	-14 (-30 to -4)	-7 (-10 to -4)	1	29 (22-36)	57 (50-64)	85 (78-92)		7-14 days after V6/ET
NOMINAL WEEK	-2	-1	0	4	8	12		
Medication Training	x[3]		x					
Pre-dose Spirometry (FEV_1, FVC), -45 and -15 min pre-dose.			x	x	x	x	x	
Complete BDI/TDI[4]			x	x	x	x	x	
Complete SGRQ			x			x	x	
Complete mMRC			x					
Randomization			x					
Administer Study Medication in Clinic			x	x	x	x		
Dispense Outpatient Study Medication			x	x	x			
Post-dose Spirometry (FEV_1, FVC), 5, 15, and 30 minutes, and 1, 1.5, and 2h			x			x		
PK sampling			x[5]	x[5]	x[5]	x[5]		
Record Rescue Medication and Study Drug in Diary, Review at Clinic Visits		x	x	x	x	x	x	

1. Visit 2 (Screening Visit 2) can be conducted on the same day as Visit 1 (Screening Visit 1) if the subject does not require washout of other COPD medications (e.g., 7 days for LAMAs) prior to the ipratropium reversibility test at Visit 2.
2. Pre-dose and at approximately 1 hour post-dose.
3. Train subject on rescue medication use.
4. BDI is performed at V3 and TDI is performed at V4, V5, and V6.
5. PK sampling will be performed pre-dose (within 30 minutes of dosing) and at any time 1 – 30 minutes post-dose at Visit 3, 4, 5, and 6. At Visit 6, an additional PK sample will be collected during the sampling interval of 1 – 4 hours post-dose.

2 INTRODUCTION

2.1 Indication

Moderate to very severe chronic obstructive pulmonary disease (COPD).

2.2 Background and Rationale

COPD is a respiratory disease characterized by airflow obstruction that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response in the airways and the lung to noxious particles or gases (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2019 [1]). In 2012, it was estimated that more than 3 million people died prematurely due to COPD and it is projected to be the third leading cause of death worldwide by 2020 (GOLD 2019 [1]).

In the People's Republic of China, the prevalence rate of COPD was reported to be between 1.20% and 8.87% depending on the provinces/cities surveyed (Zhu et al., 2018 [2]), and in 2013 there were 910,809 deaths due to COPD, which represented 31% of total deaths due to COPD in the world (Yin et al., 2016 [3]). In addition to the high prevalence of COPD in China, a separate survey across 7 provinces found that only 7.9% of patients had regular medical treatment for COPD, highlighting the need, in some regions of China at least, for improvement in the management of COPD (Zhu et al., 2018 [2]).

Pharmacologic treatment of COPD with bronchodilators is central to the management of both the symptoms and the long-term risks of the condition. Long-acting inhaled bronchodilators are convenient and are more effective for long-term symptom relief than short-acting bronchodilators; accordingly, widely accepted treatment guidelines such as those produced by GOLD recommend the use of long-acting muscarinic antagonist (LAMA) bronchodilators as first-line therapies for patients with persistent COPD symptoms (GOLD 2019 [1]).

For some patients, bronchodilator therapy may most effectively be provided using a nebulizer device. An expert panel review (Wise et al., 2016 [9]) suggests that patients with either cognitive or physical decline who cannot coordinate or generate sufficient inspiratory force for breath-actuated handheld devices are candidates for nebulized therapy. Patient characteristics also identified by the panel when considering nebulization therapy are poor adherence to current medication, frequent exacerbations despite treatment with handheld inhalers, recent hospitalization, and finally, patient preference for nebulizing their medication. Revefenacin is a potent muscarinic receptor antagonist that was designed as a once-daily agent to be administered via a mouthpiece using a standard jet nebulizer. It was approved by the United States Food and Drug Administration (US FDA) in November 2018 with the tradename Yupelri® for the maintenance treatment of patients with COPD. It is active at all of the muscarinic receptor subtypes M1 through M5, but in the lung, its pharmacological effects are mediated through competitive inhibition of M3 receptors at the smooth muscle preventing acetylcholine-induced bronchoconstriction and leading to bronchodilation.

The effects of revefenacin inhalation solution administered once daily via a standard jet nebulizer via a mouthpiece (PARI LC® Sprint Reusable Nebulizer) were evaluated for the US filing and subsequent approval in two replicate 12-week, double-blind, placebo-controlled Phase 3 efficacy and safety clinical trials (studies 0126 and 0127), and in a 52-week

long-term, active controlled (tiotropium dry powder inhaler, 18 mcg once daily) safety trial (study 0128), in moderate to very severe COPD patients.

In studies 0126 and 0127, 1229 patients were included of which 395 received the 175 mcg dose administered via a standard jet nebulizer. The primary endpoint was change from baseline in trough (pre-dose) FEV_1 at Day 85. The study population had a mean age of 64 years (range: 41 to 88) and mean smoking history of 53 pack years, with 48% identified as current smokers. At screening, the mean post-bronchodilator percent predicted FEV_1 was 55% (range: 10% to 90%), and the post-bronchodilator FEV_1/FVC ratio was 0.54 (range: 0.3 to 0.7).

Using the ITT populations in studies 0126 and 0127, revefenacin inhalation solution 175 mcg achieved a statistically significant difference from placebo of 146.26 mL, (95% CI 103.74, 188.78; p<0.0001) and 147.01 mL, (95% CI 96.98, 197.05; p < 0.0001) respectively. Furthermore, a pre-specified pooled analysis of both studies demonstrated a statistically significant difference from placebo of 148.13 mL, (95% CI 115.20, 181.06; p < 0.0001). This treatment effect is considerably greater than the minimally clinically important difference (MCID) for trough FEV_1 (Donohue 2005 [10]).

As requested by US FDA, both studies 0126 and 0127 included up to 40% patients that were taking concomitant LABA or ICS/LABA. In study 0126, 37.0% of the population were using a LABA-containing product and in study 0127, 36.7% of the population were using a LABA containing product. This enabled an assessment of the effect of revefenacin inhalation solution in a population taking additional maintenance therapy for COPD and the treatment effect of revefenacin inhalation solution was similar in those taking concomitant LABA or ICS/LABA. In a pre-specified pooled analysis of both 0126 and 0127 studies, for the concomitant LABA or ICS/LABA subgroup, where the comparison is placebo + ICS/LABA or LABA vs., revefenacin inhalation solution + ICS/LABA or LABA, revefenacin inhalation solution 175 mcg achieved a nominally statistically significant difference from placebo of 139.19 mL, (95% CI 82.87 to 195.51); (p < 0.0001).

The 52 week long-term safety study (study 0128) included 1055 subjects, of whom 335 received revefenacin inhalation solution 175 mcg and 356 received tiotropium dry powder 18 mcg. The study population had a mean age of 64 years (range: 41 to 92) and mean smoking history of 52 pack-years, with 46% identified as current smokers. At screening, the mean post-bronchodilator percent predicted FEV_1 was 54% (range: 18% to 80%), and the post-bronchodilator FEV_1/FVC ratio was 0.53 (range: 0.2 to 0.7). Approximately 50% of subjects were taking a background of ICS/LABA or LABA during the study.

The primary objective was to characterize the safety and tolerability of revefenacin inhalation solution administered once daily. Revefenacin inhalation solution was well tolerated in study 0128; the most frequently reported TEAE overall was chronic obstructive pulmonary disease (worsening or exacerbation of COPD), which was reported for 73/335 (21.8%) in the revefenacin inhalation solution 175 mcg group, and 100/356 (28.1%) in the tiotropium group.

The percentages of subjects reporting any treatment-related TEAE were generally small across treatment groups (12% to 15%). The TEAEs most frequently considered related to the study drug were worsening/exacerbation of COPD and dyspnea. The incidence of study drug-related worsening/exacerbation of COPD was similar between treatment groups (3.6%, and 2.8% in the revefenacin inhalation solution 175 mcg group and tiotropium group, respectively).

The incidence of TEAEs potentially related to anti-muscarinic activity (constipation, dry mouth, and dysuria) was low (7/335 [2.1%] in the revefenacin inhalation solution 175 mcg group, and 15/356 [4.2%] in the tiotropium group), suggesting that systemic anti-muscarinic effects were minimal during the study.

Revefenacin inhalation solution 175 mcg was well tolerated and had an adverse event profile similar to tiotropium inhalation powder (18 mcg) in study 0128; this is consistent with all other studies in the revefenacin inhalation solution clinical program where the adverse event profile has been similar to placebo and consistent with that reported for other orally inhaled anti-muscarinic products.

Although the data from studies 0126, 0127 and 0128 were derived from clinical trials with patients of predominantly Caucasian ethnicity, based on metabolism of the drug, it is unlikely to exhibit different exposure in Chinese patients, making these studies highly relevant for extrapolating the risk-benefit of revefenacin inhalation solution to the proposed study (see Section 2.2.1).

Clinical trials on other inhaled LAMAs conducted in East Asian COPD patients have demonstrated comparable efficacy and safety compared to large global registration trials conducted primarily in Caucasian patients, suggesting comparable sensitivity to this class of drugs between ethnicities. For example, Wang et al., (2015 [5]) reported that the efficacy and safety results of the GLOW7 trial on glycopyrronium in predominantly Chinese patients with moderate to severe COPD were similar to previous trials conducted in predominantly Caucasian patients. Likewise, a comparison of the efficacy data for East Asian patients compared to the overall study population of the TONADO trial on tiotropium/olodaterol versus its mono-components concluded that the lung function responses were consistent and there were no significant differences in safety outcomes between the two populations (Bai et al., 2017 [6]).

The objective of this study is therefore to confirm the safety and efficacy of revefenacin inhalation solution for the treatment of Chinese patients with moderate to very severe COPD, in order to provide a bridge for this population to the existing body of data derived from clinical trials with patients of predominantly Caucasian ethnicity.

Complete preclinical and clinical information for revefenacin inhalation solution may be found in the Single Reference Safety Document, which for this study is the Investigator Brochure.

2.2.1 Rationale for Dose Selection

The dose of revefenacin selected for this study is 175 mcg once daily, which has consistently shown to be safe and efficacious in COPD subjects. This is the approved dose of Yupelri® for maintenance treatment of COPD by the US FDA.

Compared to the Caucasian population, Chinese ethnicity does not appear to confer any altered sensitivity to inhaled LAMA as a class (Wang et al., 2015 [5] and Bai et al., 2017 [6]; see Section 2.2) and based on the metabolic profile of revefenacin it is considered unlikely to exhibit different exposure in Chinese patients despite the known ethnic differences in metabolizing enzymes and transporters.

In terms of clinical safety profile above the approved dose, daily doses of revefenacin inhalation solution of up to 700 mcg (for 7 days) or 350 mcg (for 1 month) have been shown to be safe and well tolerated in COPD patients in Phase 2 clinical studies, and single doses of 700 mcg have been shown to be without effect on cardiac repolarization in a thorough QT study in healthy subjects.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objectives

The primary objective of the study is as follows:

- To confirm the efficacy of revefenacin inhalation solution 175 mcg administered once daily via nebulization for 12 weeks compared to placebo in a population of Chinese subjects with moderate to very severe COPD.

3.1.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To confirm the safety of revefenacin inhalation solution 175 mcg administered once daily via nebulization for 12 weeks compared to placebo in a population of Chinese subjects with moderate to very severe COPD

- To characterize the effect of revefenacin inhalation solution 175 mcg on patient reported outcomes compared to placebo in a population of Chinese subjects with moderate to very severe COPD.

- To collect PK samples for population PK analysis of revefenacin inhalation solution 175 mcg in a population of Chinese subjects with moderate to very severe COPD.

3.2 Endpoints

3.2.1 Primary Endpoints

- Trough FEV_1 on Day 85 (mean of measurements at -45 and -15 minutes pre-dose)

3.2.2 Secondary Endpoints

3.2.2.1 Efficacy

- Peak FEV_1 (0-2h) on Day 1

- St. George's Respiratory Questionnaire (SGRQ) responders (total score ≥4 units) on Day 85

- Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) on Day 85

- Average count of salbutamol puffs per day (Days 1-85)

- Percentage of salbutamol rescue free 24h periods (Days 1-85)
- Trough FEV_1 on Days 29 and 57
- BDI/TDI on Days 29 and 57
- Weighted Mean FEV_1 (0-2h) on Day 1 and Day 85
- Peak FEV_1 (0-2h) on Day 85
- Trough forced vital capacity (FVC) on Days 29, 57 and 85
- SGRQ on Day 85 (continuous endpoint)
- TDI responders (focal score ≥1) on Day 85

3.2.2.2 Safety

- Adverse events (AE)
- Acute exacerbations of COPD (AECOPD)
- Laboratory tests
- Vital Signs (blood pressure and pulse rate)
- 12-lead ECG

3.2.3 Pharmacokinetic (PK)

- Population PK parameters for revefenacin inhalation solution (C_{max}, C_{trough})

4 STUDY POPULATION

4.1 Study Population

Approximately 320 subjects with moderate to very severe COPD will be randomized to ensure that at least 256 subjects complete the study.

Screening to discharge will be approximately 4 months in duration.

4.2 Inclusion and Exclusion Criteria

4.2.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the Investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Males and females of Chinese ethnicity, at least 40 years of age. Females may be of either childbearing or non-childbearing potential. All females of childbearing potential must be using an acceptable, highly effective method of contraception and have a negative pregnancy test at screening.

2. A clinical diagnosis for at least 6 months prior to screening of COPD according to GOLD guidelines (GOLD, 2019 [1]).

3. Subject is capable of performing reproducible spirometry maneuvers as described by current American Thoracic Society/European Respiratory Society (ATS/ERS) Guidelines (Graham et al., 2019 [7]) and has a post-ipratropium (500 mcg nebulized) FEV_1/FVC ratio <0.7 at Visit 2.

4. Subject has moderate to very severe COPD with a post-ipratropium (500 mcg nebulized) FEV_1 less than 80% of predicted normal (using the Global Lung Function Initiative reference range; Quanjer et al., 2012 [8]) and an absolute FEV_1 >700 mL at Visit 2

5. Current smoker or ex-smoker, with a history of at least 10 pack-years of tobacco smoking. Ex-smokers must have stopped smoking >6 months prior to Visit 1. Formulae for pack-years:

   - Average number of cigarettes per day x 1/20 x years of smoking

   Or

   - Ounces of tobacco per week x 2/7 x years of smoking

   Or

   - Grams of tobacco per week x 2/175 x years of smoking

6. Capable of self-administering (or with the help of a caregiver) study medication, assessed at training at Visit 1 and Visit 3.

7. Able to understand and complete the study requirements (including literacy, to enable diary and questionnaire completion), provide written informed consent, and agree to abide by the study protocol and its restrictions.

4.2.2 Exclusion Criteria

Subject candidates must not be enrolled in the study if they meet any of the following criteria:

1. Previously dosed with revefenacin.

2. Current diagnosis of asthma.

3. Alpha-1 anti-trypsin deficiency.

4. Other chronic or active respiratory disorder (e.g., clinically significant [as determined by the Investigator] bronchiectasis, pulmonary fibrosis, sarcoidosis, pneumoconiosis, active tuberculosis).

5. Symptoms of, or treatment for an AECOPD requiring antibiotics and/or oral/systemic corticosteroids or in-patient hospitalization during the 28 days preceding screening or during the screening period between Visit 1 and Visit 3. An AECOPD is defined as an acute event in the natural course of the disease warranting a change in the subject's regular medication specifically to address the exacerbation event, characterized by:

   Worsening, beyond normal day-to-day variation, of two or more of the following major symptoms for at least two consecutive days:

   - Dyspnea
   - Sputum volume
   - Sputum purulence

or

   Worsening, beyond normal day-to-day variation, of any one major symptom outlined above plus any one of the following minor symptoms for at least two consecutive days:

   - Sore throat
   - Colds (nasal discharge and/or nasal congestions)
   - Fever without other cause
   - Increased cough
   - Increased wheeze

6. Pneumonia requiring hospitalization within 28 days prior to screening or during the screening period between Visit 1 and Visit 3.

7. Lower respiratory tract infection requiring treatment with antibiotics during the 28 days preceding screening or during the screening period between Visit 1 and Visit 3.

8. History or presence of pulmonary hypertension, respiratory failure, cor pulmonale or right ventricular failure which may impact the safety of the subject in the clinical judgement of the Investigator.

9. History of pulmonary lobectomy, lung volume reduction surgery, or lung transplantation.

10. Use of supplemental oxygen therapy for more than 15 hours per day (includes night-time use).

11. Subjects participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the trial (maintenance program is permitted).

12. Clinically significant, abnormal chest X-ray at screening indicating an active/significant disease process other than COPD. If a prior chest X-ray or thoracic high-resolution CT scan within 12 months prior to screening is available this will be acceptable.

13. History of long QT syndrome or screening ECG with QTcF greater than 500 milliseconds (0.500 seconds).

14. History within past 5 years of paroxysmal atrial fibrillation. Subjects with continuous atrial fibrillation controlled with a rate control strategy (i.e., cardioselective β-blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be included if the ventricular rate is below 100 bpm.

15. Any other clinically significant abnormality on the 12-lead ECG at screening which in the judgment of the Investigator would put the subject at potential risk if enrolled into the trial (these subjects should not be re-screened). Clinically significant abnormalities may include but are not limited to the following: left bundle branch block, Wolff-Parkinson-White syndrome, clinically significant arrhythmias (e.g., ventricular tachycardia).

16. Current evidence of, or history within the 6 months prior to screening of unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, or myocardial infarction.

17. Subjects with hepatic impairment. A history of hepatitis B or hepatitis C may be permitted at the discretion of the Investigator, provided the subject has no signs of hepatic impairment, is asymptomatic, and liver transaminases (ALT/AST) are ≤1.5 times the upper limit of normal (ULN) at Screening.

18. History of malignancy of any organ system treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases. The only exceptions are previous in situ carcinoma of the cervix, localized basal cell carcinoma of the skin or localized squamous carcinoma of the skin if the subject has been treated and is considered cured.

19. Subject suffers from any medical condition that would preclude the use of inhaled anticholinergics, including narrow-angle glaucoma, symptomatic benign prostatic hyperplasia, bladder neck obstruction, or urinary retention.

20. Use of any investigational drug within 28 days, or 5 half-lives, prior to screening whichever is longer.

21. Use of medications with the potential to interact with revefenacin, salbutamol or ipratropium bromide (as indicated in respective Investigator Brochure or product labels), or medications with the potential to affect or confound COPD disease status. Drugs should be washed out prior to screening (further details of washout periods prior to screening are in Table 5-1) and not taken thereafter during the study until after the final dose of study drug:

    - Oral anticholinergics.
    - Oral or “systemic” (parenteral; intravenous or intra-articular, intramuscular, spinal) corticosteroids.
    - OATP1B1 and OATP1B3 inhibitors (e.g., rifampicin, cyclosporine)
    - Strong CYP3A4 inhibitors.

- Use of marijuana.
- Herbal medications and Traditional Chinese Medications.

22. History of reactions/hypersensitivity to any of the following inhaled drugs or drugs of a similar class: short- or long- acting β_2 agonists (e.g., salbutamol, formoterol), anticholinergic agents (e.g., tiotropium, ipratropium bromide), corticosteroids, sympathomimetic amines. Subjects with previous reaction to inhaled agents due to lactose sensitivity alone will be permissible for this study.

23. Subjects who are unable to stop any of the following medications, and refrain from their use throughout the study until the final dose of study drug (further details in Table 5-1):

    - Short-acting β_2 agonists (except study-supplied salbutamol).
    - Short-acting anticholinergic agents (except those used for reversibility testing).
    - Long-acting anticholinergics (except study supplied medication).
    - Combination β_2 agonists/anticholinergic agents.
    - Combination β_2 agonists/inhaled corticosteroids/anticholinergic agents.
    - Phosphodiesterase 4 inhibitors.
    - Theophyllines.
    - Leukotriene inhibitors.
    - Orally inhaled nedocromil or cromolyn sodium.
    - Oral or parenteral corticosteroids.

24. Pregnant or nursing females or females intending to become pregnant during the course of the study.

25. Clinically significant abnormal laboratory test(s) at screening deemed exclusionary by the Investigator.

26. History of illegal or recreational drug or alcohol abuse within the past 5 years.

27. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

4.2.3 Randomization Criteria

Subjects satisfying all of the inclusion and exclusion criteria will be eligible for randomization.

Subjects must be able to provide a technically valid baseline FEV_1 that fully meets the ATS/ERS criteria (Graham et al., 2019 [7]) at Visit 3 (Day 1, pre-dose).

Subjects must not have symptoms of, or treatment for, an AECOPD requiring antibiotics and/or oral/systemic corticosteroids or in-patient hospitalization in the period between screening and randomization.

4.2.4 Criteria for Study Drug Termination, Withdrawal from the Study and Study Termination

Subjects will be free to request termination of study drug or withdrawal from the study at any time for any reason.

Subjects must be withdrawn from the study prior to randomization under the following circumstances:

- Failure to satisfy all of the inclusion and exclusion criteria. If a subject is found to have not met all of the inclusion and exclusion criteria only after the subject has been randomized, then this should be documented as a protocol deviation, but the subject should not be withdrawn from the study unless requested by the subject or if there is a safety reason for withdrawing the subject.

A subject must terminate study drug for safety reasons under the following circumstances:

- An exacerbation of COPD that is classified as moderate or severe:
  - Moderate:
    Worsening symptoms that require treatment with oral/systemic corticosteroids and/or antibiotics, but do not require in-patient hospitalization (i.e., admission).
  - Severe:
    Worsening symptoms of COPD that require treatment with in-patient hospitalization (i.e., admission).
- The subject becomes pregnant during any stage from Visit 3 (Day 1).
- The subject displays findings consistent with narrow angle glaucoma.
- The subject displays findings consistent with uncontrolled prostatic hyperplasia or bladder neck obstruction.

A subject may be required to terminate study drug for other reasons including the following:

- If it is in the subject's best interest based on decision of the Principal Investigator (PI) or Sub-Investigator e.g., due to occurrence of an AE and/or other findings considered to present a safety concern to continued dosing with study drug.
- Despite education/reinforcement, the subject shows persistent inadequate compliance with required study visits/procedures, potentially compromising safety monitoring while on study drug.

- The subject takes contra-indicated medications presenting a safety concern to continued dosing with study drug.

Unless consent is withdrawn, subjects who prematurely terminate study drug will have an Early study drug Termination (ET) visit scheduled as soon as possible after their last dose of study drug, in order to minimize missing data.

The Principal Investigator and/or Mylan reserves the right to terminate the study for any reason.

The study will be terminated early if there are significant safety concerns.

4.3 Lifestyle Guidelines

Subjects are to observe the restrictions below during the study.

4.3.1 Meals and Dietary Restrictions

In order to avoid interference with pulmonary function testing, subjects should not consume excessively large meals immediately before clinic visits during which spirometry will be performed.

4.3.2 Alcohol, Caffeine and Tobacco

At all study visits, subjects will be required to:

- Abstain from alcohol for at least 4 hours prior to a clinic visit and continue abstaining from alcohol until after the final assessment of each visit.
- Abstain from smoking for at least 1 hour prior to each spirometry session.
- Abstain from xanthine (caffeine) containing products (coffee, tea, cola, chocolate, etc.) for 2 hours prior to the clinic visit and continue abstaining until after the final assessment of each visit.

4.3.3 Activity

For the 2 hours prior to spirometry testing, subjects should make every effort to refrain from unfamiliar or excessive exercise or the direct inhalation of cold air; in order to reduce the impact of breathing cold air, subjects may need to rest for a period of time (as judged by the Investigator) in the clinic prior to commencement of spirometry testing.

4.3.4 Other Restrictions

- Abstain from use of herbal medications and Traditional Chinese medications.

4.4 Contraception

4.4.1 Females - Non-childbearing Potential

Female subjects of non-childbearing potential must meet at least one of the following criteria:

1. Postmenopausal, defined as:

    - Aged 45 years or above

    - Amenorrheic for at least 2 years, **or** if amenorrheic for less than 2 years, have a serum FSH level >30 IU/L in the absence of hormone replacement therapy.

2. A documented hysterectomy and/or bilateral oophorectomy.

All other females will be considered to be of childbearing potential.

4.4.2 Females - Childbearing Potential

Female subjects of child-bearing potential must use an acceptable, highly effective method of contraception (i.e., a method with a failure rate <1% when used consistently and correctly) starting from screening through to at least 7 days after the final dose of study drug. For this study, such methods include at least one of the following:

- Abstinence (periodic abstinence is not acceptable).

- Tubal ligation.

- Intrauterine device (IUD) or intrauterine system (IUS).

- Condom.

- Male partner who has had a vasectomy for at least 6 months. Male partners with vasectomies of <6 months are NOT considered protected.

- Hormonal contraceptives (oral, injected, transdermal or implanted) with the exception of low dose gestagens, i.e., only containing lynestrenol or norethisterone, since they do not inhibit ovulation and are therefore not considered as highly-effective. The subject must remain on the hormonal contraceptive throughout the study and must have been using hormonal contraceptives for an adequate period prior to the study to ensure effectiveness (e.g., 3 months).

4.5 Pregnancy Testing

Serum or urinary pregnancy testing will be performed on all females of childbearing potential as described in the schedule of activities (results will be reviewed and must be negative prior to dosing). In the event of a positive test, the subject will be withdrawn from the study (or will not enter the study if during screening).

Any pregnancy occurring after randomization to study drug will be followed up and reported to the Sponsor as per Section 9.6.

5 STUDY DRUG

5.1 Investigational Drug

Eligible subjects will be randomly assigned to receive one of the two following investigational drugs:

A. Revefenacin inhalation solution for inhalation: 175 mcg revefenacin in a sterile, clear, colorless, aqueous solution for nebulization, supplied in an individually-pouched 3 mL low-density polyethylene unit-dose vial with a twist off top

B. Matching placebo: a sterile, clear, colorless, aqueous solution for nebulization, supplied in an individually-pouched 3 mL low-density polyethylene unit-dose vial with a twist off top

5.1.1 Administration of Study Drugs

Revefenacin inhalation solution and its matching placebo will be administered using a centrally-provided, standard jet nebulizer (PARI LC Sprint) and compressor (PARI TurboBOY) via a mouthpiece. Subjects, and if applicable their caregiver(s), will be trained at Visit 3 to administer the study drug until nebulization of the study drug solution is complete, which will take up to approximately 10 minutes and will be evidenced by spluttering of the nebulizer. They will also be trained on the cleaning and maintenance of their nebulizer in accordance with the manufacturer's instructions.

The first dose will be administered on the morning of Day 1/Visit 3 at the study site. Subsequent doses will be self-administered at home by the subject except on days with a scheduled visit to the study site. They will be advised to administer the study drug every morning at approximately the same time within the window of 06:00 and 11:00. The time of administration will be recorded by the subjects in their diary.

Subjects will be required to bring their nebulizer and both used and unused vials back to the study site at each scheduled visit.

Study drug administration must be performed in a different room from that used for PK blood sampling and processing to avoid contamination of PK samples.

In the event of any significant dosing errors, the Medical Monitor, or Mylan study contact should be contacted immediately.

5.1.2 Study Medication Compliance

Study medication compliance will be assessed during the study on the basis of:

1. Number of used and unused vials at each visit.

2. Subject diary entries.

The primary assessment of compliance will be a count of the used and unused vials; however, in the event of missing vials, the subject diary entries will be utilized to assess and record study medication compliance. The number of used and unused vials and/or diary card data on compliance will be recorded in the CRF.

Study medication compliance will be checked at Visits 4-6 to ensure that subjects are compliant (i.e., who are considered to have received 80% - 120% of the total number of doses that should have been administered in between study visits). Subjects who are non-compliant will be re-trained on the requirements of the study.

5.2 Drug Inventory

The subject will be supplied with:

- The investigational drug: revefenacin inhalation solution, or its matching placebo
- The nebulizer and compressor required to administer the investigational drug, revefenacin inhalation solution, or its matching placebo
- Salbutamol 100 mcg/dose, in a pressurized metered dose inhaler (pMDI) containing 200 doses will be provided as rescue medication. The pMDI will have a dose counter and will be supplied/re-supplied during the study to ensure subjects are provided with enough rescue medication considering their usual / actual use.

The Investigator site will also be provided with:

- Ipratropium 500 mcg as a solution for administration via jet nebulizer for reversibility testing during screening. The nebulizer used for ipratropium administration must be different from the one used by the subject for administration of investigational study drug.

5.3 Study Medication Complaints

In the event the subject has a complaint/concern during study participation regarding the study supplied study medication, they should contact the site.

In the event of a complaint/concern regarding any study medication provided by Mylan for this study, as a minimum the following information should be sent by the site via e-mail to [redacted].

- Study number.
- Principal Investigator name.
- Subject ID.
- Date of occurrence of incident/complaint.
- Description of incident/complaint (facts).
- Confirmation if the complaint caused or resulted in a SAE? If “Yes”, confirmation that the SAE has been reported.

Additional information and potentially the return of study medication may be requested by Mylan in order to investigate the complaint.

5.4 Storage, Disposition of Used and Unused Study Drug and Drug Accountability

The Investigator, or an approved representative, e.g., pharmacist, will ensure that all investigational drugs are stored in a secured area under recommended storage conditions and in accordance with applicable regulatory requirements while at the Investigator site.

Study drug should be stored in accordance with the drug label. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.

Temperature of storage facilities should be monitored and recorded on a daily basis using validated devices that record maximum and minimum temperatures. Should the storage facility experience any excursion of temperature outside of the labelled storage condition this must be reported immediately to Mylan or designee. At sites where daily monitoring and recording is not possible at weekends, then on the next working day after the weekend the temperature record (e.g., max/min thermometers) should be checked immediately for any temperature excursions. Devices used for temperature monitoring should be regularly calibrated. Affected material must be placed into quarantine until the impact of the excursion has been assessed and confirmed by Mylan.

The Investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the study drug. If Mylan supply drug accountability forms these must be used. Alternatively, Mylan may approve use of standard institution forms. In either case, the forms must identify the study drug, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Mylan or designee.

At the end of the study, Mylan will provide instructions as to disposition of any unused investigational drug. If Mylan authorizes destruction at the study site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Mylan. Destruction must be adequately documented.

5.5 Randomization

Assignment of Subject Identification number (SID), randomization number and study drug, as well as site drug inventory control will be managed by an automated Interactive Voice/Web Response system (IVRS/IWRS). A manual containing complete instructions for Web or telephone access and use will be provided to each site prior to study start. At their first clinic visit, the IVRS/IWRS will assign a SID. Each SID will be unique and serve as the primary subject identifier throughout all phases of the study. The SID must appear on all CRF pages, source documents, laboratory data, central spirometry, ECG, diary data, and PRO data. Subjects qualifying to enter the drug treatment phase, will be assigned an additional "randomization number" by the IVRS/IWRS at randomization. Subjects will be allocated to treatment within blocks for the given allocation ratio.

At Visit 3 (Day 1 of dosing), eligible subjects will be randomized to receive 175 mcg revefenacin inhalation solution or matching placebo in a 1:1 ratio through the IVRS/IWRS. The randomization will be stratified according to the subject's concomitant LABA use (Yes, No) and reversibility to ipratropium (Yes, No).

5.6 Breaking the Blind

Emergency subject unblinding will be managed by an automated IVRS/IWRS. A manual containing complete instructions for Web or telephone access and use will be provided to each site prior to study start.

5.7 Concomitant Medications

All concomitant medications taken during the study (from signing informed consent to post-study follow-up) must be recorded with indication, daily dose, and start and stop dates of administration in the CRF. All subjects will be questioned about concomitant medication at each clinic visit and at follow up.

Medications taken within 28 days prior to screening and prior to dosing with study medication will be documented as a prior medication. Medications taken after dosing with study medication will be documented as concomitant medications.

Subjects will abstain from all prohibited medications as described in the exclusion criteria section of this protocol (Section 4.2.2). Use of prohibited medication during the study will be deemed a protocol deviation and such subjects will be assessed by Mylan or designee regarding potential need to early terminate study drug (e.g., for safety reasons – see Section 4.2.4).

Prior to the ipratropium reversibility testing during screening, short acting bronchodilators must be withheld for ≥6 hours.

Inhaled maintenance corticosteroid therapy will be continued at the allowed maintenance dose throughout the treatment and washout periods. Salbutamol will be allowed as required (or "PRN") during the study. Salbutamol must be withheld for ≥6 hours before the first spirometry performed at each study visit and during the course of the entire visit when serial spirometry is performed.

Use of salbutamol as a rescue medication (number of daily puffs) will be documented in the daily diary and recorded in the eCRF. If a subject has used rescue medication on the same day as the clinic visit, prior to spirometry assessments, then both the number of puffs and the time of administration will be documented to allow evaluation of impact, if any, on spirometry measurements.

Subjects who are receiving a LABA or ICS/LABA (either QD or BID) may be enrolled into the study provided that the dose has been stable for at least 30 days prior to Visit 1 and the steroid component is equivalent to fluticasone propionate ≤1000 mcg/day. For reversibility testing at screening, subjects who are on a QD regimen should not have had their last dose within approximately the last 24 hours, and for those on a BID regimen, not within approximately the last 12 hours, prior to the reversibility test. Once randomized it is important to standardize administration of the subject's LABA or ICS/LABA together with the study drug, as the post-dose spirometry will be measuring the combined effect of receiving the LABA and the study drug. These subjects should administer their LABA or ICS/LABA in the morning after the pre-dose FEV_1 measurement and immediately prior to the nebulization of study drug. This administration should be documented in the source documents on study visit days and subjects should be instructed to follow the same procedure while at home between study visits. If subjects have used their LABA or ICS/LABA less than 24 hours (for QD products) or less than 12 hours (for BID products) prior to study visit spirometry (approximately) instead of taking it in-clinic after pre-dose FEV_1 measurement and immediately prior to study drug nebulization, then the study visit should be rescheduled.

Table 5-1 lists the medications that require washout or modification. These medications are also prohibited throughout the study to completion of Visit 6 inclusive. Subjects will be permitted to restart their routine medications after the completion of Visit 6.

Table 5-1: Restricted Medications

Medication	Washout Required (or Modification) and Prohibited Time Period
Any ICS at a dose of >1000 mcg/day fluticasone propionate or equivalent.	Subjects on a dose >1000 mcg/day fluticasone propionate or equivalent should have their dose modified to be on a stable dose of ≤1000 mcg fluticasone propionate or equivalent for at least 30 days prior to the Ipratropium Reversibility test at screening and continued through to end of V6.
LAMA – e.g., tiotropium, glycopyrronium bromide, aclidinium, umeclidinium. **PDE4 inhibitors** – roflumilast.	7 days prior to the Ipratropium Reversibility test at screening and prohibited during the course of the study through to end of V6.
LABA – e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol, vilanterol, olodaterol. **ICS/LABA** products, e.g., salmeterol/fluticasone propionate, vilanterol/fluticasone furoate, formoterol/budesonide. **LAMA/LABA** combination products, e.g., umeclidinium/vilanterol. **LAMA/ICS/LABA** combination products, e.g., umeclidinium/vilanterol/fluticasone furoate.	Subjects on a LABA or ICS/LABA product do not need to be washed out provided they have been on a stable dose for at least 30 days prior to the Ipratropium Reversibility test at screening and this is continued through to end of V6. The steroid component should be ≤1000 mcg/day fluticasone propionate or equivalent. Subjects should abstain from LABA use prior to performing the Ipratropium Reversibility test, however (i.e., 24 hours for QD LABAs and 12 hours for BID LABAs). Subjects on a LAMA/LABA combination need to be switched to the LABA only product at least 7 days prior to the Ipratropium Reversibility test at screening and maintained during the course of the study through to end of V6. Subjects on a LAMA/ICS/LABA combination need to be switched to the ICS/LABA product at least 7 days prior to the Ipratropium Reversibility test at screening and maintained during the course of the study through to end of V6.
Oral theophyllines e.g., theophylline, aminophylline.	12 hours prior to the Ipratropium Reversibility test at screening. Theophyllines must be withheld at least 12 hours prior to any spirometry and during the entire visit when serial spirometry is being performed.
Oral leukotriene inhibitors e.g., montelukast, pranlukast. **Other antimuscarinic medications** e.g., atropine, cyclopentolate, homatropine, hyoscine, tolterodine, oxybutynin and/or tropicamide.	48 hours prior to the Ipratropium Reversibility test at screening and prohibited during the course of the study through to end of V6.
Sodium cromoglycate **Nedocromil sodium**	24 hours prior to the Ipratropium Reversibility test at screening and prohibited during the course of the study through to end of V6.

Medication	Washout Required (or Modification) and Prohibited Time Period
Short acting beta-agonists **Short acting anti-muscarinics**	6 hours prior to the Ipratropium Reversibility test at screening. Subjects will be provided with salbutamol to be used as rescue medication during screening and throughout the course of the study. Salbutamol must be withheld at least 6 hours prior to any spirometry performed during the study and during the entire visit when serial spirometry is being performed. Short acting anti-muscarinics must be washed out (at least 8 hours) prior to the Ipratropium Reversibility test and are prohibited during the course of the study through to V6.
Oral or parenteral corticosteroids	28 days prior to Screening (V1) and prohibited during the course of the study through to V6. If oral/parenteral corticosteroids are required to treat an AECOPD during the study, the subject should be withdrawn because of the AECOPD. If oral/parenteral corticosteroids are required for treatment of any other non-respiratory condition, then the subject's continued participation in the study will be assessed on a case-by-case basis. (Intranasal, topical, and ophthalmic corticosteroids are permitted throughout the study).
Oral beta agonists	48 hours before each visit where spirometry is performed.
OATP1B1 and OATP1B3 inhibitors, e.g., rifampicin, cyclosporine.	28 days prior to Screening (V1) and prohibited during the course of the study through to V6.

In addition to the prohibited concomitant medications listed in Table 5-1, subjects should not be taking any other medications that are not part of a stable regimen. Prior to randomization, subjects should not be considered if they have a known hypersensitivity to a similar drug class as revefenacin and/or a history of hypersensitivity to drugs with a clinically significant reaction. Any PRN medications for conditions other than COPD must be approved by the Investigator.

5.8 Recommended Procedure in a Subject Experiencing Adverse Effects Secondary to Excessive Pharmacological Effects of Study Drug

High doses of revefenacin may lead to anti-cholinergic signs and symptoms such as dry mouth, constipation, urinary retention, bowel obstruction, dilated pupils, blurred vision, increased heart rate, decreased sweating, impaired concentration, confusion, attention deficit, and memory impairment.

Treatment of over dosage consists of discontinuation of revefenacin together with institution of appropriate symptomatic and/or supportive therapy.

6 STUDY CONDUCT

Subjects eligible for study recruitment will have the nature, purpose, and risks of the study explained to them by the Investigator. They will be provided with a written copy of the informed consent form (ICF) for the study and given sufficient time to consider the study's implications before deciding to participate. Subjects agreeing to participate in the study will sign the ICF and be given a duplicate copy before undergoing any screening or pre-screening (if required) procedures. A unique SID will be issued at the time of consent by IVRS/IWRS system.

Once a subject is randomized in this trial the site will make every effort to retain the subject for the planned duration of the trial. Clinical trial site staff are responsible for developing and implementing support and retention plans. Elements of this plan may include the following.

- Thorough explanation of the complete clinical trial visit schedule and procedural requirements during the informed consent process and re-emphasis at each clinic visit.
- A simple explanation of the key data and key time points that are critical for the trial's successful analysis, and the importance of all the treatment groups to the overall success of the trial.
- Discussion at screening, and subsequent regular review of possible barriers to clinic visit attendance and full study participation and compliance.
- Collection of contact information at screening (address, phone numbers, email), which is regularly reviewed at subsequent clinic visits.
- Use of appropriate and timely study visit reminders.
- Immediate and multifaceted follow-up on missed clinic visits, including the possible use of trained staff to complete in-person contact with subjects at their homes.

In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject so that they can appropriately be withdrawn from the study. All contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the CRF. Regardless of site plans to support and retain subjects within the trial, subjects may voluntarily withdraw from the trial for any reason and at any time.

For a subject that completes the study and all procedures it is anticipated that the duration of study would be approximately 4 months.

For details and timings of assessments, refer to Section 6.4.

6.1 Screening Procedures

Each prospective subject must agree to participate in screening procedures by signing the most recent ICF before any screening procedure is initiated. The Principal Investigator or

Medical Sub-Investigator will review the inclusion and exclusion criteria to confirm eligibility of each subject prior to randomization. This should be documented in the subject's source documentation.

6.1.1 Screening (Visits 1 and 2)

Subjects will commence screening procedures within 30 days prior to randomization, to confirm that they meet the selection criteria for the study. If the time between screening procedures and potential randomization exceeds 30 days as a result of unexpected delays, then the subject will need to be discussed with Mylan or designee to consider potential for re-screening (if re-screening is agreed, the subject will need to be reconsented and assigned a new SID via IVRS/IWRS). Re-screening for other reasons may be possible following discussion with Mylan or designee. If re-screening occurs this will be clearly documented within the site file.

The assessments for Visit 1 and Visit 2 may be conducted on the same day if the subject does not require washout of other COPD medications (e.g., 7 day washout for LAMAs: see Table 5-1 for more a more comprehensive list) prior to the spirometry assessments.

At Screening Visit 1 (Week – 2: Day -30 to Day -4 prior to Visit 3), the following will be completed in the specified order:

- Written informed consent.
- IVRS/IWRS registration.
- Complete demographics and medical history, including COPD, smoking, and exacerbation history. Exacerbation history includes the number of exacerbations and if they resulted in hospitalization or use of medication to treat and categorization per the descriptions in Section 6.4.8.1.1. If the subject's smoking status changes during the study this should be recorded in the CRF.
- Complete history of all prescription or non-prescription drugs, dietary supplements, and Traditional Chinese Medicines taken within 28 days prior to consent. History of alcohol or illicit drug use.
    - Ensure the subject is able to discontinue restricted medications (Section 5.7).
    - Ensure sufficient washout of COPD medications per Table 5-1.
- General physical examination, including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.
- Measure height and weight.
- Record vital signs – supine or semi-recumbent blood pressure and pulse rate.
- Record 12-lead ECG – supine or semi-recumbent (single measurement).
- Urine or serum pregnancy test (if female of child-bearing potential).

- Urinalysis (dipstick for blood, protein etc.). Sample to be sent for microscopy/culture if positive for blood, protein, nitrites or leukocyte esterase.
- Blood will be collected for safety laboratory tests. Laboratory tests at screening include confirmation of non-child bearing potential in any female who is 45 years of age and above who has been amenorrheic for less than 2 years, via serum FSH.
- Assess and record AEs (AEs are to be recorded starting from signature of consent).
- Check study inclusion/exclusion criteria.
- Dispense rescue medication (salbutamol pMDI) and train the subject (and caregiver, if applicable) on its use.
- Dispense daily diary.
- If results for a chest X ray or thoracic high resolution CT that was performed within 12 months prior to screening are not available, schedule and perform a chest X-ray so that the results are available prior to randomization.
- Schedule Visit 2 (if required) and remind the subject of lifestyle, study drug and concomitant medication requirements for visits.

Subjects may be discharged from the clinic following completion of all assessments.

At Screening Visit 2 (week -1; 7 (Day -10 to Day -4 prior to Visit 3), the following will be completed in the specified order:

- Review and record concomitant medications.
- Ensure sufficient washout of restricted medications per Table 5-1 prior to spirometry assessments.
- Spirometry reversibility testing pre- and post-dosing with ipratropium. Spirometry (FEV_1, FVC) will be performed pre-dose after withholding bronchodilators as specified in Table 5-1 and 45 minutes after dosing with 500 mcg ipratropium solution for inhalation administered by jet nebulizer.
- Assess and record AEs.
- Review rescue medication use recorded in daily diary. Rescue medication use should be recorded as the number of doses per day, where each puff of salbutamol is one dose.

6.2 Treatment Phase

6.2.1 Visit 3 (Day 1)

Procedures will be completed in the following order:

- Ensure sufficient washout of restricted medications per Table 5-1 prior to spirometry assessments.

- Complete the following questionnaires in this sequence: BDI, mMRC, SGRQ.
- Assess and record AEs.
- Review and record concomitant medications.
- Collect and review rescue medication use recorded in daily diary.
- Record vital signs – supine or semi-recumbent blood pressure and pulse rate – pre-dose.
- Record 12-lead ECG (single measurement; supine or semi-recumbent) pre-dose. ECG must be performed prior to spirometry and blood sampling if scheduled at the same timepoint.
- Urine or serum pregnancy test (if female of child-bearing potential).
- Blood will be collected within 30 minutes pre-dose for PK analysis.
- Spirometry (FEV_1, FVC) at -45 and -15 minutes pre-dose
    - Note that to be eligible for the study the spirometry measures must fully meet the ATS/ERS guidelines for quality and reproducibility.
- Review inclusion and exclusion criteria.
- Randomization via IVRS/IWRS (subject eligibility must be confirmed and documented by Investigator before randomizing subject). Dispense study drug via IVRS/IWRS.
- Training the subject and/or caregiver for use and maintenance of the nebulizer for study drug administration.
- Administer LABA or ICS/LABA if the subject is taking one of these drugs.
- Study drug dosing via nebulizer. Dosing time will be recorded in date, hours, and minutes corresponding to the start and completion of nebulization. Pre-dose assessment time is defined relative to the start of nebulization. Post-dose assessment time is defined relative to the completion of nebulization. Study drug administration must be performed in a different room from that used for PK blood sampling and processing to avoid contamination of PK samples.
- Spirometry (FEV_1, FVC) at the following times post-dose: 5, 15, and 30 minutes, and 1, 1.5, and 2 hours.
- Blood will be collected at any time between 1 – 30 minutes post-dose for PK analysis. The actual PK sampling time will be recorded in date, hours, and minutes.
- Record vital signs – supine or semi-recumbent blood pressure and pulse rate – at approximately 1 hour post-dose.

- Record 12-lead ECG - supine or semi-recumbent (single measurement) at approximately 1 hour post-dose. ECG must be performed prior to spirometry and blood sampling if scheduled at the same timepoint.
- Dispense rescue medication as needed.
- Dispense daily diary.

6.2.2 Visit 4 (Day 29 ± 7 days)

Procedures will be completed in the following order:

- Ensure sufficient washout of restricted medications per Table 5-1 prior to spirometry assessments.
- Complete the following questionnaire: TDI.
- Assess and record AEs.
- Review and record concomitant medications.
- Compliance check for study drug via drug returns or daily diary.
- Collect and review rescue medication use recorded in daily diary.
- Urine or serum pregnancy test (if female of child-bearing potential).
- Dispense study drug via IVRS/IWRS.
- Spirometry (FEV_1, FVC) at -45 and -15 minutes pre-dose.
- Blood will be collected within 30 minutes pre-dose for PK analysis.
- Administer LABA or ICS/LABA if the subject is taking one of these drugs.
- Study drug dosing via nebulizer. Dosing time will be recorded in date, hours, and minutes corresponding to the start and completion of nebulization. Pre-dose assessment time is defined relative to the start of nebulization. Post-dose assessment time is defined relative to the completion of nebulization. Study drug administration must be performed in a different room from that used for PK blood sampling and processing to avoid contamination of PK samples.
- Blood will be collected at any time between 1 – 30 minutes post-dose for PK analysis. The actual PK sampling time will be recorded in date, hours, and minutes.
- Dispense rescue medication as needed.
- Dispense daily diary.

6.2.3 Visit 5 (Day 57 ± 7 days)

Procedures will be completed in the following order:

- Ensure sufficient washout of restricted medications per Table 5-1 prior to spirometry assessments.
- Complete the following questionnaire: TDI.
- Assess and record AEs.
- Review and record concomitant medications.
- Compliance check for study drug via drug returns or daily diary.
- Collect and review rescue medication use recorded in daily diary.
- Urine or serum pregnancy test (if female of child-bearing potential).
- Dispense study drug via IVRS/IWRS.
- Spirometry (FEV_1, FVC) at -45 and -15 minutes pre-dose.
- Blood will be collected within 30 minutes pre-dose for PK analysis.
- Administer LABA or ICS/LABA if the subject is taking one of these drugs.
- Study drug dosing via nebulizer. Dosing time will be recorded in date, hours, and minutes corresponding to the start and completion of nebulization. Pre-dose assessment time is defined relative to the start of nebulization. Post-dose assessment time is defined relative to the completion of nebulization. Study drug administration must be performed in a different room from that used for PK blood sampling and processing to avoid contamination of PK samples.
- Blood will be collected at any time between 1 – 30 minutes post-dose for PK analysis. The actual PK sampling time will be recorded in date, hours, and minutes.
- Dispense rescue medication as needed.
- Dispense daily diary.

6.2.4 Visit 6, EoT (Day 85 ± 7 days)

Procedures will be completed in the following order:

- Ensure sufficient washout of restricted medications per Table 5-1 prior to spirometry assessments.
- Complete the following questionnaires in this sequence: TDI, SGRQ.
- Assess and record AEs.
- Review and record concomitant medications.
- Compliance check for study drug via drug returns or daily diary.

- Collect and review rescue medication use recorded in daily diary.
- Record vital signs – supine or semi-recumbent blood pressure and pulse rate – pre-dose.
- Record 12-lead ECG – supine or semi-recumbent (single measurement) pre-dose. ECG must be performed prior to spirometry and blood sampling if scheduled at the same timepoint.
- Urine or serum pregnancy test (if female of child-bearing potential).
- Blood and urine will be collected for safety laboratory tests.
- Blood will be collected within 30 minutes pre-dose for PK analysis.
- Spirometry (FEV_1, FVC) at -45 and -15 minutes pre-dose.
- Administer LABA or ICS/LABA if the subject is taking one of these drugs.
- Study drug dosing via nebulizer. Dosing time will be recorded in date, hours, and minutes corresponding to the start and completion of nebulization. Pre-dose assessment time is defined relative to the start of nebulization. Post-dose assessment time is defined relative to the completion of nebulization. Study drug administration must be performed in a different room from that used for PK blood sampling and processing to avoid contamination of PK samples.
- Spirometry (FEV_1, FVC) at the following times post-dose: 5, 15, and 30 minutes, and 1, 1.5, and 2 hours.
- Blood will be collected at any time between 1 – 30 minutes post-dose and an additional sample will be collected during the sampling interval of 1 – 4 hours post-dose for PK analysis. The actual PK sampling time will be recorded in date, hours, and minutes.
- Record vital signs – supine or semi-recumbent blood pressure and pulse rate – at approximately 1 hour post-dose.
- Record 12-lead ECG – supine or semi-recumbent (single measurement) at approximately 1 hour post-dose. ECG must be performed prior to spirometry and blood sampling if scheduled at the same timepoint.
- General physical examination, including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.

6.2.5 Early Study Drug Termination (ET) Visit

Subjects may request termination of study drug or withdrawal from the study at any time, or be required to withdraw or terminate study drug by the Investigator or Sponsor for reasons as per Section 4.2.4. If study drug is terminated or the subject withdraws or is withdrawn, the reason for termination/withdrawal should be established and recorded. If a subject does not

return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document the outcome of subject contact attempt, if possible. The Investigator will contact Mylan or designee in the event that a subject fails to complete the study or violates the protocol.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

Unless consent is withdrawn, subjects who prematurely terminate study drug will be asked to return to the clinic for an ET visit and will have this scheduled as soon as possible after their last dose of study drug.

At the ET visit the following procedures will be completed:

- Complete the following questionnaires in this sequence: TDI, SGRQ.
- Record vital signs – supine or semi-recumbent blood pressure and pulse rate.
- Record 12-lead ECG – supine or semi-recumbent (single measurement). ECG must be performed prior to spirometry and blood sampling.
- Urine or serum pregnancy test (if female of child-bearing potential).
- Blood and urine will be collected for safety laboratory tests.
- General physical examination, including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.
- Review and record concomitant medications.
- Collect and review rescue medication use recorded in daily diary.
- Two spirometry (FEV_1, FVC) assessments corresponding to -45 and -15 minutes pre-dose assessments at previous visits.
- Assess and record AEs.

Subjects may be discharged from the clinic at the discretion of the Investigator following completion of all ET assessments.

6.3 Follow Up (telephone call 7-14 days after the last dose of study medication [EoT Visit])

- Review and record concomitant medications
- Assess and record AEs.

Subjects who have a follow-up call will be reminded that AEs should be reported to the study staff up to 30 days after the last dose of study medication.

6.4 Treatment Procedures

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases the Investigator or designated representative will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the Investigator or designated representative will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The Mylan study team will be informed of these incidents in a timely fashion.

Activities specific to this protocol are expanded upon further below.

6.4.1 Blood Volume

Total blood sampling volume for an individual subject is estimated in Table 6-1 below. Additional blood samples may be taken for safety assessments, provided the total volume taken during the study does not exceed 300 mL (or the total volume permitted in the local region) during any period of 30 consecutive days, and the ethics committee/IRB is notified of the blood collection.

Table 6-1: Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times		Total Volume (mL)
		Screening	Study Period	
Safety Labs	20	1	1	40
PK	6	0	9	54
TOTAL				**94**

6.4.2 Spirometry

Standardized, centralized spirometry equipment will be provided to the sites.

Spirometry will be performed in accordance with the ATS/ERS guidelines (Graham et al., 2019 [7]) using standardized equipment to ensure quality, reproducibility and repeatability. Spirometers will be calibrated according to manufacturer's guidelines.

Spirometry testing should be performed in the seated position, with nose clips and the subject should remain in an upright position (not bending forward) while performing the maneuvers. Sufficient forced expiratory maneuvers (up to a maximum of 8) will be performed at each session to produce a minimum of 3 technically acceptable and reproducible traces. The largest FEV_1 and greatest FVC measured from technically acceptable and repeatable measurements will be recorded.

Spirometry data that is judged not to be of sufficient quality, e.g., those demonstrating clear hesitation or cough within the first second of measurement will not be acceptable for use.

Spirometry data will be assessed and over-read centrally for quality purposes by a spirometry vendor.

Acceptable repeatability is achieved when the difference between the largest and the next largest FVC is ≤0.150 L and the difference between the largest and next largest FEV_1 is ≤0.150 L. For those with an FVC of ≤1.0 L, both these values are 0.100 L.

If repeatability is not achieved after up to 8 attempts but the trace selected is of sufficient quality, i.e., there are no significant artefacts, this can still be utilized in the data analyses and will not be considered a protocol deviation.

However, at Visit 3 the two pre-dose assessments must meet all quality and repeatability requirements as described above for the subject to be eligible.

The FEV_1 will be recorded as absolute volume in liters (recorded and reported to at least 3 decimal places) and, during Screening only the post-ipratropium FEV_1, in terms of percent of predicted normal values according to age, height, race and sex using the Global Lung Function Initiative reference range programmed in the centralized spirometry equipment (Quanjer et al., 2012 [8]).

At each visit where spirometry is scheduled, subjects will be required to withhold salbutamol for 6 hours prior to the first session of spirometry maneuvers and other COPD medications per Table 5-1.

A single spirometry session will be conducted for pre- and post-bronchodilator measurements at Screening (Visit 2) but two pre-dose spirometry sessions will be conducted at Visit 3 (Day 1) through to Visit 6 (Day 85), with assessments at approximately -45 and -15 minutes prior to dosing (subjects should rest for at least 10 minutes between sessions).

At Visit 3 (Day 1) and Visit 6 (Day 85), all subjects will perform spirometry assessments up to 2 hours post-dose (time points 5, 15, and 30 minutes, and 1, 1.5, and 2 hours; single sessions at each time point). Spirometry should be commenced at the nominal time ±10% (for example 60 ±6 minutes).

- If a subject needs to use rescue medication during the serial spirometry session, the time of dosing must be recorded and a protocol deviation documented.

6.4.3 Bronchodilator Reversibility

Bronchodilator reversibility will be performed at Visit 2 with ipratropium 500 mcg solution for inhalation administered by jet nebulizer, after withholding short-acting bronchodilators for at least 6 hours and other restricted medication for the periods specified in Table 5-1. If the subject has not observed the required withholding interval, then the visit should be rescheduled.

Spirometry will be performed pre-dose and 45 minutes after dosing with ipratropium. Reversibility to ipratropium is defined as a post-bronchodilator increase of ≥12% and at least a 200 mL increase in FEV_1.

6.4.4 Baseline Dyspnea Index (BDI)/Transition Dyspnea Index (TDI)

At Visit 3 (Day 1), Visit 4 (Day 29), Visit 5 (Day 57), Visit 6 (Day 85), and/or the Early Termination visit (if applicable), the subject's dyspnea will be assessed using the interviewer-administered BDI/TDI with the result recorded in the CRF.

The BDI scores the magnitude of effort, types of tasks, both work and non-work, which make the patient breathless, as well as the level of functional impairment. The TDI measures changes from this baseline state.

The BDI will be administered at Visit 3 (Day 1), the TDI will be administered at subsequent visits.

The assessments should be administered at the start of the visit, with the same interviewer administering the assessment for an individual subject at each visit, where possible.

Further details of the BDI/TDI are described in Section 11.1.

6.4.5 Modified Medical Research Council Dyspnea Scale (mMRC)

At Visit 3 (Day 1), the subject's level of dyspnea based on the mMRC dyspnea scale will be administered by study staff with the result recorded in the CRF.

The mMRC assessment will be administered after the BDI/TDI.

Further details of the mMRC are described in Section 11.2.

6.4.6 St. George's Respiratory Questionnaire (SGRQ)

At Visit 3 (Day 1), Visit 6 (Day 85), and/or the Early Termination visit (if applicable), the subject's COPD health status based on the SGRQ will be administered by study staff with the result recorded in the CRF.

The SGRQ will be administered after the mMRC.

Further details of the SGRQ are described in Section 11.3.

6.4.7 Pharmacokinetics

Population PK sampling will be performed in subjects within 30 minutes pre-dose and at any time 1 - 30 minutes post-dose at Visits 3, 4, 5, and 6. An additional PK sample will be collected any time during a sampling window of 1 - 4 hours post-dose at Visit 6. The post-dose sampling time is relative to the end of nebulization. Blood samples for plasma PK assay will be collected, centrifuged, and split into two aliquots; each will be sent to the assay laboratory as directed by the Sponsor in separate shipments. The actual date and time of the sample collection (in date, hour, and minute) must be recorded.

PK blood sampling and processing must be performed in a different room from that used for study drug administration to avoid contamination of PK samples.

Detailed procedures for the collection of plasma PK samples are provided in the Central Lab Manual.

6.4.8 Safety Testing

6.4.8.1 Adverse Event Assessment

If a subject reports any symptoms before drug administration, they will be evaluated by medical staff and necessary measurements will be performed. The Principal Investigator or Medical Sub-Investigator will be notified before dosing to determine the course of action.

Findings from screening procedures, e.g., laboratory tests or physical examinations will be recorded as medical history. Clinically significant changes from the screening procedures will be recorded as adverse events.

Subjects will be routinely queried in regard to the presence or absence of adverse events using open ended questions. The clinic will provide documentation of any adverse events in the subject's CRF. The adverse event source documentation will minimally include the following information: date and time of assessment, the outcome of the response, and identification of the clinic staff member collecting the information.

Adverse events of special interest relevant to anti-muscarinic effects, given the treatment class of revefenacin, include the following:

- Constipation
- Dry mouth
- Dysuria
- Worsening of urinary retention
- Worsening of narrow-angle glaucoma

6.4.8.1.1 Acute Exacerbation of COPD (AECOPD)

Throughout the study, subjects will be encouraged to spontaneously report symptoms and respiratory medication increase or change that may signify worsening of disease, including AECOPD. Subjects should be evaluated by study staff at each visit for AECOPD events since the preceding visit.

An AECOPD is defined as an acute event in the natural course of the disease, warranting a change in the subject's regular medication specifically to address the exacerbation event, characterized by:

1. Worsening, beyond normal day-to-day variation, of two or more of the following major symptoms for at least two consecutive days:
   - Dyspnea.
   - Sputum volume.
   - Sputum purulence.

   or

2. Worsening, beyond normal day-to-day variation, of any one major symptom outlined above plus any one of the following minor symptoms for at least two consecutive days:

    - Sore throat.
    - Colds (nasal discharge and/or nasal congestions).
    - Fever without other cause.
    - Increased cough.
    - Increased wheeze.

The severity of a COPD exacerbation should be categorized using the definitions outlined below.

- **Mild exacerbation**: worsening symptoms that are managed with bronchodilators but do not require use of antibiotics or oral or systemic (e.g., intravenous, intramuscular) corticosteroids.
- **Moderate exacerbation**: worsening symptoms that require treatment with oral/systemic corticosteroids and/or antibiotics, but do not require in-patient hospitalization (i.e., admission).
- **Severe exacerbation**: worsening symptoms of COPD that require treatment with in-patient hospitalization (i.e., admission).

An AECOPD should be recorded as an AE.

If an exacerbation starts off mild but progresses in severity, the exacerbation should be classified by its highest level of severity. Two mild exacerbations can, at Investigator discretion, be combined into one if the two exacerbations are separated by no more than 3 exacerbation free days.

Subjects that experience a moderate or severe AECOPD should be discontinued from the study.

6.4.8.2 Laboratory Safety

The following safety laboratory tests will be performed and the data recorded in the CRF at times defined in the study schedules in Table 1-1 and Section 6.

Table 6-2: Laboratory Safety Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea and Creatinine Glucose (non-fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) AST, ALT Total Bilirubin Direct/Indirect bilirubin Alkaline phosphatase Uric acid Albumin Total protein CRP	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy/culture[a]	Serum FSH[b] Urine hCG[c,d] Breath/blood alcohol test[e]

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

b. Females who are 45 years of age and above who are amenorrheic for less than 2 years at Screening.

c. At Screening, at visits 3-6, and the Early Termination visit, if applicable.

d. Urine or serum hCG for females of childbearing potential.

e. At the Investigator's discretion an alcohol test may be performed. Where necessary blood or breath alcohol tests can be performed.

Hematology and chemistry will be analyzed by local laboratory. Urinalysis will be conducted by dipstick at site and if urine is positive for blood, protein, nitrites, or leukocyte esterase, will be analyzed via microscopy/culture by a local laboratory.

Any clinically significant findings in laboratory safety data should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.4.8.3 Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in Study Schedule (Table 1-1) and the results will be recorded in the CRF.

Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine or semi-recumbent blood pressure will be measured with the subject's arm supported at the level of the heart and recorded to the nearest mmHg after 5 minutes of rest. The same arm (preferably the dominant arm) and the same posture (i.e., supine or semi-recumbent) will be used throughout the study for each individual subject.

The same size blood pressure cuff, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring blood pressure (BP) and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

Any clinically significant changes in blood pressure and pulse rate should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.4.8.4 12-lead ECG

In this study, 12-lead ECGs will be recorded using appropriately calibrated ECG devices. ECGs should be collected at times specified in the Study Schedule (Table 1-1) and the results will be recorded in the CRF or transferred directly to the database.

All 12-lead ECGs will be single recordings.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine or semi-recumbent position. The same posture (i.e., supine or semi-recumbent) will be used throughout the study for each individual subject. Pre-dose ECGs should be performed prior to commencing pre-dose spirometry and blood sampling.

To ensure safety of the subjects, a medically qualified individual at the site will assess ECG recordings and make any comparisons to baseline measurements.

At screening, the QTcF must be ≤500 msec, and the ECG must show no clinically significant rate or rhythm abnormalities for the subject to be eligible (See Section 4.2.2).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

Any clinically significant ECG abnormalities measured at screening should be assessed for their effects on subject eligibility of the study and recorded in medical history. Any clinically significant changes between the screening and subsequent ECGs should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.4.8.5 General Physical Examination

A full general physical examination will consist of an examination of the respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland by trained medical personnel at the site. A full physical examination will be performed at Visit 1 (Screening) and Visit 6 (Day 85) or at an Early Termination visit, if applicable.

Physical examination results will be recorded in the CRF.

Height and weight will be assessed at Visit 1.

Any clinically significant finding at Screening (Visits 1 and 2) should be recorded under medical history and changes between Screening (Visits 1) and subsequent examinations should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.5 Restrictions

Study restrictions include all items listed in the Lifestyle Guidelines (Section 4.3) and the concomitant medications as described in the Exclusion Criteria (Section 4.2.2) and the Concomitant Medications (Section 5.7) sections of this protocol and will be prohibited throughout the duration of the study. If concomitant medications change during the study, a discussion between the Principal Investigator or a Medical Sub-Investigator along with Mylan should occur, and a decision to continue or discontinue the subject will be made based on the medication's pharmacology and pharmacokinetics.

6.6 Mitigation in the event of a public health emergency

In the event of any circumstances impacting the ability of enrolled subjects to attend for scheduled visits at the investigator site, such as travel restrictions imposed due to COVID-19, investigators must notify the Sponsor and make the necessary arrangements to ensure the safety of their enrolled subjects. They should also evaluate whether their subjects should continue in the clinical trial. Those that have not been randomized yet should be withdrawn from the study.

Where it is possible for randomized subjects to continue, the following operational contingencies will be implemented:

- Study medication, rescue medication, and other study supplies such as diary cards will be sent to the subject's residence to ensure sufficient quantities are available.

- Virtual visits will be conducted by telephone in place of the scheduled visits, whereby the investigator will perform those procedures specified in Section 6.2 that are feasible to be performed by telephone, such as questioning on adverse events, concomitant medications, and rescue medication use, completion of TDI, etc).

- Subjects will be reminded to bring (or send) all used and unused study medication, rescue medication, and diary cards to the site as soon as they are able after travel restrictions have been lifted.

Protocol deviations arising under such circumstances (eg, missed or delayed visits, assessments not performed, etc) will be clearly documented in the CRF and the reasons will be collected.

7 STATISTICAL ANALYSIS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the Sponsor. This will include any plans for summarizing and analyzing data impacted by a public health emergency. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

7.1 Sample Size Considerations

The null hypothesis is that there is no difference in the mean change from baseline trough FEV_1 on Day 85 between revefenacin and placebo. The alternative hypothesis is that there is a difference.

The estimate for the difference in mean change from baseline trough FEV_1 at Day 85 and the common standard deviation are based on the sample size assumptions for the revefenacin US pivotal studies (0126 and 0127) in a Western population and the GLOW7 study - a similarly designed study in a predominantly Chinese population (Wang et al., 2015 [5]).

A sample size of 256 evaluable subjects (128:128; a 1:1 ratio of revefenacin to placebo) is required to provide at least 90% power to detect a difference between revefenacin and placebo of 100 mL in the analysis of the change from baseline trough FEV_1 at Day 85 assuming a standard deviation of 245 mL and a two-sided 5% significance level.

To allow for an anticipated 20% dropout rate, approximately 320 subjects in total will be randomized. In the event of a public health emergency such as COVID-19, the Sponsor may consider increasing enrollment to overcome any additional loss of information for the primary endpoint due to the inability of subjects to attend for scheduled clinic visits. The maximum number of subjects to be randomized under such circumstances will be limited to 428 (an additional 20% increase in enrollment).

7.2 Analysis Set Definitions

7.2.1 Safety Analysis Set

The safety analysis set (SS) will include all subjects who received at least one dose of study drug. Data will be summarized according to the treatment a subject actually received.

7.2.2 Full Analysis Set

The full analysis set (FAS) will include all randomized subjects who received at least one dose of study drug and have at least one recorded post-baseline efficacy assessment. Data will be summarized and analyzed according to the treatment a subject was assigned to receive at randomization.

7.2.3 Per Protocol Analysis Set

The per protocol analysis set (PP) will include all subjects in the FAS who had no major protocol violation that would impact significantly on the primary efficacy endpoint. The list of major protocol deviations will be finalized prior to database lock. All decisions to exclude subjects from the PP analysis set will be made prior to unblinding in the final blinded data review (BDR) meeting and report. Data will be summarized and analyzed according to the treatment a subject actually received at randomization.

7.2.4 Population Pharmacokinetic Analysis Set

The population pharmacokinetic analysis set (PPK) will include all subjects who receive at least one dose of study medication and who provide at least one post dose concentration sample for the Population PK analysis. All analyses using the PPK set will group subjects according to treatment actually received.

7.3 Primary Endpoints

7.3.1 Definition of Primary Endpoints

The primary efficacy endpoint is the change from baseline trough FEV_1 on Day 85.

- Baseline FEV_1 is defined as the average of the -45 and -15 minute measurements prior to dosing of study medication on Day 1 (Visit 3).
- Trough FEV_1 measurements will be the pre-dose FEV_1 measures on Day 29, 57 and 85 calculated as the average of the -45 and -15 minute measurements prior to dosing of study medication.
- If a public health emergency prevents FEV_1 data from being measured at site then information on the reasons for the missing assessments will be recorded in the CRF.

7.3.2 Statistical Methodology for Primary Endpoints

The analysis of the primary endpoint will be based on a mixed model repeated measures (MMRM) analysis including changes from baseline trough FEV_1 measurements on Days 29, 57 and 85 as the dependent variable. The model will include independent fixed-effect terms for concomitant LABA use, reversibility to ipratropium, smoking status, age, sex, treatment and baseline FEV_1 as a covariate. A time effect (visit) and its interaction terms with treatment and baseline FEV_1 will be included. The variance estimation will be based on an unstructured covariance matrix. The Kenward-Roger method for approximating the denominator degrees of freedom will be used.

7.3.3 Primary Analysis for Primary Endpoint

The primary analysis of the primary efficacy endpoint will be based on the FAS population and includes all randomized subjects who received at least one dose of study drug and have at least one recorded post-baseline FEV_1 assessment. Available data for a subject prior to discontinuing study treatment will be used in the MMRM analysis. Missing data is assumed as missing at random (MAR). The robustness of the conclusions to this assumption will be assessed with a missing data sensitivity analysis.

The difference between revefenacin and placebo on Day 85 will be estimated from the least squares means (LSmeans) along with the 95% confidence interval (CI) and associated 2-sided p-values.

7.3.4 Secondary/Sensitivity Analyses for Primary Endpoint

The same primary analysis model will be replicated in the PP population.

A sensitivity analysis using a two-dimensional tipping point imputation method will be applied to the MMRM analysis (FAS population) to assess the robustness of the conclusions to the assumption that missing data is MAR. In the tipping point analysis a succession of delta adjustments via multiple imputation methods will be used to impute the missing revefenacin and placebo trough FEV_1 values at each timepoint. The tipping point is denoted as the mean trough FEV_1 value that would have to be imputed to overturn a statistically

significant result. Clinical judgement will be applied to the plausibility of the tipping point. The detail of the imputation method will be included in the SAP.

In addition, missing trough FEV_1 data on Day 85 will be imputed using a Last-Observation-Carried-Forward (LOCF) single imputation method. Change from baseline FEV_1 at Day 85 will be analyzed using an analysis of covariance (ANCOVA) using the FAS population. The model will include independent fixed-effect terms for concomitant LABA use, reversibility to ipratropium, smoking status, age, sex, treatment and baseline FEV_1 as a covariate.

LSmeans for Day 85 will be derived for both treatment groups. The difference between revefenacin and placebo on Day 85 will be estimated from the LSmeans along with the 95% CI and associated 2-sided p-values.

7.3.5 Missing Data

Missing imputed data methods will be performed in the primary and sensitivity analyses as described above for trough FEV_1. Otherwise, missing data will not be imputed.

7.3.6 Sub-Group Analyses

For the primary endpoint the follow subgroups are pre-defined for the purpose of sensitivity analyses:

- Baseline smoking status [current smoker, ex-smoker]
- Age group [<65, >=65 years]
- Sex [Male, Female]
- Reversibility to ipratropium [yes, no]
- Concomitant ICS use [yes, no]
- Concomitant LABA use [yes, no]
- Baseline post bronchodilator % predicted FEV_1 [50% to <80%, 30% to <50%, <30%]
- GOLD categories [A, B, C, D]

Forest plots will be produced for these subgroups. Additional subgroups and analyses may be defined in the SAP.

7.4 Secondary Efficacy Endpoints

In all the secondary efficacy analyses missing data will not be imputed and will be assumed to be missing at random (MAR). Secondary efficacy analyses will be performed using the FAS population. If a public health emergency prevents data from being measured or requires data to be assessed remotely via a virtual visit, then information on the reasons and the data impacted will be recorded in the CRF.

7.4.1 Spirometry

7.4.1.1 Trough FEV_1 on Days 29 and 57

The changes from baseline trough FEV_1 on Days 29 and 57 will be estimated from the MMRM analysis used for the primary analysis of the primary endpoint.

7.4.1.2 Trough FVC on Days 29, 57 and 85

The changes from baseline trough FVC on Days 29, 57 and 85 will be analyzed using the same MMRM analysis described for the primary analysis of the primary endpoint. The baseline FEV_1 covariate will be replaced with the baseline trough FVC recorded on Day 1.

7.4.1.3 Peak FEV_1 (0-2h) on Day 1 and Day 85

Lung function assessments will be made after study treatments (5, 15, and 30 minutes, and 1, 1.5, and 2 hours) on Days 1 and 85.

Analysis of Covariance (ANCOVA) model will be used to assess the difference between treatment groups for change from baseline Peak FEV_1 after the first dose on Day 1. The ANCOVA model will include fixed-effect terms for concomitant LABA use, reversibility to ipratropium, smoking status, age, sex, treatment and baseline FEV_1 as a covariate.

The difference between revefenacin and placebo on Day 1 will be estimated from the LSmeans along with the 95% CI and associated 2-sided p-values.

A separate analysis will be performed for Peak FEV_1 on Day 85 using the same ANCOVA model.

7.4.1.4 Weighted Mean FEV_1 (0-2h) on Day 1 and Day 85

Lung function assessments will be made after study treatments (5, 15, and 30 minutes, and 1, 1.5, and 2 hours) on Days 1 and 85.

The area under the curve (AUC), (0 to 2h) will be calculated using the trapezoidal rule including observed data points from pre-dose (0 hours) through to the 2 hour observation. For all observations the nominal time of the observation should be used. For the calculation of AUC, the first, last and at least one time point between first and last must be available. Otherwise, the AUC is set to missing.

The weighted mean (WM) FEV_1 is derived by dividing AUC by the total time (nominally 2 hours).

An ANCOVA model will be used to assess the difference between treatment groups for WM FEV_1 on Day 1 and Day 85 in separate models. Each ANCOVA model will include fixed-effect terms for concomitant LABA use, reversibility to ipratropium, smoking status, age, sex, treatment and baseline FEV_1 as a covariate.

The difference between revefenacin and placebo on Day 1 and Day 85 will be estimated from the LSmeans along with the 95% CI and associated 2-sided p-values.

7.4.2 Patient Reported Outcomes (PROs)

7.4.2.1 SGRQ on Day 85 (continuous endpoint)

Baseline SGRQ endpoints will be those recorded on Day 1. The change from baseline SGRQ scores on Day 85 will be summarized and analyzed as a continuous endpoint.

An ANCOVA model will be used to assess the difference between treatment groups for change from baseline SGRQ on Day 85. The ANCOVA model will include fixed-effect terms for concomitant LABA use, reversibility to ipratropium, smoking status, age, sex, treatment and baseline SGRQ as a covariate. For subjects who discontinue study treatment, the data from the SGRQ completed at the Early Termination (ET) visit will be carried forward in the analyses.

The difference between revefenacin and placebo on Day 85 will be estimated from the LSmeans along with the 95% CI and associated 2-sided p-values.

7.4.2.2 SGRQ Responders (total score ≥4 units) on Day 85

A decrease from baseline of ≥4 units in SGRQ total score is considered clinically meaningful and will be defined as a responder.

The number and percentage of responders on Day 85 in each treatment group will be summarized. A comparison between revefenacin and placebo will be evaluated with the odds ratio (OR) and corresponding 95% confidence interval from a logistic regression model. The model will include fixed-effect terms for concomitant LABA use, reversibility to ipratropium, smoking status, age, sex, treatment and baseline SGRQ total score as a covariate.

For subjects who discontinue study treatment, the SGRQ completed at the Early Termination (ET) visit will be carried forward and used to derive a responder.

7.4.2.3 BDI/TDI on Days 29, 57 and 85

Baseline BDI score will be recorded on Day 1. The TDI represents changes from baseline and will be recorded on Days 29, 57 and 85.

The TDI focal score will be analyzed using the same MMRM analysis described for the primary analysis of the primary endpoint. The baseline FEV_1 covariate will be replaced with the BDI focal score. Estimates for TDI on Days 29, 57 and 85 will be derived from the model.

The difference between revefenacin and placebo on Days 29, 57 and 85 will be estimated from the LSmeans along with the 95% CI and associated 2-sided p-values.

7.4.2.4 TDI Responders (focal score ≥1 unit) on Days 29, 57 and 85

A TDI focal score of ≥1 unit is considered clinically meaningful and will be defined as a responder.

The number and percentage of responders on Days 29, 57 and 85 in each treatment group will be summarized. A comparison between revefenacin and placebo will be evaluated with the odds ratio (OR) and corresponding 95% confidence interval from a logistic regression model including the proportion of responders at each visit (Days 29, 57 and 85) as the dependent variable. The MMRM logistic model will include the same independent fixed-effect terms as for the primary analysis of the primary endpoint. The baseline FEV_1 covariate will be replaced with the BDI focal score as a covariate. Estimates for the proportion of TDI responders on Days 29, 57 and 85 will be derived from the model.

7.4.3 Rescue Medication Usage

7.4.3.1 Average Count of Salbutamol Puffs Per Day (Days 1-85)

The average count of rescue salbutamol puffs per day will be calculated for each monthly interval by dividing the total salbutamol puff counts for each of the 3 monthly intervals by the total number of days on study for that month.

The average count of salbutamol puffs per day will be analyzed using the same MMRM analysis described for the primary analysis of the primary endpoint with the time variable Month (1, 2, 3) replacing Visit. The average count of salbutamol puffs per day for the study (Days 1-85) will be estimated from the model-derived average of each of the 3 months using an appropriate contrast statement as well as the LSmean differences, 95% CI and associated 2-sided p-values.

7.4.3.2 Percentage of Salbutamol Rescue Free 24h Periods (Days 1-85)

A 24h rescue-free period is defined as a day without a “yes” for rescue use per the daily diary.

The percentage of salbutamol rescue free 24h periods will be calculated for each monthly interval by dividing the number of 24h rescue-free periods for each of the 3 monthly intervals by the total number of days on study for that month.

The percentage of salbutamol rescue free 24h periods will be analyzed using the same MMRM analysis described for the primary analysis of the primary endpoint with the time variable Month (1, 2, 3) replacing Visit. The average percentage of salbutamol rescue free 24h periods for the study (Days 1-85) will be estimated from the model-derived average of each of the 3 months using an appropriate contrast statement as well as the LSmean differences, 95% CI and associated 2-sided p-values.

7.5 Safety Endpoints

Safety endpoints will be summarized using the SS population. There are no planned analyses for the comparison of treatments for the safety endpoints.

7.5.1 Adverse Events

Adverse events will be summarized and listed. All AEs that occur after the first dose of study medication through 30 days after the last dose will be considered to be treatment emergent AEs. The number and percentage of subjects with at least one treatment emergent AE will be presented by treatment group and events further summarized by maximum severity and relationship to study medication. Summary statistics (N, %) of AEs of special interest will be also be separately tabulated.

7.5.2 Acute Exacerbations of COPD (AECOPD)

A summary of acute exacerbations of COPD reported with an AE preferred term of COPD will be descriptively summarized by severity. Exacerbation data will be summarized (N, %) for all exacerbations; moderate and severe exacerbations; and severe only exacerbations.

7.5.3 Other Safety Endpoints

Descriptive statistics will be provided for the following safety data. No inferential analysis of this safety data is planned. Any ECG, BP, and pulse rate abnormalities of potential clinical concern will be described.

7.5.3.1 Vital Signs

Pre-dose systolic BP, diastolic BP and pulse rate will be listed and descriptively summarized (N, mean, standard deviation, minimum and maximum) by treatment group and visit. Baseline (defined as the pre dose value collected on Visit 3) and changes from baseline will be similarly summarized.

7.5.3.2 12-lead ECG

ECG data; QT, QTc (Fridericia's), heart rate (HR), QRS duration, PR and RR interval will be listed.

Baseline and change from baseline for QT, QTcF, HR, QRS, RR and PR will be summarized using descriptive statistics (N, mean, standard deviation, minimum and maximum) by treatment and study week.

For QTcF a classification of absolute values and increases from baseline will be performed. The number of subjects with maximum absolute QTcF <450 msec, 450 msec ≤QTcF <480 msec, 480 msec ≤QTcF <500 msec and QTcF values ≥500 msec will be tabulated by treatment and visit. The number of subjects with maximum increase from baseline QTcF <30 msec, 30 msec ≤QTcF <60 msec and QTcF ≥60 msec will be tabulated by treatment and visit.

7.5.3.3 Laboratory Tests

Laboratory data (clinical chemistry, hematology, and urinalysis parameters) will be listed and descriptively summarized (N, mean, standard deviation, minimum and maximum) by treatment group and visit.

Baseline (defined as the data collected at Visit 3) and changes from baseline will be similarly summarized.

Changes from baseline that result in out of normal range values will be listed and summarized.

7.6 PK Analyses

For all pharmacokinetic data analyses, the PPK population will be used.

Samples for PK determination of drug concentrations of revefenacin and its major metabolite, THRX-195518, in plasma will be determined by a bioanalytical laboratory using validated bioanalytical methods. Details of the validated bioanalytical method used will be provided in a separate bioanalytical report.

The plasma concentration data for revefenacin and THRX-195518 will be listed, summarized on the basis of time intervals, and plotted using a scatter plot with time relative to the

preceding revefenacin dosing time. Summary statistics (mean, standard deviation, minimum, maximum, number of subjects, and coefficient of variation) will be calculated for plasma concentrations for each time interval and by treatment group.

Population PK analysis of revefenacin concentrations in COPD subjects will be performed using modeling. The population PK analysis will be conducted and reported separately. Details of the PPK model building will be described in a separate population PK analysis plan.

Exploratory exposure-response analysis may be conducted using individual predictions of exposure from the population PK analysis in this study. Outcomes from this analysis will be reported separately, if conducted.

7.7 Other Analyses

Summary statistics will be provided for demographics and baseline characteristics, medical history and prior and concomitant medications.

7.8 Interim Analyses

An interim analysis is not planned for this study.

8 ADMINISTRATIVE PROCEDURES

8.1 Source Documentation Forms

All clinical data will be recorded by the clinical staff on raw data sheets and/or recorded electronically using validated software. If computerized systems are used to create, modify, maintain, archive, retrieve or transmit source data, they must comply with the applicable regulatory regulations and/or guidance.

The nature and location of all source documents will be documented separately. Source data may be directly captured from devices, transferred from 3rd parties (e.g. laboratory data) or entered manually into CRF/database.

8.2 Access to Data/Source Documentation

The Investigator or designated representative will permit full access to data and source documentation for the purpose of clinical monitoring, audits, IRB/IEC review and regulatory inspections.

8.3 Final Clinical Study Report and Case Report Forms (CRFs)

A written clinical study report will be provided in accordance with the International Conference on Harmonization (ICH) E-3 guidelines including Annex I (Synopsis) documenting the clinical execution of the study. This report will include a description of any protocol deviations. The final report will also include reasons for withdrawals and any necessary treatment(s). The report will also include tables presenting demographics (separate summary tables for enrolled and completed subjects), and adverse events recorded during the study. In addition, the clinical study report will include a Quality Assurance statement, documenting that the report has been reviewed for completeness, accuracy, and compliance with the protocol and applicable local and federal regulations. For final clinical reporting

purposes only, adverse events deemed “definite”, “probable” or “possible” will be included in the treatment-related summaries/listings.

Case Report Forms (CRFs) containing data transcribed from subject source documents (as appropriate) and copies of other source documents will be supplied by the clinical site. The Principal Investigator must sign each subject’s CRF after completion of data entry, signifying that the data entered in the CRF is complete and accurate. Electronic CRFs may be provided.

8.4 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety and well-being of the study subjects requires medical treatment, the study will be conducted as described in the approved protocol (and amendments, if applicable), GCP and applicable SOPs. In addition, the study will be conducted in accordance with the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted. Any deviation(s) from the protocol will be recorded and presented in the final report.

All protocol deviations will be reviewed in a blinded manner during the course of the study and decisions to exclude subjects from statistical analysis sets will be made prior to unblinding and the reasons documented.

8.5 Data Handling and Record Retention

All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

A CRF is required to be completed for each subject receiving study medication. The CRF is property of the Sponsor and the Investigator must review all CRFs prior to submission to the Sponsor.

The CRF may be considered as the source document. The Investigator must seek prospective agreement to the Sponsor in writing to use the CRF as source document prior the start of the study. In addition, items directly recorded in the CRF must be documented that they will be considered as source.

All records pertaining to the receipt and return of study supplies (particularly study medication) and copies of final case report forms, worksheets, and other pertinent source documents must be retained in accordance with ICH-GCP and the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

The Investigator must obtain in writing the Sponsor’s agreement to dispose of any records, even if the retention period has been reached.

8.6 Confidentiality

Information furnished to Clinical Investigators and IRBs/Ethics Committees will be maintained in confidence by the Clinical Investigator and IRB/Ethics Committee. By signing this protocol, the Investigator affirms to the Sponsor that he/she will maintain, in confidence,

information furnished to the IRB/Ethics Committee relevant to this study under appropriate understanding of confidentiality with such IRB/Ethics Committee.

By signing the protocol, the Investigator agrees that within local regulatory restrictions and institutional and ethical considerations, the Sponsor may consult and/or copy source documents (e.g., laboratory/X-ray reports, ECG tracings, workbooks, medical records) in order to verify CRF data.

8.7 Ethics and Regulatory Authorities

Guidelines will be followed with regard to the treatment of human subjects in the study, in accordance with the requirements of the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6) in addition to the regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

8.7.1 Institutional Review Board/Ethics Committee

The Investigator is responsible for obtaining initial and continuing review (at intervals not more than once per year) of the study by an IRB/Ethics Committee, or in accordance with applicable government regulations of the country where the study is being conducted as well as the country where the study will be submitted. This study will not enroll any subjects until the IRB/Ethics Committee provides written approval of the protocol and the informed consent to the Investigator. In addition, a copy of the IRB/Ethics Committee approval documents must be provided to the Sponsor prior to enrolling any subjects into the study.

8.7.2 Regulatory Authority

This clinical study protocol, title and a list of investigational sites, IEC(s)/IRB(s) approvals, as well as other relevant documentation will be submitted to the local Regulatory Authorities for review and approval prior to trial start. Upon completion, the Regulatory Authorities will be notified the study has ended. The study will only be undertaken in compliance with the local regulatory requirements.

8.8 Informed Consent

A properly executed, written informed consent in compliance with current GCP guidelines and ICH guidelines shall be obtained from each volunteer prior to entering the study. A copy of the informed consent document to be used will be submitted by the Investigator to an independent institutional review board (e.g., IRB or ethics committee) and the Sponsor and/or its agent for review and approval prior to the start of the study. The Investigator shall provide a copy of the signed and dated informed consent to the subject, and a signed and dated copy shall be maintained in the volunteer's medical record.

8.9 Disclosure and Publication of Clinical Study Data

The disclosure and publication of clinical study data will be detailed in the clinical trial agreement with the Investigators.

8.10 End of Trial

The end of trial is considered to be the date of last subject last visit or the date of early termination of the study whichever is the later.

9 ADVERSE EVENT REPORTING

9.1 Assessment of Safety

9.1.1 Safety Parameters

Safety will be assessed by the monitoring of adverse clinical events, electrocardiograms, vital signs, clinical laboratory evaluations, and physical examinations. All adverse events occurring during the study must be recorded according to Section 9.2.

Findings from screening procedures, e.g., laboratory tests or physical examinations will be recorded as medical history. Clinically significant changes from the screening procedures will be recorded as adverse events.

The adverse event collection period begins at signing of informed consent and continues until 30 days after the last dose of study medication. Adverse events occurring during this period need to be reported to the Sponsor according to Section 9.4 (Collection and Recording of Adverse Events). The Investigator is also responsible for notifying the Sponsor if he/she becomes aware of any adverse event after the study period has ended and it is considered related to the study medication (i.e., an adverse drug reaction). Once an AE is detected, it should be followed until its resolution or until it is judged by the Principal Investigator to be stable or permanent.

9.2 Definitions

Adapted from ICH Harmonised Tripartite Guideline: Clinical Safety Data Management Definition and Standards for Expedited Reporting: E2A

9.2.1 Adverse Event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physical findings, symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

Clinically significant changes from baseline in laboratory assessments, vital signs, ECGs, and physical examination are to be recorded as adverse events. Clinically significant abnormalities include:

- a result associated with accompanying signs/symptoms
- a result that requires additional diagnostic testing or medical/surgical intervention

- a result that leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy

- a result considered to be an adverse event by the Investigator or Sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

An abnormal safety assessment (e.g., laboratory, vital signs, ECG) associated with a clinical diagnosis that has been recorded as an AE does not require a separate AE entry

Events meeting the definition of an AE also include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug or drug-food interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. (Please refer to the Section 9.3: Special Situations for further details)

- A symptom or medical complication related to a protocol-mandated intervention, including screening procedures

9.2.2 Serious Adverse Event (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- Fatal
- Life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: In patient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the study drug or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization or accommodation problems and without medical background does not need to be considered an SAE.

  Events NOT to be reported as SAEs are hospitalizations for the following:

  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
  - Admission to a hospital or other institution for general care due to social or economic reasons (e.g., no access to local ambulatory medical care)
  - Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

  Hospitalization also does not include the following:

  - Rehabilitation facilities
  - Hospice facilities
  - Respite care (e.g., caregiver relief)
  - Skilled nursing facilities
  - Nursing homes

- Results in persistent or significant disability or incapacity

- A congenital anomaly or birth defect
- An important medical event
  - NOTE: medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject and / or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
  - The seriousness criterion of "medically significant" should **only** be selected when none of the other seriousness criteria apply to the event but the Investigator still considers the event as serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

9.2.3 Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose of the investigational product should be considered adverse drug reactions (ADRs). The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an AE is at least a reasonable possibility. All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to an investigational product will be designated as ADRs.

All AEs, with the causal relationship to the study drug reported as "possible", "probable" or "definite" will be considered ADRs. If the relationship to the study drug is not given, then the AE must be treated as if the relationship were "possible."

9.2.4 Expected/Unexpected Adverse Event

An expected AE is defined as one whose nature, severity or outcome is consistent with the applicable reference safety information described of the study drugs.

9.2.5 Pre-existing Condition

Any medical condition that is present at the time that the participant is screened will be considered as baseline medical history and not reported as an AE. A baseline or preexisting condition should be recorded as an adverse event only if the frequency, intensity, or the character of the condition worsens during the study period.

9.2.6 General Physical Examination Findings

Any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

9.2.7 Post-study Adverse Event/Serious Adverse Event

At the last scheduled contact with the subject the Investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The Investigator should notify the study Sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

9.3 Special Situations

The following situations may by associated with a serious outcome and should be evaluated for expedited reporting to the Sponsor.

- Any diagnosis of **Cancer** or **Neoplasm** is to be reported as a serious adverse event.
- **Emergency Room Visits**: Events that result in emergency room visits that do not result in admission to the hospital are not routinely considered to be serious events; however, these events should be evaluated for one of the other serious outcomes (e.g., life-threatening, other serious [medically significant] events).
- **Overdose**: Overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent; this should be reported regardless of sequelae. Signs and symptoms associated with accidental overdose are to be recorded as adverse events or as serious AEs. If adverse events associated with overdose fulfil any of the serious criteria (as defined in section 'Serious Adverse Event'), a completed SAE report form is required to be submitted.
- Reports of **Drug-drug interaction** and **Drug Abuse and Medication Errors**: drug interactions or abuse of the study medication must be recorded as AEs. Medication errors will be captured as protocol deviations while any associated signs or symptoms must be recorded as AEs on the CRF. In addition, any serious consequence of drug interactions, drug abuse, or medication error must be reported immediately if these fulfil any of the SAE criteria.

9.4 Collection and Recording of Adverse Events

During the Adverse Event Reporting Period, the Investigator will record all adverse events. At each contact with the subject, the Investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and in the appropriate adverse event module of the case report form (CRF). Information to be collected includes AE name or term (in standard medical terminology) and final diagnosis, event description, time and date of onset, clinician's assessment of severity, seriousness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), action taken with the study drug, treatment for the event and time (if available) and date of resolution/stabilization of the event.

Any findings from protocol specified safety assessments that are associated with the indication being studied are not to be reported as AEs or SAEs, unless judged by the Investigator to be more severe than expected for the subject's condition.

All clearly related signs, symptoms, and abnormal results of diagnostic procedures should be grouped under one diagnosis on the CRF where possible and appropriate.

The clinical course of each event should be followed until resolution or stabilization. Adverse events that are still ongoing at the end of the study period must be followed up to determine the outcome. Any adverse event that occurs after the study period and is related to the study treatment or study participation should be recorded; and if serious, the Investigator should also immediately report it to the Sponsor.

9.5 Classification of an Adverse Event

9.5.1 Severity

The Investigator will assign a severity rating to each AE. For purposes of consistency, the following scale is to be used:

Grade 1 - MILD	Does not interfere with subject's usual function
Grade 2 - MODERATE	Interferes to some extent with subject's usual function
Grade 3 - SEVERE	Interferes significantly with subject's usual function

It is important to distinguish between severe AEs and Serious AEs. Severity is a classification of intensity, whereas an SAE is an AE that meets any of the regulatory specified criteria (see definitions, Serious Adverse Event).

NOTE: an acute exacerbation of COPD (AECOPD) should have the severity graded per the definitions in Section 6.4.8.1.1.

9.5.2 Causality

For all adverse events, sufficient information should be obtained by the Investigator to determine the causality of the adverse event. The Investigator is required to assess causality of each AE.

An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. The Investigator must make an assessment of the relationship of each AE (serious and non-serious) to the study treatment(s) and record this relationship in the CRF.

Factors that need to be considered when making a causality assessment include: Temporal relationship, Clinical and pathological characteristics of the event(s), Pharmacological plausibility, Exclusion of confounding factors (medical and medication history), Drug interactions, De-challenge/re-challenge, Dose relationship.

A suspected relationship (definite, probable, possible) between the events and the study medication means, in general, that there are facts (evidence) or arguments to suggest a causal relationship. Receipt of additional or clarifying information may warrant reassessment of causality. The Investigator is responsible for assessing relationship of AEs to study treatment in accordance with the following definitions:

Category	Causality	Description
DEFINITE	Causal relationship is certain	For example: the temporal relationship between drug exposure and the adverse event (AE) onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
PROBABLE	High degree of certainty for causal relationship	For example: the temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to de-challenge (re-challenge is not required), and other causes have been eliminated or are unlikely.
POSSIBLE	Causal relationship is uncertain	For example: the temporal relationship between study treatment exposure and the AE onset/course is reasonable or unknown, dechallenge information is either unknown or equivocal; could also be explained by disease or other drugs.
UNLIKELY	Causal relationship is improbable	Another explanation is more likely such as disease, environment, or other medication. Does not represent a known reaction to study drug.
UNRELATED/NOT RELATED	No possible relationship	The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is impossible

For SAEs, if the relationship to the study treatment(s) is considered to be unlikely or not related, an alternative suspected etiology should be provided when possible (e.g., concomitant medications, intercurrent illness/events, study-related procedure).

9.5.3 Expectedness

The Sponsor or its designated representative will be responsible for determining whether an AE is expected or unexpected.

9.5.4 Outcome

For all adverse events, the Investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Sponsor or its designated representative.

The outcome at the time of last observation will be classified as:

RECOVERED/RESOLVED where the subject recuperated and is free of any pathological conditions resulting from the prior disease or injury

RECOVERED WITH SEQUELAE where the subject recuperated but retained pathological conditions resulting from the prior disease or injury.

NOT RECOVERED/NOT RESOLVED (i.e., ongoing) where the subject has not recuperated from the condition or injury and the event is still considered ongoing

RECOVERING where the subject has begun to recuperate from the condition or injury but the event is considered ongoing at a reduced intensity

FATAL where the condition or injury results in the subject's death. The Investigator should identify the principal cause of death and assign Fatal outcome to that event. Other concurrent ongoing AE/SAEs present at the time of death would remain Not recovered/Not resolved.

UNKNOWN can be selected if none of the other situations apply or are known. Follow-up should be conducted to obtain one of the preceding outcomes.

Action Taken with the Study Treatment and combination treatment for an Adverse Event:

Action	**Description**
Dose reduced	The dose regimen was reduced by changing its frequency, strength, or amount
Treatment interrupted	The treatment was temporarily discontinued
Treatment withdrawn	The treatment was permanently discontinued
Unknown	Not known, not observed, not recorded, or refused
No action taken	The AE did not result in any modification of dose or frequency of dosing
Not applicable	The AE occurred prior to first dose or following last scheduled dose

9.6 Reporting of Serious Adverse Events and Pregnancy Exposures

Investigators and the Sponsor or its designated representative must conform to the serious adverse event reporting timelines, formats and requirements of the various entities to which they are responsible.

9.6.1 Investigator Reporting: Notifying the Study Sponsor

Immediate notification of SAEs by the Investigator to Sponsor or its designated representative is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Sponsor or its designated representative will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Investigators.

Serious adverse events must be reported to the study Sponsor within 24 hours. To report such events, a Serious Adverse Event (SAE) Report form must be completed and signed by the Investigator or designee and forwarded to:

Email: [redacted]

Fax: [redacted]

If the initial notification using the completed 'SAE report form' is not possible, the notification may be made via email/fax or over telephone with the following minimum necessary information:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Current status (outcome of event-if known and whether study medication is continuing)
- The reason why the event is classified as serious
- Investigator assessment of the causality between the event and study treatment

The Investigator should provide further information on the SAE as soon as possible, preferably within 48 hours of awareness. This should include a copy of the completed SAE Report form, and any other diagnostic information and medical records that will assist in the understanding of the event.

Subject identifying information must not be visible on SAE forms or any supporting documentation provided by the Investigator. Any information that could be used to identify

the subject (e.g., name, address, medical record number) must be de-identified before submission to Mylan or its designee. The subject's study specific ID number should be recorded on every page of documentation forwarded to the Sponsor.

The PI should provide the final diagnosis as the SAE term whenever possible in the SAE report form and CRF. The signs and symptoms should be provided in the narrative only, not as SAE terms. The PI should only list all signs and symptoms as SAE terms if no diagnosis is available at the time of report.

9.6.2 Follow-up

New information and any important missing information from prior reports on a serious adverse event must be provided promptly to the study Sponsor. In addition, the Investigator may be requested by Sponsor/designee to obtain specific additional follow-up information in an expedited fashion. The Investigator should respond to targeted follow-up requests as soon as possible and preferably within 48 hours from receipt of the request.

9.6.3 Investigator Reporting: Notification of Ethics Committee

Investigators are responsible for safety reporting to their local Ethics Committee (LEC) and complying with their local EC's reporting requirements. Copies of each report and documentation of LEC notification and receipt will be kept in the Investigator's study file.

9.6.4 Investigator Reporting of Pregnancy - Notifying the Study Sponsor

All subjects who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation as detailed in the inclusion and exclusion criteria. Pregnancy testing will be conducted throughout the study, as detailed in the schedule of assessments.

A subject who is found to be pregnant at the screening visit will be excluded from the study and will be a screening failure.

Subjects who have been enrolled in the study should be instructed to contact the Investigator or study staff immediately if pregnancy occurs or is suspected. Early Termination visit assessments are required as soon as possible after learning of the pregnancy. Pregnant females will be discontinued from study treatment by the Investigator. A male that has a partner that becomes pregnant during the study will not be discontinued from study treatment.

Details of the pregnancy should be recorded on the Pregnancy Report form and reported to Sponsor or designee within 24 hours of awareness by email ([redacted]) or facsimile ([redacted]) from the time of initial awareness, even if beyond the closure of the clinical database.

The Investigator is also responsible for following the pregnancy every 3 months or until delivery or termination and informing the Sponsor about its outcome. Reports where the embryo or fetus may have been exposed to the study drug(s), should be followed-up in order to collect information on the:

- outcome of the pregnancy,

- outcome for both mother and fetus (malformation/anomalies diagnosed since initial report)

- development of the child after birth (developmental assessment, infant illnesses, hospitalizations, drug therapies, breastfeeding)

Healthy newborns should be followed-up at 1 month after birth to confirm no congenital anomalies were subsequently detected (if possible).

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or termination of a pregnancy for medical reasons will be recorded as an AE or an SAE. A spontaneous abortion is always considered to be a SAE and will be reported to the Sponsor.

Elective termination (i.e., without medical reasons) of an uncomplicated pregnancy is considered an elective procedure and not an AE; nevertheless, Mylan requests the outcome (e.g., elective termination) be reported within 24 hours of awareness and sent as a follow-up on the Delivery and Infant Follow-up Form).

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as at least possibly related to the study treatment, must be promptly reported to Sponsor or designee.

IF THE STUDY CENTER BECOMES AWARE OF A PREGNANCY IN A FEMALE PARTNER OF A MALE SUBJECT, STUDY PERSONNEL SHOULD CONTACT THEIR CLINICAL RESEARCH ASSOCIATE TO OBTAIN A PARTNER PREGNANCY ICF. CONSENT OF THE PREGNANT PARTNER MUST BE OBTAINED BEFORE ANY DETAILS OF THE PREGNANCY CAN BE SHARED WITH SPONSOR OR ITS DESIGNATED REPRESENTATIVE. IF THE PREGNANT PARTNER PROVIDES CONSENT TO HAVE THE PREGNANCY FOLLOWED, THE STUDY CENTER SHOULD COLLECT THE INFORMATION SPECIFIED ON THE PREGNANCY REPORT FORM AND FORWARD THE COMPLETED FORM TO SPONSOR EVERY 3 MONTHS UNTIL THE PREGNANCY OUTCOME HAS BEEN OBTAINED.

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11 PATIENT REPORTED MEASURES

11.1 BDI/TDI

At Visit 3 (Day 1), Visit 4 (Day 29), Visit 5 (Day 57), Visit 6 (Day 85), and the Early Termination Visit, if applicable, the subject's dyspnea will be assessed using the interviewer-administered BDI/TDI.

This appendix consists of 3 parts: Part I: Instructions for administration of both dyspnea indices; Part II: The BDI; Part III: The TDI.

The content of these Indexes is as published (Mahler et al., 1984 [11]).

PART I: Instructions for application of dyspnea indexes

General comments

The objective of the BDI and TDI is to measure or quantitate the severity of breathlessness (shortness of breath) in symptomatic patients.

The initial questions to the patient should be, "Do you experience shortness of breath?" If the patient answers "No," the interviewer should ask whether any physical activities cause the patient to experience breathlessness. If the answer to the question is "Yes," additional questions will be necessary.

The Dyspnea Indexes were devised so that grading breathlessness could be performed as part of obtaining a history from the patient. Specific questions should be asked based on the criteria of the various grades for functional impairment, magnitude of task, and magnitude of effort that provoke breathlessness. This approach was selected instead of a questionnaire answered by the patient in order to allow an interviewer with some medical training and/or background to grade breathlessness in a simple and brief encounter. Our past and present experience indicates that the grading process can be completed easily within 4-5 minutes of conversation with the patient.

Furthermore, the Dyspnea Indexes were devised so that a variety of medical personnel would be able to interview the patient and grade his or her breathlessness. These individuals include physicians, nurses, respiratory therapists, cardiopulmonary technicians, as well as others with some medical experience. Note however, that it is important that for a given patient, the same individual should perform the interviews and complete the BDI and all subsequent TDI measurements.

Specific Comments

BDI

1A. Functional Impairment: Activities

Ask if patient has stopped doing any activities because of breathlessness. If so, ask for specific examples (e.g., stopped doing housework or yard work).

1B. Functional Impairment: Work

Ask if the patient has stopped work because of breathlessness.

For retired individuals, ask if the patient would be able to work at his or her last job (i.e., ability to work despite breathlessness).

Combine the patient's responses for activities and work in order to select a grade for Functional Impairment.

2. Magnitude of Task

Ask what types of activities make the patient breathless.

Give examples based on criteria listed or the different grades and then select grade.

3. Magnitude of Effort

Ask how much effort in daily activities makes the patient breathless.

Give examples based on criteria listed for the different grades and then select grade.

TDI

This instrument measures change from the baseline state. It is recommended that the interviewer refer to the grades from the BDI as references and for reminding the patient of his or her comments before picking a grade from the TDI.

Change in Functional Impairment

Ask the patient to recall his or her breathlessness at the first or baseline visit, or you may describe this information (from the BDI) to the patient.

Ask whether there has been any change since the first or baseline visit. Any activities started or stopped? Any modifications in job/work activities?

Change in Magnitude of Task

Ask the patient to recall his or her breathlessness at the first or baseline visit, or you may describe this information (from the BDI) to the patient.

Ask what activities cause breathlessness now (e.g., walking on a level surface, climbing stairs, at rest, bathing, etc.). Ask if this represents any change since the first or baseline visit.

Change in Magnitude of Effort

Describe the patient's previous report of breathlessness relative to effort and need to pause while performing activities.

Ask whether there has been any change since the first or baseline visit.

PART II: BDI

Functional Impairment

_____ Grade 4: No Impairment. Able to carry out usual activities and occupation without shortness of breath.

_____ Grade 3: Slight Impairment. Distinct impairment in at least one activity but no activities completely abandoned. Reduction, in activity at work or in usual activities, that seems slight or not clearly caused by shortness of breath.

_____ Grade 2: Moderate Impairment. Patient has changed jobs and/or has abandoned at least one usual activity due to shortness of breath.

_____ Grade 1: Severe Impairment. Patient unable to work or has given up most or all usual activities due to shortness of breath.

_____ Grade 0: Very Severe Impairment. Unable to work and has given up most or all usual activities due to shortness of breath.

_____ W: Amount Uncertain. Patient is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.

_____ X: Unknown. Information unavailable regarding impairment.

_____ Y: Impaired for Reasons Other than Shortness of Breath. For example, musculoskeletal problem or chest pain.

Usual activities refer to requirements of daily living, maintenance or upkeep of residence, yard work, gardening, shopping, etc.

Magnitude of Task

_____ Grade 4: Extraordinary. Becomes short of breath only with extraordinary activity such as carrying very heavy loads on the level, lighter loads uphill, or running. No shortness of breath with ordinary task.

_____ Grade 3: Major. Becomes short of breath only with such major activities as walking up a steep hill, climbing more than three flights of stairs, or carrying a moderate load on the level.

_____ Grade 2: Moderate. Becomes short of breath with moderate or average tasks such as walking up a gradual hill, climbing fewer than three flights of stairs, or carrying a light load on the level.

_____ Grade 1: Light. Becomes short of breath with light activities such as walking on the level, washing, or standing.

_____ Grade 0: No Task. Becomes short of breath at rest while sitting, or lying down.

_____ W: Amount uncertain. Patient's ability to perform tasks is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be specified. Details are not sufficient to allow impairment to be categorized.

_____ X: Unknown. Information unavailable regarding limitation of magnitude of task.

_____ Y: Impaired for Reasons Other than Shortness of Breath. For example, musculoskeletal problem or chest pain.

Magnitude of Effort

_____ Grade 4: Extraordinary. Becomes short of breath only with the greatest imaginable effort. No shortness of breath with ordinary effort.

_____ Grade 3: Major. Becomes short of breath with effort distinctly submaximal, but of major proportion. Tasks performed without pause unless the task requires extraordinary effort that may be performed with pauses.

_____ Grade 2: Moderate. Becomes short of breath with moderate effort. Tasks performed with occasional pauses and requiring longer to complete than the average person.

_____ Grade 1: Light. Becomes short of breath with little effort. Tasks performed with little effort or more difficult tasks performed with frequent pauses and requiring 50-100% longer to complete than the average person might require.

_____ Grade 0: No effort. Becomes short of breath at rest while sitting, or lying down.

_____ W: Amount Uncertain. Patient's exertional ability is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.

_____ X: Unknown. Information unavailable regarding limitation of effort.

_____ Y: Impaired for Reasons Other than Shortness of Breath. For example, musculoskeletal problems or chest pain.

PART III: TDI

Change in Functional Impairment

_____ -3: Major Deterioration. Formerly working and has had to stop working and has completely abandoned some of usual activities due to shortness of breath.

_____ -2: Moderate Deterioration. Formerly working and has had to stop working or has completely abandoned some of usual activities due to shortness of breath.

_____ -1: Minor Deterioration. Has changed to a lighter job and/or has reduced activities in number or duration due to shortness of breath. Any deterioration less than preceding categories.

_____ 0: No Change. No change in functional status due to shortness of breath.

_____ +1: Minor Improvement. Able to return to work at reduced pace or has resumed some customary activities with more vigor than previously due to improvement in shortness of breath.

_____ +2: Moderate Improvement. Able to return to work at nearly usual pace and/or able to return to most activities with moderate restriction only.

_____ +3: Major Improvement. Able to return to work at former pace and able to return to full activities with only mild restriction due to improvement of shortness of breath.

_____ Z: Further Impairment of Reasons Other than Shortness of Breath. Patient has stopped working, reduced work, or has given up or reduced other activities for other reasons. For example, other medical problems, being “laid off” from work, etc.

Change in Magnitude of Task

_____ -3: Major Deterioration. Has deteriorated two grades or greater from baseline status.

_____ -2: Moderate Deterioration. Has deteriorated at least one grade but fewer than two grades from baseline status.

_____ -1: Minor Deterioration. Has deteriorated less than one grade from baseline. Patient with distinct deterioration within grade, but has not changed grades.

_____ 0: No Change. No change from baseline.

_____ +1: Minor Improvement. Has improved less than one grade from baseline. Patient with distinct improvement within grade, but has not changed grades.

_____ +2: Moderate Improvement. Has improved at least one grade but fewer than two grades from baseline.

_____ +3: Major Improvement. Has improved two grades or greater from baseline.

_____ Z: Further Impairment for Reasons Other than Shortness of breath. Patient has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

Change in Magnitude of Effort

_____ -3: Major Deterioration. Severe decrease in effort from baseline to avoid shortness of breath. Activities now take 50-100% longer to complete than required at baseline.

_____ -2: Moderate Deterioration. Some decrease in effort to avoid shortness of breath, although not as great as preceding category. There is greater pausing with some activities.

_____ -1: Minor Deterioration. Does not require more pauses to avoid shortness of breath, but does things with distinctly less effort than previously to avoid breathlessness.

_____ 0: No Change. No change in effort to avoid shortness of breath.

_____ +1: Minor Improvement. Able to do things with distinctly greater effort without shortness of breath. For example, may be able to carry out tasks somewhat more rapidly than previously.

_____ +2: Moderate Improvement. Able to do things with fewer pauses and distinctly greater effort without shortness of breath. Improvement is greater than preceding category, but not of major proportion.

_____ +3: Major Improvement. Able to do things with much greater effort than previously with few, if any, pauses. For example, activities may be performed 50-100% more rapidly than at baseline.

_____ Z: Further Impairment for Reasons Other than Shortness of Breath. Patient has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

11.2 mMRC

The mMRC dyspnea scale will be completed by the subject at Visit 3 (Day 1). Subjects will circle the grade according to the description that best describes them currently.

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on the level or walking up a slight hill.
2	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
3	I stop for breath after walking about 100 meters or after a few minutes on the level.
4	I am too breathless to leave the house or I am breathless when dressing or undressing.

11.3 SGRQ

The SGRQ will be completed by the subject at Visit 3 (Day 1) and Visit 6 (Day 85).

More information on this questionnaire can be found at:
http://www.healthstatus.sgul.ac.uk/sgrq

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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UK/ English (original) version 1

continued…

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St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 3 months.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 3 months, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 3 months, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 3 months, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 3 months, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 3 months how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one*:

- No ☐
- Yes ☐

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

	Please tick (✓) in ***each box*** that applies to you ***because of your breathing***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

	Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***: True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

12 PROTOCOL AMENDMENT DETAILS

Global Amendment 1, 15 July 2020

Reasons for Amendment

The protocol was amended to address comments from the regulatory agency, the local ethics committee of the lead investigator site, and the lead investigator, to provide guidance in case of a public health emergency restricting subject and investigator movements, and to update safety reporting requirements according to the latest applicable guidances:

- To add the brand name of the nebulizer and compressor used for study drug administration as requested by the regulatory agency.
- To change the responsibility for recording adverse events from the Principal Investigator to the Investigator as requested by the local ethics committee of the lead investigator site.
- To reduce the blood volume for pharmacokinetics from 10 mL per sample to 6 mL per sample.
- To add a physical examination at the Early Termination visit.
- To document the contingencies to be implemented to enable study continuation in the event of a public health emergency limiting the ability of subjects and investigators to attend the investigator site (eg, increasing the number of subjects that may be randomized, shipment of study drug and other study supplies to the subject, performing virtual visits by telephone, etc).
- To update safety reporting requirements according to the latest relevant guidances.

Additional amendments have been made in order to correct typographical errors and to provide further clarification on aspects of the protocol.

Sections changed

Synopsis of protocol (Background and Rationale)

Changed from:

The airflow limitation is usually both progressive and associated with an abnormal inflammatory response in the airways and the lung to noxious particles or gases (Global Initiative for the Treatment of Obstructive Lung Disease [GOLD], 2019 [1]).

Changed to:

The airflow limitation is usually both progressive and associated with an abnormal inflammatory response in the airways and the lung to noxious particles or gases (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2019 [1]).

Synopsis of protocol (Methodology and Treatments: Study drug administration)

Changed from:

Study drug will be administered using a centrally-provided, standard jet nebulizer and compressor via a mouthpiece.

Changed to:

Study drug will be administered using a centrally-provided, standard jet nebulizer (PARI LC Sprint) and compressor (PARI TurboBOY) via a mouthpiece.

Synopsis of protocol (Inclusion/Exclusion Criteria: Inclusion Criteria)

Changed from:

5. History of at least 10 pack-years of tobacco smoking. Ex-smokers must have stopped smoking >6 months prior to Visit 1

Changed to:

5. Current smoker or ex-smoker, with a history of at least 10 pack-years of tobacco smoking. Ex-smokers must have stopped smoking >6 months prior to Visit 1

Synopsis of protocol (Inclusion/Exclusion Criteria: Exclusion Criteria)

Changed from:

17. Subjects with hepatic impairment. A history of hepatitis B or hepatitis C may be permitted at the discretion of the Investigator, provided the subject is asymptomatic and liver transaminases (ALT/AST) are ≤1.5 times the upper limit of normal (ULN) at Screening.

Changed to:

17. Subjects with hepatic impairment. A history of hepatitis B or hepatitis C may be permitted at the discretion of the Investigator, provided the subject has no signs of hepatic impairment, is asymptomatic, and liver transaminases (ALT/AST) are ≤1.5 times the upper limit of normal (ULN) at Screening.

Synopsis of protocol (Statistical Methods: Sample size estimation)

Changed from:

To allow for a 20% dropout rate, approximately 320 subjects in total will be randomized.

Changed to:

To allow for a 20% dropout rate, approximately 320 subjects in total will be randomized. In the event of a public health emergency such as COVID-19, the Sponsor may consider increasing enrollment to overcome any additional loss of information for the primary endpoint due to the inability of subjects to attend for scheduled clinic visits. The maximum

number of subjects to be randomized under such circumstances will be limited to 428 (an additional 20% increase in enrollment).

Synopsis of protocol (Statistical Methods: Analysis Populations)

Changed from:

- Per Protocol Set (PP): all subjects in the FAS who had no major protocol violation that would impact on the endpoints of interest.

Changed to:

- Per Protocol Set (PP): all subjects in the FAS who had no major protocol violation that would impact significantly on the primary efficacy endpoints.

Table 1-1: Study Schedule

New addition:

Physical examination added to Early Term (ET) visit

2.2 Background and Rationale

Changed from:

The airflow limitation is usually both progressive and associated with an abnormal inflammatory response in the airways and the lung to noxious particles or gases (Global Initiative for the Treatment of Obstructive Lung Disease [GOLD], 2019 [1]).

Changed to:

The airflow limitation is usually both progressive and associated with an abnormal inflammatory response in the airways and the lung to noxious particles or gases (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2019 [1]).

3.2.1 Secondary Endpoints

Section number changed from 3.2.1 to 3.2.2

3.2.1.1 Efficacy

Section number changed from 3.2.1.1 to 3.2.2.1

3.2.1.2 Safety

Section number changed from 3.2.1.2 to 3.2.2.2

3.2.2 Pharmacokinetic (PK)

Section number changed from 3.2.2 to 3.2.3

4.2.1 Inclusion Criteria

Changed from:

5. History of at least 10 pack-years of tobacco smoking. Ex-smokers must have stopped smoking >6 months prior to Visit 1.

Changed to:

5. Current smoker or ex-smoker, with a history of at least 10 pack-years of tobacco smoking. Ex-smokers must have stopped smoking >6 months prior to Visit 1.

4.2.2 Exclusion Criteria

Changed from:

17. Subjects with hepatic impairment. A history of hepatitis B or hepatitis C may be permitted at the discretion of the Investigator, provided the subject is asymptomatic and liver transaminases (ALT/AST) are ≤1.5 times the upper limit of normal (ULN) at Screening.

Changed to:

17. Subjects with hepatic impairment. A history of hepatitis B or hepatitis C may be permitted at the discretion of the Investigator, provided the subject has no signs of hepatic impairment, is asymptomatic, and liver transaminases (ALT/AST) are ≤1.5 times the upper limit of normal (ULN) at Screening.

5.1.1 Administration of Study Drugs

Changed from:

Revefenacin inhalation solution and its matching placebo will be administered using a centrally-provided, standard jet nebulizer and compressor via a mouthpiece.

Changed to:

Revefenacin inhalation solution and its matching placebo will be administered using a centrally-provided, standard jet nebulizer (PARI LC Sprint) and compressor (PARI TurboBOY) via a mouthpiece.

Table 6-1: Blood Volume

Changed from:

Sample Type	Sample Volume (mL)	Number of Sampling Times		Total Volume (mL)
		Screening	Study Period	
Safety Labs	20	1	1	40
PK	10	0	9	90
TOTAL				**130**

Changed to:

Sample Type	Sample Volume (mL)	Number of Sampling Times		Total Volume (mL)
		Screening	Study Period	
Safety Labs	20	1	1	40
PK	6	0	9	54
TOTAL				**94**

6.2.5 Early Study Drug Termination (ET) Visit

New text added:

- General physical examination, including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.

6.4.8.5 General Physical Examination

Changed from:

A full general physical examination will consist of an examination of the abdomen, cardiovascular system, lungs, lymph nodes, musculoskeletal and neurological systems, skin, extremities, head, ears, eyes, nose, and thyroid gland by trained medical personnel at the site.

Changed to:

A full general physical examination will consist of an examination of the respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland by trained medical personnel at the site

New section added:

6.6 Mitigation in the event of a public health emergency

In the event of any circumstances impacting the ability of enrolled subjects to attend for scheduled visits at the investigator site, such as travel restrictions imposed due to COVID-19, investigators must notify the Sponsor and make the necessary arrangements to ensure the safety of their enrolled subjects. They should also evaluate whether their subjects should continue in the clinical trial. Those that have not been randomized yet should be withdrawn from the study.

Where it is possible for randomized subjects to continue, the following operational contingencies will be implemented:

- Study medication, rescue medication, and other study supplies such as diary cards will be sent to the subject's residence to ensure sufficient quantities are available.

- Virtual visits will be conducted by telephone in place of the scheduled visits, whereby the investigator will perform those procedures specified in Section 6.2 that are

feasible to be performed by telephone, such as questioning on adverse events, concomitant medications, and rescue medication use, completion of TDI, etc).

- Subjects will be reminded to bring (or send) all used and unused study medication, rescue medication, and diary cards to the site as soon as they are able after travel restrictions have been lifted.

Protocol deviations arising under such circumstances (eg, missed or delayed visits, assessments not performed, etc) will be clearly documented in the CRF and the reasons will be collected.

7 STATISTICAL ANALYSIS

Changed from:

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

Changed to:

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the Sponsor. This will include any plans for summarizing and analyzing data impacted by a public health emergency. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

7.1 Sample Size Considerations

Changed from:

To allow for an anticipated 20% dropout rate, approximately 320 subjects in total will be randomized.

Changed to:

To allow for an anticipated 20% dropout rate, approximately 320 subjects in total will be randomized. In the event of a public health emergency such as COVID-19, the Sponsor may consider increasing enrollment to overcome any additional loss of information for the primary endpoint due to the inability of subjects to attend for scheduled clinic visits. The maximum number of subjects to be randomized under such circumstances will be limited to 428 (an additional 20% increase in enrollment).

7.2.3 Per Protocol Analysis Set

Changed from:

The per protocol analysis set (PP) will include all subjects in the FAS who had no major protocol violation that would impact on the primary efficacy endpoint. Significant protocol

deviations are defined in Section 8.4 and will be further defined in the SAP. The list of major protocol deviations will be finalized prior to database lock and unblinding as part of the final blinded data review (BDR). Data will be summarized and analyzed according to the treatment a subject actually received at randomization.

Changed to:

The per protocol analysis set (PP) will include all subjects in the FAS who had no major protocol violation that would impact significantly on the primary efficacy endpoint. The list of major protocol deviations will be finalized prior to database lock. All decisions to exclude subjects from the PP analysis set will be made prior to unblinding in the final blinded data review (BDR) meeting and report. Data will be summarized and analyzed according to the treatment a subject actually received at randomization.

7.3.1 Definition of Primary Endpoints

New text:

- If a public health emergency prevents FEV_1 data from being measured at site then information on the reasons for the missing assessments will be recorded in the CRF.

7.4 Secondary Efficacy Endpoints

Changed from:

In all the secondary efficacy analyses missing data will not be imputed and will be assumed to be missing at random (MAR). Secondary efficacy analyses will be performed using the FAS population.

Changed to:

In all the secondary efficacy analyses missing data will not be imputed and will be assumed to be missing at random (MAR). Secondary efficacy analyses will be performed using the FAS population. If a public health emergency prevents data from being measured or requires data to be assessed remotely via a virtual visit, then information on the reasons and the data impacted will be recorded in the CRF.

8.4 Adherence to Protocol

Changed from:

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

- Subject did not meet efficacy-defined inclusion criteria (e.g., inclusion criteria 2, 3, 4, 5)
- Subject did not meet exclusion criteria which may potentially impact the primary efficacy endpoint (to be reviewed and assessed on a case-by-case basis)
- Subject who is not 80-120% compliant with study medication

- Subject received an excluded concomitant treatment or medication (e.g., a concomitant LAMA)

Additional criteria may be specified in the SAP.

Changed to:

All protocol deviations will be reviewed in a blinded manner during the course of the study and decisions to exclude subjects from statistical analysis sets will be made prior to unblinding and the reasons documented.

9.4 Collection and Recording of Adverse Events

Changed from:

During the Adverse Event Reporting Period, the PI will record all adverse events.

Changed to:

During the Adverse Event Reporting Period, the Investigator will record all adverse events.

9.6.1 Investigator Reporting: Notifying the Study Sponsor

Changed from:

The Investigator should provide further information on the as soon as possible, preferably within 48 hours of awareness.

Changed to:

The Investigator should provide further information on the SAE as soon as possible, preferably within 48 hours of awareness

In order to meet the signature requirements of institutions that require a wet signature, Global Protocol Amendment 1 (Version 2.0, dated 15 JUL 2020) has been wet-signed:

Authored by:	Signature/Date:
[redacted] Clinical Scientist	
Approved by:	
[redacted] [redacted] Global Clinical Respiratory	