# CLINICAL STUDY PROTOCOL

## Protocol No. TB-DPI-301

**A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Crossover, Multicenter Clinical Study to Assess the Efficacy and Safety of Once Daily Administration of Lupin Tiotropium Bromide Inhalation Powder Compared to SPIRIVA® HANDIHALER® and Placebo in Patients with COPD including a 12-Week Open-Label Extension to Assess Inhaler Robustness**

**Protocol Version (Date):** **1.0 (18-Nov-2016)**

**Amendment (Date):** **Amendment 1 (11-May-2017)**

**Sponsor:** **Lupin Inc.**

**This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312) and ICH Guidelines. All Investigators will agree to comply with US Federal Regulations concerning written informed consent and the rights of human patients as outlined in CFR Part 50. Essential study documents will be archived in accordance with applicable country regulations**.



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# SPONSOR SIGNATORY

Signed: [redacted] Date: 11 May 2017

Lupin Inc.

# INVESTIGATOR AGREEMENT

**A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Crossover, Multicenter Clinical Study to Assess the Efficacy and Safety of Once Daily Administration of Lupin Tiotropium Bromide Inhalation Powder Compared to SPIRIVA® HANDIHALER® and Placebo in Patients with COPD including a 12-Week Open-Label Extension to Assess Inhaler Robustness**

**IND/EudraCT number: NA**

I have carefully read the foregoing protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current GCP guidelines and will attempt to complete the study within the time designated.

I will provide copies of the protocol and all other information submitted by the Sponsor relating to pre-clinical and prior clinical experience to all personnel for whom I am responsible that participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all subject information (case report forms, shipment and drug return forms and all other information collected during the study) in accordance with the current GCP and local regulations.

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| Site Principal Investigator's name | [redacted] Lupin Inc. Representative's name |
| Signature | [redacted] Signature |
| Date (dd-Mmm-yyyy) | 11 May 2017 Date (dd-Mmm-yyyy) |
| Institution | |

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# 1 SYNOPSIS

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| **Protocol Number** | TB-DPI-301 |
| **Title of Study** | A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Crossover, Multicenter Clinical Study to Assess the Efficacy and Safety of Once Daily Administration of Lupin Tiotropium Bromide Inhalation Powder Compared to SPIRIVA® HANDIHALER® and Placebo in Patients with COPD including a 12-Week Open-Label Extension to assess Inhaler Robustness |
| **Name of Active Ingredients** | Tiotropium bromide |
| **IND/EudraCT No.** | Not applicable |
| **Indication** | Chronic Obstructive Pulmonary Disease (COPD) |
| **Phase of Clinical Development** | 3 |
| **Study Centers** | The study is planned to be conducted at approximately 40 investigational centers in the United States of America (USA). Additional centers in the USA may be added as needed. |
| **Objectives**<br>Primary Objective | The primary objective of this study is to show clinical bioequivalence (BE) in the efficacy of the Lupin Tiotropium Bromide Inhalation Powder, 18 mcg administered as a single dose versus SPIRIVA HANDIHALER, 18 mcg based on the adjusted mean change in forced expiratory volume in the first second ($FEV_1$) area under the curve from time zero to 24 hours postdose ($AUC_{0-24h}$) on day 1. |
| Secondary Objectives | The secondary objectives of this study are to evaluate the safety and tolerability of Lupin Tiotropium Bromide Inhalation Powder and SPIRIVA HANDIHALER in patients 40 years of age and older with COPD. |
| Other Objectives | For a subset of the Lupin tiotropium dry powder inhalers (DPIs), LUPINHALER™, used during the open-label extension (Part 2) the following objectives will be assessed:<br>• ruggedness of the LUPINHALER during 72 days of in-patient use<br>• in vitro performance post 72 days of in-patient use |
| **Study Design Overview** | This is a 2-part clinical study. Part 1 is a randomized, double-blind, double-dummy, placebo-controlled, 3-period, single-dose crossover study that will evaluate the clinical BE of single-dose treatment of Lupin Tiotropium Bromide Inhalation Powder, 18 mcg and SPIRIVA HANDIHALER, 18 mcg in patients 40 years of age and older with established COPD. Part 2 is a 12-week open-label extension of Part 1, which will enroll a subset of patients (approximately 120 patients) at select investigational centers who have successfully completed Part 1 of the study, to assess robustness of the LUPINHALER over 72 days of treatment. The duration of patient participation for Part 1 is approximately 14 weeks and for patients participating in both Part 1 and Part 2, the duration of patient participation is approximately 26 weeks.<br>Part 1 of the study consists of a screening period up to 30 days, followed by a single-blind placebo run-in period of 14 (+2) days and 3 single-dose, double-blind treatment periods (visits 2-4) each separated by a 21-day (+3 days) washout period. Each double-blind treatment period begins with administration of the study medication at the investigational center, followed by lung function assessments collected over a 24-hour period. For patients |

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| | ending participation in the study after completing Part 1 and not enrolling into the open-label extension (Part 2), a follow-up visit via phone contact will be conducted 7 days (±3 days) after the completion of treatment period 3 (visit 4).<br><br>The screening period, of up to 30 days, allows for adequate washout of the following COPD therapies, along with other prohibited medications per protocol:<br><br>• long-acting anti-muscarinic agent (LAMA) medications (including mono products and combination products containing LAMAs [eg, LAMA/LABA]) will not be permitted within 21 days of the screening visit (visit 1)<br>• long-acting beta agonist (LABA) mono products will not be permitted within 7 days of the screening visit (visit 1)<br>• inhaled corticosteroid (ICS) mono products and ICS/LABA combination products will not be permitted within 30 days of the screening visit (visit 1)<br><br>If a patient is washing out of ICS (monotherapy) or ICS/LABA combination therapy as stated above, an additional 3 day window is permitted to complete the assessments for the screening visit (visit 1).<br><br>If the patients were formerly taking LAMA, LABA, or ICS/LABA therapy, the medications will need to be discontinued and may be replaced at the discretion of the Investigator with the short-acting anti-muscarinic agent (SAMA) medication, ipratropium bromide, for use during the course of the study. Patients who have not taken LAMA, LABA or ICS/LABA combination products within the time period specified above, or who are not on medications that are restricted according to the protocol criteria, and who have met the selection criteria (eg, reversibility and baseline safety measures) at the screening visit (visit 1) will begin the 14 (+2) day single-blind placebo run-in period.<br><br>All patients enrolled in the screening/run-in periods will be supplied with the following; ediary/electronic flow meter to measure lung function for monitoring disease stability during the screening and run-in periods; short-acting bronchodilator (SABA), ie, albuterol/salbutamol metered dose inhaler (MDI); 90 mcg ex-actuator or equivalent, for use during the course of the study. Dispensation of the albuterol/ salbutamol MDI is not required during the screening period if the patient is taking this medication as part of their current COPD therapy. Once the patient is enrolled in the run-in period, dispensation/administration of the study albuterol/salbutamol MDI is required and the patient will discontinue the use of their own albuterol/salbutamol MDI. Patients enrolled in the run-in period will also be supplied with placebo Lupin Tiotropium Bromide Inhalation Powder (placebo LUPINHALER) for once daily administration (2 inhalations from one capsule) in the morning throughout the single-blind run-in period. Patients will be required to measure $FEV_1$ prior to dosing in the morning at approximately the same time each day. The $FEV_1$ results and usage of study medication/albuterol/salbutamol MDI will be monitored and recorded in the ediary. Patients will also complete the Exacerbations of Chronic Pulmonary Disease Tool (EXACT®) Patient Reported Outcome (PRO) within the ediary, once daily, each evening before bedtime, during the screening and run-in periods.<br><br>Patients will present at the investigational center for visit 2 on day 0 between 0600 and 1000 having withheld the prohibited/restricted medications for the prescribed protocol-defined period and without conducting lung function |

measurements on the electronic flow meter (home device). Patients will record albuterol/salbutamol MDI usage in their diaries on the mornings prior to this visit. Patients meeting all of the randomization criteria will be randomly assigned to 1 of the following 6 treatment sequences in a double-dummy manner using a Williams design Latin Square:

| Treatment sequence | Treatment period 1 | Treatment period 2 | Treatment period 3 |
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| A (TRP) | Lupin Tiotropium Bromide Inhalation Powder 18 mcg | SPIRIVA HANDIHALER 18 mcg | Placebo |
| B (RPT) | SPIRIVA HANDIHALER 18 mcg | Placebo | Lupin Tiotropium Bromide Inhalation Powder 18 mcg |
| C (PTR) | Placebo | Lupin Tiotropium Bromide Inhalation Powder 18 mcg | SPIRIVA HANDIHALER 18 mcg |
| D (PRT) | Placebo | SPIRIVA HANDIHALER 18 mcg | Lupin Tiotropium Bromide Inhalation Powder 18 mcg |
| E (TPR) | Lupin Tiotropium Bromide Inhalation Powder18 mcg | Placebo | SPIRIVA HANDIHALER 18 mcg |
| F (RTP) | SPIRIVA HANDIHALER 18 mcg | Lupin Tiotropium Bromide Inhalation Powder 18 mcg | Placebo |

In order to maintain the patient blind, a specified member of the investigational center (ie, unblinded administrator) will load and dispense the study medication to the patient and instruct the patients to take 2 full inhalations from each of 2 inhalers. The unblinded administrator will also apply an opaque covering to the chamber windows prior to patient administration to obstruct capsule identification in each inhaler.

Patients will undertake 2 baseline $FEV_1$ measurements at 0 hours (-30 and -15 minutes before study medication administration) followed by serial $FEV_1$ measurements at 5 and 30 minutes postdose, and at 1, 2, 4, 6, 8, 10, 12, 23, and 24 hours postdose. The 23 and 24 hour $FEV_1$ measurements will be taken on the 2$^{nd}$ day of the visit (day 1) in the morning at the investigational center. Prior to and for the duration of the $FEV_1$ measurements at the investigational center visits (day 0 and day 1), patients should refrain from using albuterol/salbutamol MDI and other prohibited medication; patients should not smoke for at least 1 hour prior to lung function assessments during the visit; and patients should adhere to the dietary restrictions as per protocol.

After completion of all assessments at visit 2, the patients will enter a 21-day (+3 days) washout phase where the patients may continue to use albuterol/salbutamol MDI and other medications permitted per protocol (eg, SAMA). Patients will continue to measure lung function for monitoring disease stability during the double-blind treatment period. On days of non-investigational center visits, patients will be required to measure $FEV_1$ once daily prior to dosing in the morning at approximately the same time each day. The $FEV_1$ will be recorded in the ediary/electronic flow meter. Patients will also complete the EXACT once daily, each evening before bedtime

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| | within the ediary. On days of investigational center visits, patients will perform the $FEV_1$ measurements and administer the study medication at the investigational center, and the EXACT will be collected at home in the evening before bedtime. Usage of albuterol/salbutamol MDI will also be recorded in the ediary.<br><br>Prior to visit 3 (days 21 and 22) and visit 4 (days 42 and 43) patients should observe the same smoking, dietary and medication restrictions as visit 2. Patients will record albuterol/salbutamol MDI usage in their diaries on the mornings prior to these visits; however, no $FEV_1$ measurements will be performed in the morning using the electronic flow meter (home device). Patients should present at the investigational center so that the start of lung function testing will be within ±1 hour from the lung function testing at visit 1. Patients will then undertake 2 baseline $FEV_1$ measurements at 0 hours (-30 and -15 minutes before study medication administration), followed by serial $FEV_1$ measurements at 5 and 30 minutes postdose, and at 1, 2, 4, 6, 8, 10, 12, 23, and 24 hours postdose. After completion of all assessments at visit 3 (days 21 and 22), the patient will enter a 21-day (+3 days) washout phase where the patient may continue to use albuterol/salbutamol MDI and other medications permitted per protocol (eg, SAMA).<br><br>After completion of visit 4 (days 42 and 43), a subset of patients (approximately 120 patients) at select investigational centers who successfully completed Part 1 and continue to meet the continuation criteria will be eligible for enrollment into a 12-week open-label extension to examine the robustness of the LUPINHALER. Patients who successfully completed the 3 single-dose treatments in Part 1 and who are not enrolled into the open-label extension (Part 2) will be contacted via phone 7 days (±3 days) after the visit for a final safety check and then formally discharged from the study.<br><br>The open-label extension (Part 2) will consist of 7 visits (visit 5 through visit 10, and follow-up), and will begin on the last day of visit 4 (Part 1). Visits 6 and 8 will be conducted via telephone contact. The final safety follow-up for those patients participating in Part 2 will be conducted via telephone 7 days (±3 days) after the last active treatment of the open-label extension (ie, visit 10).<br><br>Patients participating in the open-label extension will begin study activities on the same day as the final visit in the double-blind treatment period (visit 4), which will be considered the first day of the open-label extension (visit 5). Patients will be issued a 90-day supply of the Lupin Tiotropium Bromide Inhalation Powder, 18 mcg for once-daily administration (to be taken at home each morning) during a 72-day treatment phase. Treatment with the Lupin Tiotropium Bromide Inhalation Powder will begin on visit 5 after all $FEV_1$ assessments and study activities were completed for Part 1. Patients will be permitted to resume other non-study medications and albuterol/salbutamol MDI as permitted per protocol. LAMA medications (mono and combination therapies), other than the study medication, are prohibited in Part 2 of the study. Patients will assess functionality of the LUPINHALER daily and record this data in the ediary.<br><br>Patients will measure lung function to monitor disease stability via the ediary/electronic flow meter during the open-label extension. Patients will be required to measure $FEV_1$ twice daily: upon awakening in the morning immediately prior to dosing with the study medication and at 2 (+2) hours after study medication administration. The $FEV_1$ results and albuterol/salbutamol MDI/study medication usage will be monitored and recorded in the ediary/electronic flow meter. Patients will also complete the |

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| | EXACT once daily, each evening before bedtime within the ediary.<br>At visit 6 and visit 8, patients will be contacted via telephone by investigational center personnel to monitor AEs and any issues regarding the inhaler function.<br>The patients will return to the investigational center on visit 7 and visit 9 for an overall assessment of safety and tolerability, to verify inhaler technique, and to assess any inhaler issues/malfunctions.<br>On visit 10, patients will return for a final treatment visit, in which vital signs will be assessed, inhaler issues/malfunctions assessed, and the ediary/electronic flow meter, albuterol/salbutamol MDI, and study medication collected and stored appropriately. The patient should be contacted via phone 7 ±3 days after the final treatment visit (visit 10) for a final safety check and to be formally discharged from the study.<br>If at any time patients experience a perceived issue with their inhaler, the ediary system will alert the investigational center who will arrange the necessary corrective action, if required. The investigational center should endeavor to complete the electronic case report form (eCRF) within 24 hours of notification of an issue.<br>Safety will be monitored throughout Part 1 and Part 2 of the study by vital signs measurements, albuterol/salbutamol MDI and concomitant medication usage, physical examinations, head, ears, eyes, nose, throat (HEENT)/chest examinations, spirometry ($FEV_1$) measurements, electrocardiography (ECGs), ER-S: COPD scores (derived from the EXACT), COPD exacerbations, and adverse events (AEs). During the screening and run-in periods, safety will be assessed via $FEV_1$ measurements, ER-S: COPD scores, and monitoring of AEs and COPD exacerbations. |
| **Number of Patients Planned** | For Part 1 of the study, in order to have 180 completed per-protocol (PP) patients, approximately 240 male and female patients 40 years of age and older with established COPD will be randomly assigned in order to account for a potential withdrawal rate of 30% from the PP population. Patients will be assigned to 1 of 6 treatment sequences as described in section **7.6**. No estimates of within-patient variability for the primary variable were available in the public domain. As this is necessary for sample size estimation, a blinded interim analysis will be performed in order to assess this variability compared to the estimate used to initially estimate sample size. The blinded interim analysis has the potential to increase the sample size if necessary to maintain 90% power.<br>For Part 2, a subset of patients (approximately 120 patients) who successfully completed Part 1 will be enrolled into the open-label extension to ensure that at least 100 inhalers are returned to Lupin for evaluation of pharmaceutical performance. |
| **Diagnosis and Main Criteria for Enrollment**<br><br>Inclusion Criteria | 1. Patient is able to give signed written informed consent prior to study entry.<br>2. Male or female patients 40 years of age and older, inclusive, as of the screening visit (visit 1).<br>3. Patient has a diagnosis of COPD according to the Global Initiative Chronic Obstructive Lung Disease (GOLD) guidelines 2016.<br>4. Ability to perform acceptable and repeatable spirometry according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 criteria and/or protocol defined criteria.<br>Note: If the patient cannot meet the criterion, the visit may be rescheduled as per the retest criteria (section **9.3.6**). |

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| | 5. Patient is able to achieve an inspiratory flow rate of ≥40 L/min using the In-Check DIAL at the screening visit (visit 1).<br>6. Patient is able to demonstrate proper inhalation technique using the DPI.<br>7. Post-bronchodilator $FEV_1$ of <80% of the predicted value during the screening visit (visit 1). National Health and Nutrition Examination Survey (NHANES) III normative values will be used for all patients with adjustments to these values made for African American patients. All spirometry tests should be carried out in accordance with the ATS/ERS 2005 criteria (Miller et al 2005).<br>Note: If the patient cannot meet the criterion, the visit may be rescheduled as per the retest criteria (section **9.3.6**).<br>8. Post-bronchodilator $FEV_1$/FVC ratio of ≤0.70 at the screening visit (visit 1).<br>Note: If the patient cannot meet the criterion, the visit may be rescheduled as per the retest criteria (section **9.3.6**).<br>9. Patient has demonstrated ≥15% reversibility of $FEV_1$ within 30 or 60 minutes following 68 mcg of ipratropium bromide inhalation (pMDI) at the screening visit (visit 1). If required, spacers are permitted for use during reversibility testing for ipratropium administration. Patients who do not demonstrate a positive improvement of at least 15% in $FEV_1$ measured at 30 or 60 minutes post inhalation will not be eligible to participate in the study. However, based on Investigator judgment, patients will be allowed to retest once no sooner than 24 hours and no later than 2 weeks after the initial failure (see section **9.3.6**). Reversibility values of 14.50-14.99 will be rounded to 15.<br>10. Patient is a current smoker or non-smoker with a minimum 10 pack-years of historical use (the equivalent of one pack per day for 10 years).<br>11. Patient is able to withhold all inhaled SABAs for at least 6 hours and SAMAs for at least 8 hours prior to lung function assessments on study visit days.<br>12. Patient is medically able to tolerate permitted medications without a significant adjustment of dosage, formulation, dosing interval for the duration of the study, and judged able by the Investigator to withhold them for the specified minimum time intervals prior to each clinic visit.<br>13. Patient is free of any concomitant conditions or treatments that could interfere with study conduct, influence the interpretation of study observations/results, or put the patient at increased risk during the study (eg, patient is not able to self-administer study medication or self-complete the ediary).<br>14. Patient did not experience an AE that in the opinion of the Investigator would result in failure to meet the inclusion/exclusion criteria during the screening period.<br>15. If female, is currently not pregnant, breast feeding, or attempting to become pregnant (for 4 weeks before the screening visit (visit 1) and throughout the duration of the study), and is of<br>• nonchildbearing potential, defined as:<br>– ≥1 year post-menopausal<br>– surgically sterile (tubal ligation, oophorectomy, or hysterectomy)<br>– diagnosed as infertile and not undergoing treatment to reverse |

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| | infertility<br>or is of<br>• childbearing potential**,** has a negative serum pregnancy test at the screening visit (visit 1), and willing to commit to using a consistent and acceptable method of birth control as defined below for the duration of the study or exclusively has same-sex partners:<br>– systemic contraception used for ≥1 month prior to screening, including birth control pills, transdermal patch (EVRA® or equivalent), vaginal ring (NUVARING® or equivalent), levonorgestrel implant (NORPLANT® or equivalent), or injectable progesterone (DEPO-PROVERA® or equivalent)<br>– double barrier methods (condoms, cervical cap, diaphragm, and vaginal contraceptive film with spermicide)<br>– intrauterine device (IUD) with a low failure rate <1% per year<br>– monogamous with a vasectomized male partner or exclusively has same-sex partners<br>or is of<br>• childbearing potential and not sexually active, has a negative serum pregnancy test at the screening visit (visit 1), and willing to commit to using a consistent and acceptable method of birth control as defined above for the duration of the study, in the event the patient becomes sexually active<br>**If male** and sexually active, the patient is willing to commit to an acceptable method of birth control for the duration of the study or exclusively has same-sex partners. |
| Exclusion Criteria | 1. Known respiratory disorder other than COPD, including but not limited to the following: alpha-1-antitrypsin deficiency, cystic fibrosis, significant asthma, active bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, pulmonary edema, or interstitial lung disease.<br>2. Evidence or history of other clinically significant disease or abnormality (such as congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, stroke, glaucoma or cardiac dysrhythmia), sleep apnea, malignancy (excluding basal cell carcinoma). In addition, historical or current evidence of significant hematologic, hepatic, neurologic, psychiatric, renal, pulmonary, or other diseases that in the opinion of the Investigator, would put the patient at risk through study participation, or would affect the study analyses if the disease exacerbated during the study.<br>3. Known active tuberculosis.<br>4. Hospitalization for a COPD exacerbation or pneumonia within 12 weeks prior to the screening visit (visit 1).<br>5. History of frequent COPD exacerbations of moderate to severe severity averaging 2 or more per year, or 2 or more exacerbations per year which resulted in hospitalization, averaged over the last 3 years.<br>6. Treatment for a non-hospitalized COPD exacerbation or pneumonia requiring antibiotics and/or systemic corticosteroids within 12 weeks prior to the screening visit (visit 1).<br>7. History of paradoxical bronchospasm, narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction, which, in the Investigator's opinion, would contraindicate the use of an anticholinergic agent. |

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| | 8. The patient is pregnant or lactating, or plans to become pregnant or donate gametes (ova or sperm) during the study period or for 30 days after the patient's last study-related visit (for eligible patients only, if applicable). Eligible female and male patients unwilling to employ appropriate contraceptive measures to ensure that pregnancy will not occur during the study will be excluded. Any patient becoming pregnant during the study will be withdrawn from the study.<br>9. Treatment with any protocol prohibited medications during the prescribed washout period before the screening visit (visit 1).<br>10. Inability to discontinue COPD medications during the screening, run-in, and treatment periods.<br>11. Documented or suspected viral or bacterial, upper respiratory infection (URI) or lower respiratory infection (LRI), sinusitis, sinus infection, rhinitis, pharyngitis, middle ear infection, urinary tract infection, or illness within 6 weeks prior to the screening visit (visit 1).<br>12. History of allergy or hypersensitivity to anticholinergic/muscarinic receptor antagonist agent, beta-2 agonists, lactose/milk proteins, or specific intolerance to aerosolized tiotropium bromide containing products, or known hypersensitivity to any of the proposed ingredients or components of the delivery system.<br>13. Factors (eg, infirmity, disability, or geographic location) that the Investigator feels would likely limit the patient's compliance with the study protocol or scheduled clinic visits.<br>14. Current evidence or known history of alcohol or substance abuse within 2 years of the screening visit (visit 1).<br>15. Positive urine drug screen at the screening visit (visit 1). If a patient has a positive urine drug screen for a class of drug which is consistent with a medication that the patient is currently prescribed (excluding inhaled marijuana), the patient can be considered eligible for the study after the prescription is confirmed by the Investigator.<br>16. Clinically significant abnormalities as judged by the Investigator on the 12-lead ECG at the screening visit (visit 1).<br>17. History of a positive test for infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C.<br>18. Patient is either an employee of the investigational center or an immediate relative of an employee of the investigational center.<br>19. History of lung volume reduction surgery, lung resection or on active phase of pulmonary rehabilitation within the previous 12 months prior to the screening visit (visit 1).<br>20. Chronic oxygen use for >12 hours/day.<br>21. Patient does not maintain regular day/night waking/sleeping cycles (eg. night shift workers). |
| Randomization Criteria | 1. Patient continues to be in general good health, and continues to meet all study entry criteria.<br>2. Patient has not experienced an AE that would result in failure to continue to meet selection criteria.<br>3. Patient has had no significant changes in COPD medications or taken any prohibited medication during the screening and run-in period.<br>4. Patient has had no COPD exacerbation during the screening and run-in period as defined in section **6.5**. |

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| | 5. Patient has withheld all inhaled SABAs for at least 6 hours and SAMAs for at least 8 hours prior to lung function assessments at visit 2.<br>6. Patient has not had a viral/bacterial URI or LRI during the screening and run-in period. A patient who develops symptoms of a URI or LRI during the screening and run-in period may rescreen once no sooner than 6 weeks after resolution of symptoms, and at the discretion of the Investigator (see section **9.3.7**).<br>7. Patient has not had clinically significant abnormalities as judged by the Investigator on the 12-lead ECG at visit 2.<br>8. Patient has no clinically significant laboratory abnormality as judged by the Investigator at the screening visit (visit 1).<br>9. Patient has demonstrated ediary compliance to placebo run-in medication within the margins of at least ≥75% and ≤125% of projected use.<br>10. Patient has completed diary data on a minimum of 5 days out of the last 7 days prior to randomization (not including the day of randomization) and has achieved a minimum of 75% compliance with the ediary during the run-in period. |
| Continuation Criteria | 1. Patient continues to be in general good health, and continues to meet study eligibility criteria.<br>2. Patient has not had a moderate to severe COPD exacerbation during the double-blind period in Part 1 as defined in section **6.5**.<br>3. Patient has not had a viral/bacterial URI or LRI during the double-blind treatment in Part 1. See section **6.5**.<br>4. Patient's pre-bronchodilator $FEV_1$ at visits 3 through 4 does not vary by more than ±10% of the value obtained at the randomization visit (visit 2). Retests will be permitted at discretion of the Investigator and per the retest criteria is section **9.3.6**.<br>Note: The pre-bronchodilator $FEV_1$ value constitutes the average of the 2 values taken at 30 and 15 minutes before dosing with study medication.<br>5. Patient has not had clinically significant abnormalities as judged by the Investigator on the 12-lead ECG at visits 3-4.<br>6. Patient has not experienced an AE that would result in failure to continue to meet the selection/continuation criteria. |
| **Study Endpoints**<br>Primary Endpoint | The primary endpoint is the change from baseline in $FEV_1AUC_{0\text{-}24h}$ on day 1. |
| Safety Endpoints | Safety will be assessed throughout Part 1 and Part 2 of the study by monitoring the following:<br>• AEs<br>• SABA (albuterol/salbutamol MDI) and concomitant medication use<br>• vital signs measurements<br>• physical examinations<br>• HEENT and chest examinations<br>• COPD exacerbations<br>• 12-lead ECGs |
| Other Endpoints | For a subset of the LUPINHALERs used during the open-label extension (Part 2), the following endpoints will be assessed:<br>• ruggedness of the LUPINHALER during 72 days of in-patient use: |

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| | • percent (%) of overall inhalers with reported problems or malfunctions; comprised of problems/malfunctions encountered with the device (eg, lack of efficacy, mechanical problems, problems with device after it has been dropped) during 72 days of in-patient use<br>• in vitro performance of 100 inhalers post 72 days of in-patient use |
| **Test Product, Dose, and Mode of Administration** | **Test product:** Tiotropium bromide inhalation powder, 18 mcg<br>**Manufacturer:** Lupin Limited<br>**Mode of Administration:** Oral inhalation via LUPINHALER<br>**Dose:** Part 1: Single-dose of 2 inhalations from one capsule at visits 2-4, per the treatment sequence<br>Part 2: Two inhalations from one capsule, once daily in the morning for 72 days of treatment |
| **Reference Product, Dose, and Mode of Administration** | **Reference product:** SPIRIVA HANDIHALER (tiotropium bromide inhalation powder), 18 mcg<br>**Manufacturer:** Boehringer Ingleheim<br>**Mode of Administration:** Oral inhalation<br>**Dose:** (Part 1 only), Single-dose of 2 inhalations from one capsule at visits 2-4, per the treatment sequence |
| **Test Placebo Product, Dose, and Mode of Administration** | **Placebo product:** Identical to Lupin test product with no active ingredient (placebo LUPINHALER)<br>**Manufacturer:** Lupin Limited<br>**Mode of Administration:** Oral inhalation<br>**Dose:** (Part 1 only), Single-dose of 2 inhalations from one capsule at visits 2-4, per the treatment sequence |
| **Reference Placebo, Dose, and Mode of Administration** | **Placebo product:** SPIRIVA HANDIHALER reference product with no active ingredient using the Lupin placebo capsule (placebo SPIRIVA HANDIHALER)<br>**Manufacturer:** Boehringer Ingleheim<br>**Mode of Administration:** Oral inhalation<br>**Dose:** (Part 1 only), Single-dose of 2 inhalations from one capsule at visits 2-4, per the treatment sequence |
| **Statistical Methods**<br>**Sample Size Determination** | The sample size estimation was determined based on demonstrating equivalence between the Test (T) product (Lupin Tiotropium Bromide Inhalation Powder) and the Reference (R) product (SPIRIVA HANDIHALER) for the primary endpoint change from baseline in $FEV_1$ $AUC_{0-24}$ on the treatment day, and to demonstrate that both the Test (T) and Reference (R) products are superior to the placebo. Bioequivalence (BE) will be demonstrated if the 90% confidence interval (CI) on the T to R ratio for the endpoint is contained within the interval (0.80, 1.25). Superiority will be demonstrated by showing that each active treatment's response for the endpoint is greater than, and statistically different from ($p<0.05$, two-sided), that of the placebo (P). For the equivalence evaluation, the results in the PP analysis set will be considered definitive and for the superiority evaluations, those in the Intent-to-Treat (ITT) population will be considered definitive.<br>A review of the literature did not yield any estimates of within-patient variability of baseline-adjusted $FEV_1$ $AUC_{0-24}$ from a crossover study using a similar patient population with similar objectives. From a review of studies on clinicaltrials.gov, there were a number of estimates available of between-patient variability for baseline-adjusted $FEV_1$ $AUC_{0-24}$. From the 12 studies reviewed, the mean coefficient of variation (CV) for the variable |

| | |
|---|---|
| | was 121%. Within-patient variability is generally much less than between-patient variability. As a starting point for the sample size estimation it was assumed that the within-patient variability would be about 50% of the between-patient variability, or a CV of 60%.<br><br>The goal of the study is to complete 180 patients per protocol. With a sample size in each of the 6 sequence groups of 30, for a total sample size of 180, a crossover design will have 90% power to reject both the null hypothesis that the ratio of the test mean to the standard mean is below 0.80 and the null hypothesis that the ratio of test mean to the standard mean is above 1.25 (ie, that the test and standard are not equivalent), in favor of the alternative hypothesis that the means of the 2 treatments are equivalent, assuming that the expected ratio of means is 1.00, the between-patient coefficient of variation is 1.21, the intra-patient coefficient of variation is 0.60. In order to allow for a potential 30% premature withdrawal rate or loss from the PP population due to protocol deviations, 240 patients will be randomized in total, 40 to each of the 6 treatment sequences. .<br><br>As no estimates of within-patient variability were available in the public domain, a blinded interim analysis will be conducted in order to assess the within-patient variability. The blinded interim analysis will be done to ascertain if an increase in sample size is necessary maintain 90% power to complete the study with a 90% CI for the relative bioavailability of the Test (T) to the Reference (R) product inside of the pre-specified interval 0.80-1.25. |
| Analysis of Primary Endpoints | This crossover study will follow a Williams design with 6 treatment sequences balanced for first order carryover effects. A mixed model analysis consisting of fixed effects of treatment, visit, and sequence, and the random effect of patient will be carried out.<br><br>The analysis of primary endpoints for BE will be performed with this model on the PP population which will include all patients in the PP population who have generated $FEV_1$ data over 24 hours.<br><br>The 90% CI on the ratio of the T-to-R means will be constructed using Fieller's method. Bioequivalence (BE) will be declared if the 90% CI is entirely contained within the BE interval, 0.800 to 1.250.<br><br>Adequate study sensitivity will be demonstrated if the Test (T) and Reference (R) products are shown to be statistically superior to placebo (two-sided, $p<0.05$, by applying the mixed model analysis to the ITT population. |
| Analysis of Safety Endpoints | All safety endpoints will be tabulated by treatment on the safety analysis set without formal inferential statistics. AEs will be mapped using Medical Dictionary for Regulatory Activities (MedDRA) with respect to the system organ class and preferred term. Incidence of treatment-emergent AEs and serious adverse events (SAEs) will be tabulated. Observed and change from baseline in vital signs, physical examinations, HEENT and chest examinations, COPD exacerbations, and ECGs will be tabulated by study medication. |

# 2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| ANCOVA | analysis of covariance |
| ATS | American Thoracic Society |
| $AUC_{0-24}$ | area under the curve from time zero to 24 hours postdose |
| CDER | Center for Drug Evaluation and Research |
| CDMS | clinical data management system |
| CFR | Code of Federal Regulation |
| CI | confidence interval |
| CRF | case report form |
| CRO | Contract research organization |
| COPD | chronic obstructive pulmonary disease |
| CV | coefficient of variation |
| CYP3A4 | cytochrome P450 3A4 |
| DALYS | Disability Adjusted Life Years |
| DPI | dry powder inhaler |
| ECG | Electrocardiogram |
| ERS | European Respiratory Society |
| ER-S | Evaluating Respiratory Symptoms |
| ET | early termination |
| EU | European Union |
| eCRF | electronic case report form |
| EXACT PRO (EXACT) | Exacerbations of Chronic Pulmonary Disease Tool Patient Reported Outcome |
| FDA | Food and Drug Administration |
| $FEV_1$ | forced expiratory volume in the first second |
| GCP | Good Clinical Practice |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| HEENT | head, ears, eyes, nose, and throat |
| HIPAA | Health Insurance Portability and Accountability Act Authorization |
| HIV | human immunodeficiency virus |
| [redacted] | [redacted] |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IRT | interactive response technology |
| ITT | intent-to-treat |
| IUD | intrauterine device |

| | |
|---|---|
| Iv | Intravenous |
| LABA | long-acting beta agonist |
| LAMA | long-acting anti-muscarinic agent |
| LCM | Local Clinical Management |
| LLT | lowest level term |
| LRI | lower respiratory infection |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MDI | metered dose inhaler |
| NHANES III | National Health and Nutrition Examination Survey III |
| OTC | over-the-counter |
| P | Placebo |
| PD | pharmacodynamics(s) |
| PFTs | pulmonary function tests |
| PK | Pharmacokinetic |
| PT | preferred term |
| pMDI | pressurized metered dose inhaler |
| PP | per-protocol |
| PRN | as needed |
| R | Reference |
| RLD | reference listed drug |
| SABA | short-acting beta agonist |
| SAMA | short-acting anti-muscarinic agent |
| SAE(s) | serious adverse event(s) |
| SAP | statistical analysis plan |
| sNDA | Supplemental New Drug Application |
| SOC | system organ class |
| SUSAR | serious unexpected adverse reactions |
| T | Test |
| $t_{max}$ | time to maximum bronchodilator response |
| URI | upper respiratory infection |
| USA | United States of America |
| USC | United States Code |

# 3 INTRODUCTION

## 3.1 BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease which is characterized by persistent airflow limitation that is usually progressive and is associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases (**Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2016**). Exacerbations and associated co-morbidities contribute to the overall severity in individual patients and present targets for treatment (**GOLD 2016**).

Chronic obstructive pulmonary disease (COPD) is the 4$^{th}$ leading cause of mortality globally (**GOLD 2016**) and this is set to increase in prevalence partially in response to historical smoking trends over past decades, although outdoor, occupational and indoor pollutants are also a major risk factor in development of COPD.

In the United States of America (USA) the estimated direct costs of COPD are around $29.5 billion annually with indirect costs of $20.4 billion; in Europe the burden of COPD makes up around 6% of the total healthcare budget. Fewer than 6% of the adult population have been diagnosed with COPD although there is a significant level of under diagnosis and the overall incidence is likely to be higher than this (van den Boom 1998).

Disease progression is generally associated with increasing levels for disability. The overall impact of disability and mortality can be quantified by Disability Adjusted Life Years (DALYs) which represent the sum of years lost due to premature mortality plus the sum of years lived with disability. Chronic obstructive pulmonary disease (COPD) is set to rise from the twelfth highest driver for DALYs in 1990 to the seventh highest by 2030 (**Mathers 2006**).

The goals of COPD therapy are focused initially on smoking cessation for subjects who continue to smoke followed by relief of symptoms, moderation of exacerbation frequency and severity and improvement in health quality and exercise tolerance (**GOLD 2016**).

Initial treatments for intermittent symptoms tend to be short-acting bronchodilators (SABAs) which are generally either beta-agonists (eg, albuterol) or anticholinergics (eg, ipratropium). The duration of action of SABAs is limited and as symptoms progress these are largely substituted by long-acting bronchodilators (LABAs), which include a variety of beta-agonists or anticholinergic medications. Long-acting bronchodilators (LABAs) can be used in isolation or as a combination of mechanisms for greater symptom control, or with the addition of broad spectrum anti-inflammatory medications such as inhaled corticosteroids for patients with more severe disease or at increased risk of exacerbations. The anticholinergic medications work by blocking the effect of acetylcholine on muscarinic receptors which results in smooth muscle relaxation and bronchodilation, which opens the airways and lowers airway resistance.

Tiotropium bromide is one of a number of long-acting anticholinergic medications approved for use with COPD. Tiotropium bromide under the trade name SPIRIVA® was approved by the Food and Drug Administration (FDA) in 2004 as a single-dose dry powder device delivered by the HANDIHALER® device for the long-term, once daily

maintenance treatment of bronchospasm associated with COPD. In 2009, a supplementary New Drug Application (sNDA) was granted for the indication to be expanded to include COPD exacerbation reduction. Tiotropium has been shown to reduce exacerbations and related hospitalization, improve health status (**Barr 2005**) and increase the effectiveness of pulmonary rehabilitation (**Cheyne 2013**), in addition to providing a maintenance therapy for bronchospasm.

Lupin Inc. is developing Tiotropium Bromide Inhalation Powder, equivalent to 18 mcg tiotropium/capsule (hereinafter referred to Lupin Tiotropium Bromide Inhalation Powder) as a substitutable product for SPIRIVA HANDIHALER. The strategy for the proposed clinical development of Lupin Tiotropium Bromide Inhalation Powder includes a total of 2 pivotal clinical studies: one assessing pharmacokinetic (PK) bioequivalence (BE) and one assessing pharmacodynamics (PD) BE of Lupin Tiotropium Bromide Inhalation Powder and SPIRIVA HANDIHALER. In addition, pilot studies are planned to examine the PK endpoints of Lupin Tiotropium Bromide Inhalation Powder compared to SPIRIVA HANDIHALER. Refer to section **3.2** regarding recent clinical experience with Tiotropium Bromide Inhalation Powder.

## 3.2 CLINICAL EXPERIENCE WITH TIOTROPIUM BROMIDE INHALATION POWDER ADMINISTERED BY A DRY POWDER HANDIHALER (DPI)

SPIRIVA is marketed in 2 different delivery formats: as a single-dose DPI delivering 18 mcg of tiotropium from a capsule via the HANDIHALER device and as a multiple dose aqueous solution aerosolized mist inhaler delivering 1.25 or 2.5 mcg tiotropium per actuation via the RESPIMAT® device. These devices are marketed in the USA, Europe and, Japan under the same SPIRIVA trade name.

SPIRIVA has been found to the well tolerated with the most common side effect of dry mouth. Uncommon potential side effects include constipation, increased heart rate, blurred vision, glaucoma, urinary deficiency and urinary retention. Because Lupin Tiotropium Bromide Inhalation Powder is designed to be a substitutable product for SPIRIVA HANDIHALER, the safety profile is expected to be similar to SPIRIVA.

To date, 2 clinical studies (Study LBC-P-055-15 and LBC-P-006-15) with Lupin Tiotropium Bromide Inhalation Powder have been conducted.

Study LBC-P-055-15 was a randomized, open-label, single-dose, 3-period Phase 1, PK crossover study being conducted in healthy male subjects 18-45 years of age under fasting conditions. The primary objective of the study was to assess the systemic levels and relative bioavailability of a single orally-administered dose of tiotropium (36 mcg), administered as 2 inhalations from 1 batch of Lupin tiotropium capsules 18 mcg (×2 capsules) via both the LUPINHALER and HANDIHALER, and 1 batch of SPIRIVA capsules 18 mcg (×2 capsules) via the HANDIHALER.

Preliminary safety results from this study indicate that Tiotropium Bromide Inhalation Powder was well tolerated by the healthy subjects, ages 18 to 45 years. No SAEs were reported. The final statistical analyses and PK results are not available at this time. Because this was a pilot study used to screen a formulation of test product which is not

representative of the exhibit batch to be used in the pivotal BE in vivo studies, data is on file and not presented in this section.

Study LBC-P-0006-15 was a randomized, open-label, single-dose, 3-period Phase 1, PK crossover study being conducted in healthy male subjects 18-45 years of age under fasting conditions. The primary objective of the study was to assess the systemic levels and relative bioavailability of a single orally-administered dose of tiotropium (18 mcg), from 2 different batches of Lupin tiotropium capsules 18 mcg (×1 capsule) via the LUPINHALER, and 1 batch of SPIRIVA capsules 18 mcg (×1 capsule) via the HANDIHALER.

Preliminary safety results from this study indicate that Tiotropium Bromide Inhalation Powder was well tolerated by the healthy subjects, ages 18 to 45 years. No SAEs were reported. The final statistical analyses and PK results are not available at this time.

## 3.3 STUDY PURPOSE

Lupin Inc. is developing Tiotropium Bromide Inhalation Powder as a substitutable product for SPIRIVA HANDIHALER. This study is designed to show BE in terms of efficacy between the Lupin Tiotropium Bromide Inhalation Powder, 18 mcg administered as a single dose versus SPIRIVA HANDIHALER, 18 mcg. This study will also assess device robustness of the LUPINHALER.

# 4 STUDY OBJECTIVES

## 4.1 PRIMARY OBJECTIVE

The primary objective of this study is to show clinical BE in the efficacy of the Lupin Tiotropium Bromide Inhalation Powder, 18 mcg administered as a single dose versus SPIRIVA HANDIHALER, 18 mcg based on the adjusted mean change in forced expiratory volume in the first second ($FEV_1$) area under the curve from time zero to 24 hours postdose ($AUC_{0-24h}$) on day 1.

## 4.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to evaluate the safety and tolerability of the Lupin Tiotropium Bromide Inhalation Powder and SPIRIVA HANDIHALER following single doses of 18 mcg in patients 40 years of age and older with COPD.

## 4.3 OTHER OBJECTIVES

For a subset of the Lupin tiotropium DPIs (LUPINHALER™) used during the open-label extension (Part 2) the following objectives will be assessed:

- ruggedness of the LUPINHALER during 72 days of in-patient use
- in vitro performance post 72 days of in-patient use

## 4.4 STUDY ENDPOINTS

### 4.4.1 Primary Efficacy Endpoint

The primary endpoint is the change from baseline in $FEV_1$ $AUC_{0-24h}$ on day 1. On each study day in Part 1, baseline is defined as the average of the $FEV_1$ values recorded at approximately 30 minutes and 15 minutes before dosing.

### 4.4.2 Safety Endpoints

Safety will be assessed throughout Part 1 and Part 2 of the study by monitoring the following:

- adverse events (AEs)
- SABA (albuterol/salbutamol MDI) and concomitant medication use
- vital signs measurements
- physical examinations
- head, ears, eyes, nose, and throat (HEENT) and chest examinations
- COPD exacerbations
- 12-lead electrocardiograms (ECGs)

### 4.4.3 Other Endpoints

For a subset of the LUPINHALERs used during the open-label extension (Part 2), the following endpoints will be assessed:

- ruggedness of the LUPINHALER during 72 days of in-patient use
  - percent (%) of overall inhalers with reported problems or malfunctions; comprised of misuse episodes (eg, impact and moisture) and issues identified (eg, mechanical problems and COPD worsening/seems ineffective) during 72 days of in-patient use
- in vitro pharmaceutical performance of 100 inhalers post 72 days of in-patient use

  The data resulting from the in vitro evaluation of the pharmaceutical performance will be presented in a separate report.

# 5 INVESTIGATIONAL PLAN

## 5.1 OVERALL DESIGN AND PLAN OF THE STUDY

This is a 2-part clinical study:

- **Part 1** is a randomized, double-blind, double-dummy, placebo-controlled, 3-period, single-dose crossover study that will evaluate the clinical BE of single-dose treatment of Lupin Tiotropium Bromide Inhalation Powder, 18 mcg and SPIRIVA HANDIHALER, 18 mcg in patients 40 years of age and older with established COPD.
- **Part 2** is a 12-week open-label extension of Part 1, which will enroll a subset of patients at select investigational centers who successfully completed Part 1 of the study, to assess robustness of the LUPINHALER over 72 days of treatment.

The duration of patient participation for Part 1 is approximately 14 weeks and for patients participating in both Part 1 and Part 2, the duration of patient participation is approximately 26 weeks.

### 5.1.1 Part 1: Double-Blind Treatment Period

Part 1 of the study consists of a screening period up to 30 days, followed by a single-blind placebo run-in period of 14 (+2) days and 3 single-dose, double-blind treatment periods (visits 2-4) each separated by a 21-day (+3 days) washout period. Each double-blind treatment period begins with administration of the study medication at the investigational center, followed by lung function assessments collected over a 24-hour period. For patients ending participation in the study after completing Part 1 and not enrolling into the open-label extension (Part 2), a follow-up visit via phone contact will be conducted 7 days (±3 days) after the completion of treatment period 3 (visit 4).

The screening period, of up to 30 days, allows for adequate washout of the following COPD therapies, along with other prohibited medications per protocol:

- long-acting anti-muscarinic agent (LAMA) medications (including mono products and combination products containing LAMAs [eg, LAMA/LABA]) will not be permitted within 21 days of the screening visit (visit 1)
- long-acting beta agonist (LABA) mono products will not be permitted within 7 days of the screening visit (visit 1)
- inhaled corticosteroid (ICS) mono products and ICS/LABA combination products will not be permitted within 30 days of the screening visit (visit 1)

If a patient is washing out of ICS (monotherapy) or ICS/LABA combination therapy as stated above, an additional 3 day window is permitted to complete the assessments for the screening visit (visit 1).

If the patients were formerly taking LAMA, LABA, or ICS/LABA therapy, the medications will need to be discontinued and may be replaced at the discretion of the Investigator with the short-acting anti-muscarinic agent (SAMA) medication, ipratropium bromide, for use during the course of the study. Patients who have not taken LAMA,

LABA or ICS/LABA combination products within the time period specified above, or who are not on medications that are restricted according to the protocol criteria, and who have met the selection criteria (eg, reversibility and baseline safety measures) at the screening visit (visit 1) will begin the 14 (+2) day single-blind placebo run-in period.

All patients enrolled in the screening/run-in periods will be supplied with the following; ediary/electronic flow meter to measure lung function for monitoring disease stability during the screening and run-in periods; short-acting bronchodilator (SABA), ie, albuterol/salbutamol metered dose inhaler (MDI); 90 mcg ex-actuator or equivalent, for use during the course of the study. Dispensation of the albuterol/ salbutamol MDI is not required during the screening period if the patient is taking this medication as part of their current COPD therapy. Once the patient is enrolled in the run-in period, dispensation/administration of the study albuterol/salbutamol MDI is required and the patient will discontinue the use of their own albuterol/salbutamol MDI. Patients enrolled in the run-in period will also be supplied with a placebo Lupin Tiotropium Bromide Inhalation Powder (placebo LUPINHALER) for once daily administration (2 inhalations from one capsule) in the morning throughout the single-blind run-in period. Patients will be required to measure $FEV_1$ prior to dosing in the morning at approximately the same time each day. The $FEV_1$ results and usage of study medication/albuterol/salbutamol MDI will be monitored and recorded in the ediary. Patients will also complete the Exacerbations of Chronic Pulmonary Disease Tool (EXACT®) Patient Reported Outcome (PRO) within the ediary, once daily, each evening before bedtime during the screening and run-in periods.

Patients will present at the investigational center for visit 2 on day 0 between 0600 and 1000 having withheld the prohibited/restricted medications for the prescribed protocol period and without conducting lung function measurements on the electronic flow meter (home device). Patients will record albuterol/salbutamol MDI usage in their diaries on the mornings prior to this visit. Patients meeting all of the randomization criteria will be randomly assigned to 1 of 6 treatment sequences in a double-dummy manner using a Williams design Latin Square as described in section 7.

In order to maintain the patient blind, a specified member of the investigational center (ie, unblinded administrator) will load and dispense the study medication to the patient and instruct the patients to take 2 full inhalations from each of 2 inhalers. The unblinded administrator will also apply an opaque covering to the chamber windows prior to patient administration to obstruct capsule identification in each inhaler.

Patients will undertake 2 baseline $FEV_1$ measurements at 0 hours (-30 and -15 minutes before study medication administration) followed by serial $FEV_1$ measurements at 5 and 30 minutes postdose, and at 1, 2, 4, 6, 8, 10, 12, 23, and 24 hours postdose. The 23 and 24 hour $FEV_1$ measurements will be taken on the 2nd day of the visit (day 1) in the morning at the investigational center. Prior to and for the duration of the $FEV_1$ measurements at the investigational center visits (day 0 and day 1), patients should refrain from using albuterol/salbutamol MDI and other prohibited medication; patients should not smoke for at least 1 hour prior to lung function assessments during the visit; and patients should adhere to the dietary restrictions as per protocol.

After completion of all assessments at visit 2, the patients will enter a 21-day (+3 days) washout phase where the patients may continue to use albuterol/salbutamol MDI and other medications permitted per protocol (eg, SAMA). Patients will continue to measure lung function for monitoring disease stability during the double-blind treatment period. On days of non-investigational center visits, patients will be required to measure $FEV_1$ once daily prior to dosing in the morning at approximately the same time each day. The $FEV_1$ will be recorded in the ediary/electronic flow meter. Patients will also complete the EXACT once daily, each evening before bedtime within the ediary. On days of investigational center visits, patients will perform the $FEV_1$ measurements and administer the study medication at the investigational center, and the EXACT will be collected at home in the evening before bedtime. Usage of albuterol/salbutamol MDI will also be recorded in the ediary.

Prior to visit 3 (days 21 and 22) and visit 4 (days 42 and 43) patients should observe the same smoking, dietary and medication restrictions as visit 2. Patients will record albuterol/salbutamol MDI usage in their diaries on the mornings prior to these visits; however, no $FEV_1$ measurements will be performed in the morning using the electronic flow meter (home device). Patients should present at the investigational center so that the start of lung function testing will be within ±1 hour from the lung function testing at visit 1. Patients will then undertake 2 baseline $FEV_1$ measurements at 0 hours (-30 and -15 minutes before study medication administration), followed by serial $FEV_1$ measurements at 5 and 30 minutes postdose, and at 1, 2, 4, 6, 8, 10, 12, 23, and 24 hours postdose. After completion of all assessments at visit 3 (days 21 and 22), the patient will enter a 21-day (+3 days) washout phase where the patient may continue to use albuterol/salbutamol MDI and other medications permitted per protocol (eg, SAMA).

After completion of visit 4 (days 42 and 43), a subset of patients (approximately 120 patients) at select investigational centers who successfully completed Part 1 and continue to meet the continuation criteria will be eligible for enrollment into a 12-week open-label extension to examine the robustness of the LUPINHALER. Patients who successfully completed the 3 single-dose treatments in Part 1 and who are not enrolled into the open-label extension (Part 2) will be contacted via phone 7 days (±3 days) after the visit for a final safety check and then formally discharged from the study.

### 5.1.2 Part 2: Open-Label Extension

The open-label extension (Part 2) will consist of 7 visits (visit 5 through visit 10, and follow-up), and will begin on the last day of visit 4 (Part 1). Visits 6 and 8 will be conducted via telephone contact. The final safety follow-up for those patients participating in Part 2 will be conducted via telephone 7 days (±3 days) after the last active treatment of the open-label extension (ie, visit 10).

Patients participating in the open-label extension will begin study activities on the same day as the final visit in the double-blind treatment period (visit 4), which will be considered the first day of the open-label extension (visit 5). Patients will be issued a 90-day supply of the Tiotropium Bromide Inhalation Powder, 18 mcg for once-daily administration (to be taken at home each morning) during a 72-day treatment phase. Treatment with the Lupin Tiotropium Bromide Inhalation Powder will begin on visit 5 after all $FEV_1$ assessments and study activities were completed for Part 1. Patients will

be permitted to resume other non-study medications and albuterol/salbutamol MDI as permitted per protocol. LAMA medications (mono and combination therapies), other than the study medication, are prohibited in Part 2 of the study. Patients will assess functionality of the LUPINHALER daily and record this data in the ediary.

Patients will measure lung function to monitor disease stability via the ediary/electronic flow meter during the open-label extension. Patients will be required to measure $FEV_1$ twice daily: upon awakening in the morning immediately prior to dosing with the study medication and at 2 (+2) hours after study medication administration. The $FEV_1$ results and albuterol/salbutamol MDI/study medication usage will be monitored and recorded in the ediary/electronic flow meter. Patients will also complete the EXACT once daily, each evening before bedtime within the ediary.

At visit 6 and visit 8, patients will be contacted via telephone by investigational center personnel to monitor AEs and any issues regarding the inhaler function.

The patients will return to the investigational center on visit 7 and visit 9 for an overall assessment of safety and tolerability, to verify inhaler technique, and to assess any inhaler issues/malfunctions.

On visit 10, patients will return for a final treatment visit, in which vital signs will be assessed, inhaler issues/malfunctions assessed, and the ediary/electronic flow meter, albuterol/salbutamol MDI, and study medication collected and stored appropriately. The patient should be contacted via phone 7 ±3 days after the final treatment visit (visit 10) for a final safety check and to be formally discharged from the study.

If at any time patients experience a perceived issue with their inhaler, the ediary system will alert the investigational center who will arrange the necessary corrective action, if required. The investigational center should endeavor to complete the electronic case report form (eCRF) within 24 hours of notification of an issue.

Safety will be monitored throughout Part 1 and Part 2 of the study by vital signs measurements, albuterol/salbutamol MDI and concomitant medication usage, physical examinations, head, ears, eyes, nose, throat (HEENT)/chest examinations, spirometry ($FEV_1$) measurements, electrocardiography (ECGs), ER-S: COPD scores (derived from the EXACT), COPD exacerbations, and AEs. During the screening and run-in periods, safety will be assessed via $FEV_1$ measurements, ER-S: COPD scores, and monitoring of AEs and COPD exacerbations.

Refer to section **9.2.2.5** for details regarding COPD exacerbations.

## 5.2 DOSE RATIONALE

The dose of the test product, Lupin Tiotropium Bromide Inhalation Powder, 18 mcg will be administered as 2 inhalations once daily via LUPINHALER, and is the maintenance dose of the marketed comparator product in this study (SPIRIVA HANDIHALER, 18 mcg).

# 6 SELECTION OF STUDY POPULATION

For Part 1 of the study, patients will include male and female patients 40 years of age and older with COPD. Part 2 of the study will enroll a subset of approximately 120 patients (from select investigational centers) who have successfully completed Part 1 of the study meeting and continue to meet the continuation criteria). The duration of patient participation for Part 1 is approximately 14 weeks and for patients participating in both Part 1 and Part 2, the duration of patient participation is approximately 26 weeks.

For Part 1, 240 patients will need to be randomized to allow for a 30% withdrawal rate with a goal of completing at least 180 per-protocol (PP) patients (40 per treatment sequence). A blinded interim analysis will be performed in order to assess variability with the potential to increase the sample size to maintain 90% power.

## 6.1 INCLUSION CRITERIA

A patient will be eligible for enrollment if all of the following inclusion criteria apply:

1. Patient is able to give signed written informed consent prior to study entry.
2. Male or female patients 40 years of age and older, inclusive, as of the screening visit (visit 1).
3. Patient has a diagnosis of COPD according to the GOLD guidelines 2016.
4. Ability to perform acceptable and repeatable spirometry according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 criteria and/or protocol defined criteria.

   Note: If the patient cannot meet the criterion, the visit may be rescheduled as per the retest criteria (section **9.3.6**).
5. Patient is able to achieve an inspiratory flow rate of ≥40 L/min using the In-Check DIAL by achieving ≥40 L/min inspiratory flow rate at the screening visit (visit 1).
6. Patient is able to demonstrate proper inhalation technique using the DPI.
7. Post-bronchodilator $FEV_1$ of <80% of the predicted value at the screening visit (visit 1). National Health and Nutrition Examination Survey (NHANES) III normative values will be used for all patients with adjustments to these values made for African American patients. All spirometry tests should be carried out in accordance with the ATS/ERS 2005 criteria (**Miller et al 2005**).

   Note: If the patient cannot meet the criterion, the visit may be rescheduled as per the retest criteria (section **9.3.6**).
8. Post bronchodilator $FEV_1$/FVC ratio of ≤0.70 at the screening visit (visit 1).

   Note: If the patient cannot meet the criterion, the visit may be rescheduled as per the retest criteria (section **9.3.6**).
9. Patient has demonstrated ≥15% reversibility of $FEV_1$ within 30 or 60 minutes following 68 mcg of ipratropium bromide inhalation (pMDI) at the screening visit (visit 1). If required, spacers are permitted for use during reversibility testing for

ipratropium administration. Patients who do not demonstrate a positive improvement of at least 15% in $FEV_1$ measured at 30 or 60 minutes post inhalation will not be eligible to participate in the study. However, based on Investigator judgment, patients will be allowed to retest once no sooner than 24 hours and no later than 2 weeks after the initial failure (see section **9.3.6**). Reversibility values of 14.50-14.99 will be rounded to 15.

10. Patient is a current smoker or non-smoker with a minimum 10 pack-years of historical use (the equivalent of one pack per day for 10 years).
11. Patient is able to withhold all inhaled SABAs for at least 6 hours and SAMAs for at least 8 hours prior to lung function assessments on study visit days.
12. Patient is medically able to tolerate permitted medications without a significant adjustment of dosage, formulation, dosing interval for the duration of the study, and judged able by the Investigator to withhold them for the specified minimum time intervals prior to each clinic visit.
13. Patient is free of any concomitant conditions or treatments that could interfere with study conduct, influence the interpretation of study observations/results, or put the patient at increased risk during the study (eg, patient is not able to self-administer study medication or self-complete the ediary).
14. Patient did not experience an AE that in the opinion of the Investigator would result in failure to meet the inclusion/exclusion criteria during the screening period.
15. If female, is currently not pregnant, breast feeding, or attempting to become pregnant (for 4 weeks before the screening visit (visit 1) and throughout the duration of the study), and is of

    - nonchildbearing potential, defined as:
        - ≥1 year post-menopausal
        - surgically sterile (tubal ligation, oophorectomy, or hysterectomy)
        - diagnosed as infertile and not undergoing treatment to reverse infertility

    or is of

    - childbearing potential, has a negative serum pregnancy test at the screening visit (visit 1), and willing to commit to using a consistent and acceptable method of birth control as defined below for the duration of the study or exclusively has same-sex partners:
        - systemic contraception used for ≥1 month prior to screening, including birth control pills, transdermal patch (EVRA® or equivalent), vaginal ring (NUVARING® or equivalent), levonorgestrel implant (NORPLANT® or equivalent), or injectable progesterone (DEPO-PROVERA® or equivalent)
        - double barrier methods (condoms, cervical cap, diaphragm, and vaginal contraceptive film with spermicide)

- intrauterine device (IUD) with a low failure rate <1% per year
- monogamous with a vasectomized male partner or exclusively has same-sex partners

or is of

- childbearing potential and not sexually active, has a negative serum pregnancy test at the screening visit (visit 1), and willing to commit to using a consistent and acceptable method of birth control as defined above for the duration of the study, in the event the patient becomes sexually active

**If male** and sexually active, the patient is willing to commit to an acceptable method of birth control for the duration of the study or exclusively has same-sex partners.

## 6.2 EXCLUSION CRITERIA

A patient who meets any of the following exclusion criteria must not be enrolled:

1. Known respiratory disorder other than COPD, including but not limited to the following: alpha-1-antitrypsin deficiency, cystic fibrosis, significant asthma, active bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, pulmonary edema, or interstitial lung disease.
2. Evidence or history of other clinically significant disease or abnormality (such as congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, stroke, glaucoma or cardiac dysrhythmia), sleep apnea, malignancy (excluding basal cell carcinoma). In addition, historical or current evidence of significant hematologic, hepatic, neurologic, psychiatric, renal, pulmonary, or other diseases that in the opinion of the Investigator, would put the patient at risk through study participation, or would affect the study analyses if the disease exacerbated during the study.
3. Known active tuberculosis.
4. Hospitalization for a COPD exacerbation or pneumonia within 12 weeks prior to the screening visit (visit 1).
5. History of frequent COPD exacerbations of moderate to severe severity averaging 2 or more per year, or 2 or more exacerbations per year which resulted in hospitalization, averaged over the last 3 years.
6. Treatment for a non-hospitalized COPD exacerbation or pneumonia requiring antibiotics and/or systemic corticosteroids within 12 weeks prior to the screening visit (visit 1).
7. History of paradoxical bronchospasm, narrow angle glaucoma, prostatic hypertrophy or bladder neck obstruction, which, in the Investigator's opinion, would contraindicate the use of an anticholinergic agent.
8. The patient is pregnant or lactating, or plans to become pregnant or donate gametes (ova or sperm) during the study period or for 30 days after the patient's

last study-related visit (for eligible patients only, if applicable). Eligible female and male patients unwilling to employ appropriate contraceptive measures to ensure that pregnancy will not occur during the study will be excluded. Any patient becoming pregnant during the study will be withdrawn from the study.

9. Treatment with any protocol prohibited medications during the prescribed washout period before the screening visit (visit 1).
10. Inability to discontinue COPD medications during the screening, run-in, and treatment periods.
11. Documented or suspected viral or bacterial, upper respiratory infection (URI) or lower respiratory infection (LRI), sinusitis, sinus infection, rhinitis, pharyngitis, middle ear infection, urinary tract infection, or illness within 6 weeks prior to the screening visit (visit 1).
12. History of allergy or hypersensitivity to anticholinergic/muscarinic receptor antagonist agent, beta-2 agonists, lactose/milk proteins, or specific intolerance to aerosolized tiotropium bromide containing products, or known hypersensitivity to any of the proposed ingredients or components of the delivery system.
13. Factors (eg, infirmity, disability, or geographic location) that the Investigator feels would likely limit the patient's compliance with the study protocol or scheduled clinic visits.
14. Current evidence or known history of alcohol or substance abuse within 2 years of the screening visit (visit 1).
15. Positive urine drug screen at the screening visit (visit 1). If a patient has a positive urine drug screen for a class of drug which is consistent with a medication that the patient is currently prescribed (excluding inhaled marijuana), the patient can be considered eligible for the study after the prescription is confirmed by the Investigator.
16. Clinically significant abnormalities as judged by the Investigator on the 12-lead ECG at the screening visit (visit 1).
17. History of a positive test for infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C.
18. Patient is either an employee of the investigational center or an immediate relative of an employee of the investigational center.
19. History of lung volume reduction surgery, lung resection or on active phase of pulmonary rehabilitation within the previous 12 months prior to the screening visit (visit 1).
20. Chronic oxygen use for >12 hours/day.
21. Patient does not maintain regular day/night waking/sleeping cycles (eg, night shift workers).

## 6.3 RANDOMIZATION CRITERIA

1. Patient continues to be in general good health, and continues to meet all study entry criteria.
2. Patient has not experienced an AE that would result in failure to continue to meet selection criteria.
3. Patient has had no significant changes in COPD medications or taken any prohibited medication during the screening and run-in period.
4. The patient has had no COPD exacerbation during the screening and run-in period as defined in section **6.5**.
5. Patient has withheld all inhaled SABAs for at least 6 hours and SAMAs for at least 8 hours prior to lung function assessments at visit 2.
6. Patient has not had a viral/bacterial URI or LRI during the screening and run-in period. A patient who develops symptoms of a URI or LRI during the screening and run-in period may rescreen no sooner than 6 weeks after resolution of symptoms, and at the discretion of the Investigator (see section **9.3.7**).
7. Patient has not had clinically significant abnormalities as judged by the Investigator on the 12-lead ECG at visit 2.
8. Patient has no clinically significant laboratory abnormality as judged by the Investigator at the screening visit (visit 1).
9. Patient has demonstrated ediary compliance to run-in medication within the margins of at least ≥75% and ≤125% of projected use.
10. Patient has completed diary data on a minimum of 5 days out of the last 7 days prior to randomization (not including the day of randomization) and achieved a minimum of 75% compliance with the ediary during the single-blind run-in period.

## 6.4 CONTINUATION CRITERIA

1. Patient continues to be in general good health, and continues to meet study eligibility criteria.
2. Patient has not had a moderate to severe COPD exacerbation during the double-blind period in Part 1 as defined in section **6.5**.
3. Patient has not had a viral/bacterial URI or LRI during the double-blind treatment in Part 1. See section **6.5**.
4. Patient's pre-bronchodilator $FEV_1$ at visits 3 through 4 does not vary by more than ±10% of the value obtained at the randomization visit (visit 2). Retests will be permitted at discretion of the Investigator and per the retest criteria is section **9.3.6**.

   Note: The pre-bronchodilator $FEV_1$ value constitutes the average of the 2 values taken at 30 and 15 minutes before dosing with study medication.

5. Patient has not had clinically significant abnormalities as judged by the Investigator on the 12-lead ECG at visits 3-4.
6. Patient has not experienced an AE that would result in failure to continue to meet the selection/continuation criteria.

## 6.5 WITHDRAWAL CRITERIA

Patients may be discontinued from study treatment and assessments at any time. Patients are also free to discontinue their participation in the study at any time, without prejudice to further treatment. Wherever possible, patients should be seen and assessed by the Investigator(s).

In the eCRF, study completion or discontinuation will be documented with the reason for any discontinuation.

**Study-specific (predefined COPD alert)** criteria for withdrawal are listed below.

The following criteria would require mandatory withdrawal from the study:

- a moderate or severe COPD exacerbation occurring during the double-blind treatment period in Part 1:

  An exacerbation is defined as worsening of symptoms of COPD for at least 2 consecutive days and classified as mild when patients do not require treatment with systemic corticosteroids and/or antibiotics; moderate when treatment with systemic corticosteroids and/or antibiotics are required; or severe when hospitalization or visit to the emergency care/acute care unit is required. A separate exacerbation is considered when an interval of clinical improvement of at least 7 days is observed. Note: A patient's exacerbation should be deemed a moderate to severe exacerbation even if the symptoms have worsened in less than 2 consecutive days, if the patient was treated with systemic corticosteroids and/or antibiotics, was hospitalized, or visited the emergency care/acute care unit.

The following alert criteria should be evaluated by the Investigator for consideration of whether the patient should be withdrawn from the study.

These criteria would include the following:

- COPD exacerbation during Part 2 that prohibits the patient from administering their study medication (Lupin Tiotropium Bromide Inhalation Powder) once daily
- use of medication for respiratory symptoms not allowed by the study protocol
- viral or bacterial respiratory infection during Part 1 which results in an increase in the symptoms of COPD from the patient's normal baseline level
- prior to randomization (Part 1): a decrease in $FEV_1$ of more than 20% from the predose $FEV_1$ at the screening visit (visit 1)
- post randomization (Part 1 and Part 2): more than 3 occurrences of a decrease in $FEV_1$ of more than 20% from the predose $FEV_1$ at the randomization visit (visit 2)
- >20% decrease from the mean morning baseline $FEV_1$ on more than 3 of the last 7 (rolling) days during Part 1 (commencing once the predose pre-bronchodilator

study qualifying $FEV_1$ (ie, pre-PFT) is performed at the screening visit [visit 1]) or Part 2

- viral or bacterial respiratory infection during Part 2 which results in an increase in the symptoms of COPD from the patient's normal baseline level
- increase of ≥2 on the ER-S: COPD daily respiratory symptoms (RS) Total Score during Part 1 (commencing at the start of the screening period) or Part 2
- ≥12 or more albuterol/salbutamol puffs per day on more than 2 of the last 7 (rolling) days during Part 1 (commencing at the start of the screening period) or Part 2

Other possible reasons for a patient discontinuing participation in the study may include:

- patient withdrew consent
- Sponsor requested patient to be withdrawn
- protocol deviation/noncompliance
- AE
- lack of efficacy
- lost to follow-up/failure to return
- pregnancy
- other (specify within eCRF)

## 6.6 REPLACEMENT OF PATIENTS WHO WITHDRAW OR ARE DISCONTINUED

Patients who withdraw, are discontinued, or are lost to follow-up will not be replaced. However, the final number of patients to be randomized will be determined following the blinded interim analysis. The rate of patient early termination will be considered during the blinded interim analysis to help define the final number of patients to be randomized.

The date the patient is withdrawn from the study and the reason for discontinuation will be recorded in the eCRF. If there are multiple reasons for early discontinuation, the worst case scenario should be chosen.

If a patient is withdrawn because of an AE, the event will be followed until the medical condition returns to baseline or is considered stable or chronic. Discontinuation of patients due to AEs, including those due to abnormal laboratory results, should be promptly reported to Lupin Inc.

If a patient is lost to follow-up (fails to return for study visits), a reasonable effort should be made to determine why the patient failed to return. The occurrence of lost to follow-up will be documented in the eCRF.

Every effort should be made for all randomly assigned patients prematurely discontinuing, regardless of cause, to undergo final evaluation procedures, in accordance with the early termination (ET) visit as described in section **9.3.5**.

# 7 TREATMENTS

## 7.1 TREATMENTS ADMINISTERED

For Part 1, each patient will receive a single-dose of the following 3 treatments below in a double-blind, double-dummy crossover design.

- **Lupin Tiotropium Bromide Inhalation Powder, 18 mcg**
  - 2 inhalations from one Lupin capsule via LUPINHALER (Lupin Tiotropium Bromide Inhalation Powder, 18 mcg)
  - 2 inhalations from one Lupin placebo capsule via HANDIHALER (Placebo SPIRIVA HANDIHALER)
- **SPIRIVA HANDIHALER, 18 mcg**
  - 2 inhalations from one SPIRIVA capsule via HANDIHALER (SPIRIVA HANDIHALER 18 mcg)
  - 2 inhalations from one Lupin placebo capsule via LUPINHALER (Placebo LUPINHALER)
- **Placebo**
  - 2 inhalations from one Lupin placebo capsule via LUPINHALER (Placebo LUPINHALER)
  - 2 inhalations from one Lupin placebo capsule via HANDIHALER (Placebo SPIRIVA HANDIHALER)

Patients will be randomly assigned to these treatments via 1 of 6 treatment sequences as described in **Table 7-1**. Each treatment period will be followed by a 21-day (+3 days) washout period.

On each study day, the order of administration of the LUPINHALER and HANDIHALER will be randomly assigned via a randomization schedule separate from the main crossover randomization schedule.

For Part 2, a subset of approximately 120 patients will administer Lupin Tiotropium Bromide Inhalation Powder, 18 mcg once daily (2 inhalations from 1 capsule) in the morning for 72 days.

Patients will administer study medication as per the instructions in **Appendix A**.

## 7.2 IDENTITY OF INVESTIGATIONAL PRODUCT

Lupin Tiotropium Bromide Inhalation Powder, designed to be substitutable for SPIRIVA HANDIHALER, consists of a capsule dosage form containing a dry powder formulation of tiotropium intended for oral inhalation with the LUPINHALER. Each [redacted] Lupin capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide [redacted]) blended with [redacted] (which may contain milk proteins) as the carrier. The LUPINHALER is similar in size and shape to the HANDIHALER, and based on exactly the same operating principles.

## 7.3 IDENTITY OF COMPARATORS

SPIRIVA HANDIHALER (manufactured by Boehringer Ingleheim) consists of a capsule dosage form containing a dry powder formulation of tiotropium intended for oral inhalation only with the HANDIHALER device. Each light green, hard gelatin SPIRIVA capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate (which may contain milk proteins) as the carrier. The dry powder formulation within the SPIRIVA capsule is intended for oral inhalation only. The active component of SPIRIVA HANDIHALER is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1α, 2β, 4β, 5α, 7β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.02,4]nonane bromide monohydrate.

Placebo products, similar to the Lupin Tiotropium Bromide Inhalation Powder and SPIRIVA HANDIHALER are comprised of a DPI and capsule (gelatin capsule for use in placebo SPIRIVA HANDIHALER and [redacted] capsule for use in placebo LUPINHALER) containing no active drug, just [redacted]. Placebo SPIRIVA HANDIHALER will be used in the double-blind portion of Part 1 and placebo LUPINHALER will also be used during the single-blind run-in period and double-blind portion of Part 1.

## 7.4 ANCILLARY SUPPLIES

Albuterol/Salbutamol Medication

Patients will be dispensed an albuterol/salbutamol pressurized metered dose inhaler (pMDI) for use during Part 1 and for patients participating in Part 2 of the study.

Note: Dispensation of the albuterol/salbutamol MDI is not required during the screening period if the patient is taking this medication as part of their current COPD therapy. Once the patient is enrolled in the run-in period, dispensation/administration of the study albuterol/salbutamol MDI is required and the patient will discontinue the use of their own albuterol/salbutamol MDI.

Placebo trainers

Placebo product (LUPINHALER with placebo inhalation powder capsules) identical to the Lupin Tiotropium Bromide Inhalation Powder with no active drug contained in the capsules [redacted] will be provided for training purposes.

ediary/electronic flow meter

For the screening period, run-in period, Part 1 and Part 2 of the study, patients will be issued an ediary/electronic flow meter to record COPD symptom scores (EXACT); albuterol/salbutamol MDI usage; study medication usage (run-in and Part 2 only); and $FEV_1$ measurements at home. Diary collection begins at the time of signing the ICF. eDiaries/electronic flow meters will be dispensed on the 1st day of the screening period prior to patients beginning any medication washout, to assist with safety monitoring throughout the screening period.

In addition device robustness data will be tracked via the ediary system.

In-Check DIAL device

For Part 1 of the study, patients will be trained on inhaler technique using the In-Check DIAL, a hand held inspiratory flow measurement device. Refer to section **9.2.3.5** and **Appendix B** for further details.

## 7.5 SUPPLY OF STUDY MEDICATION

The Sponsor will provide an adequate amount of the study medication together with the appropriate release statement approving the study medication for human use in this clinical study. All medications supplied by the Sponsor will be manufactured, tested, and released according to the current legal requirements and Good Manufacturing Practice (GMP).

The study medication will be packed and shipped in appropriate storage boxes. Study medication should be examined immediately upon arrival at the study center. If the study medication supplies appear to be damaged, quarantine the study medication, and contact the Sponsor

Study medication must be kept in a secure, limited-access storage area, under the appropriate conditions. Only authorized personnel will have access to the study medication at the investigational centers.

Store Lupin Tiotropium Bromide Inhalation Powder, SPIRIVA HANDIHALER, placebo LUPINHALER, and placebo SPIRIVA HANDIHALER at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. The capsules (Lupin and SPIRIVA products) should not be exposed to extreme temperature or moisture. Do not store the capsules in the DPIs.

For storage of the albuterol/salbutamol pMDI, refer to the package insert.

## 7.6 METHOD OF ASSIGNING PATIENTS TO TREATMENT SEQUENCES

Based on a Williams design Latin square, patients will be randomly allocated to treatment via 1 of the 6 treatment sequences shown in **Table 7-1** below. The randomization schedule will be generated within the Biometrics Department of the designated Contract Research Organization (CRO) by a statistician not involved in the study.

**Table 7-1. Randomization Scheme**

| Treatment sequence | Treatment period 1 | Treatment period 2 | Treatment period 3 |
|---|---|---|---|
| A (TRP) | Lupin Tiotropium Bromide Inhalation Powder 18 mcg | SPIRIVA HANDIHALER 18 mcg | Placebo |
| B (RPT) | SPIRIVA HANDIHALER 18 mcg | Placebo | Lupin Tiotropium Bromide Inhalation Powder 18 mcg |
| C (PTR) | Placebo | Lupin Tiotropium Bromide Inhalation Powder 18 mcg | SPIRIVA HANDIHALER 18 mcg |

| Treatment sequence | Treatment period 1 | Treatment period 2 | Treatment period 3 |
|---|---|---|---|
| D (PRT) | Placebo | SPIRIVA HANDIHALER 18 mcg | Lupin Tiotropium Bromide Inhalation Powder 18 mcg |
| E (TPR) | Lupin Tiotropium Bromide Inhalation Powder 18 mcg | Placebo | SPIRIVA HANDIHALER 18 mcg |
| F (RTP) | SPIRIVA HANDIHALER 18 mcg | Lupin Tiotropium Bromide Inhalation Powder 18 mcg | Placebo |

Patients will be randomly assigned to the treatment sequences by means of a computer generated randomization list after confirmation of all eligibility criteria. The randomization list and study medication will be assigned via interactive response technology (IRT).

Additionally, on each study day, as this is a double-dummy study, the order of administration of the LUPINHALER and HANDIHALER will be assigned based on even/odd calendar days. On odd calendar days (eg, 1, 3, 5, 29, 31), the LUPINHALER will be dosed first. On even calendar days (eg, 2, 4, 6, 28, 30), the HANDIHALER will be dosed first.

A subset of approximately 120 patients (at select investigational centers) will be enrolled into the open-label phase of the study (Part 2). These patients will not be randomized and all patients in Part 2 will receive Lupin Tiotropium Bromide Inhalation Powder.

## 7.7 BLINDING

### 7.7.1 Part 1

This study will use commercially available SPIRIVA medication and inhalers which have attributes that make proper blinding of the assigned treatment a challenge; therefore there are some additional steps required to keep the patient and investigational center staff blinded to treatment allocation for Part 1 of the study.

The SPIRIVA HANDIHALER and capsules are color-branded and labelled and would be recognizable to investigational center staff and patients who have previously used the medication. To avoid the problem of bias, a double-blind, double-dummy approach will be adopted.

The patients will administer study medication from 2 inhalers at each investigational center visit in Part 1 given by a specified unblinded administrator. The inhalers will represent the commercially available HANDIHALER devices (from the USA) and the LUPINHALER.

The unblinded administrator is not permitted to take part in any clinical or safety assessments and should not discuss the nature of the study medication administration with the other study team members.

The unblinded administrator will collect the study medication from the pharmacy, remove the capsule from the relevant blister strips and prepare the inhalers out of sight of the patient. The unblinded administrator will then obscure the observation windows in

the device with opaque tape and dispense to blinded study personnel, who will assist the patient to complete dosing as per the instructions for use (**Appendix A**).

As indicated in the randomization scheme (**Table 7-1**), at each treatment visit the patient will receive either:

- one active dose from 1 of the 2 inhalers; other inhaler contain placebo dose
- 2 placebo doses

Training of the patient on inhaler technique and dosing of the study medication will be undertaken by blinded study personnel. The unblinded administrator will acknowledge all shipments, prepare blinded study medication, and dispense the blinded study medication to the blinded study personnel so that the core study team who are responsive for efficacy and safety assessments are unaware of the inhalers administered. In addition, the unblinded administrator will witness dose administration in the double-blind portion of Part 1.

The patient will self-administer the medication at the investigational center on each study day guided by this blinded study team member. $FEV_1$ testing will continue postdose by the blinded study team.

Used inhalers, with the capsules contained in the inhaler, will be returned to the pharmacy (or designated study medication room) by the unblinded study team member for storage to aid drug accountability.

### 7.7.2 Part 2

Part 2 will be conducted via an open-label design; therefore, no blinding is required. Used inhalers and unused capsules will be returned to the investigational center.

## 7.8 TREATMENT COMPLIANCE

For Part 1, compliance with administration of study medication during the double-blind treatment will be monitored by investigational center personnel through observation of dose administration at each treatment visit. Compliance during the single-blind run-in period will be monitored via ediary by investigational center personnel. Diary and $FEV_1$ data will be transferred to the study database at regular intervals. If during the single-blind run-in period, a patient is found to be less than 75% compliant with the completion of the ediary or <75% and >125% compliant with administration of placebo LUPINHALER, the patient will not be eligible to continue participation in the study.

For Part 2, detailed compliance will be determined by reviewing the recorded dosing and study procedure data from the ediaries at each investigational center visit. Diary and $FEV_1$ data will be transferred to the study database at regular intervals. If at any visit in Part 2, patients are found to noncompliant with study medication administration, the patient should be counseled on the importance of taking study medication as directed by the Investigator. Patients are requested to administer treatment for 72 +3 days.

## 7.9 DOSING PROCEDURES

For Part 1, during the single-blind run-in period, patients will administer the placebo LUPINHALER once daily, in the morning for 14 (+2) days after completing $FEV_1$ measurements. Patients will administer the 1st dose at the investigational center in the presence of investigational center personnel after completing spirometry procedures. Patients are to withhold their morning dose of placebo run-in medication on the morning of visit 2.

For Part 1, prior to study visits 2 through 4, patients should refrain from using albuterol/salbutamol MDI and other prohibited medication; patients should not smoke at least 1 hour prior to lung function assessments during the visits; and patients should adhere to the dietary restrictions as per protocol (see section **8.2**). Patients will be trained on the correct use of the study medication. Patients will administer 2 inhalations from each of 2 inhalers of the assigned study medication in the morning with the assistance of the blinded administrator. Patients may stay overnight at the investigational center or at nearby housing facility (eg, hotel) to complete the $FEV_1$ serial measurements over a 24-hour period. In certain cases, the patient may return home after the 12 hour $FEV_1$ measurement and return for the 23 and 24 $FEV_1$ measurements, at the discretion of the Investigator.

After administration of study medication, the patient will enter a washout period of 21 days + 3 days between treatment periods, where the patient may continue to use albuterol/salbutamol MDI and other medications permitted per protocol (see section **8**). For visits 2 through 4, patients should present at the investigational center so that the start of lung function testing will be within ±1 hour from the lung function testing at visit 1.

For Part 2 of the study, patients will be trained on the correct use of the DPI by the blinded study personnel. The dose should be taken at home in the morning. Predose $FEV_1$ measurements should be performed upon awakening in the morning immediately prior to dosing with the study medication; postdose $FEV_1$ measurements are to be performed 2 (+2) hours after study medication administration.

## 7.10 STUDY MEDICATION ACCOUNTABILITY

The Investigator is responsible for study medication accountability (including test, reference, placebo, and albuterol/salbutamol MDI), reconciliation, and record maintenance. In accordance with applicable regulatory requirements, the Investigator or designated investigational center staff must maintain study medication accountability records.

Study medication accountability records must be maintained at the investigational center at all times. The identification number of the patient, the date, expiry date and quantity of study medication dispensed will be recorded. The returned medication should be noted on the appropriate inventory forms.

At study conclusion, all used and unused study medication (with the exception of used capsules during the run-in period and open-label extension), albuterol/salbutamol medication, and placebo trainers must be returned to the Sponsor or Sponsor's designee. Documented evidence of destruction should be made available to the Sponsor.

See section **7.11** for retention samples.

Instructions on how to manage device problems (eg, malfunction and damage) will be described in the study procedures manual.

## 7.11 RETENTION

Drug retains will be handled as described in the study procedures manual and maintained by the study site for at least 5 years, as determined by Lupin Inc., to demonstrate the packaging of these medications if requested and required by regulatory authorities.

## 7.12 EMERGENCY CODE BREAKING

In case of a serious adverse event (SAE) or pregnancy, the Investigator may unblind the patient's study medication assignment via IRT when the code is needed to make treatment decisions for the patient. The Sponsor should be notified of the event prior to breaking the code, if possible. If this is not possible, the Sponsor should be notified immediately afterwards, and the patient's treatment code should not be revealed to the Sponsor. The circumstances leading to the breaking of the code should be fully documented in the Investigator's study files and in the patient's source documentation. The patient's treatment assignment should not be recorded in any study documents.

# 8 PROHIBITED AND RESTRICTED MEDICATIONS AND PROCEDURES

Medications (including vitamins and over-the-counter [OTC] medications and therapies) used within 90 days before the screening visit (visit 1) will be recorded in the eCRF. The administration of any additional medication during the study (including OTC medications and vitamins) beyond those specified in the protocol will be clearly documented both in the source document and the eCRF.

No medication, other than the study medication and allowed medications, should be taken during the study. Exceptions to this rule apply to medication that may be needed to treat AEs. Such administration will be clearly documented and cross-referenced with the AE on the eCRF. If administration of any prohibited medication becomes necessary during the study for medical reasons, the Investigator should consult with the Sponsor to determine whether to continue or withdraw the patient from further participation in the study.

All other therapies prohibited as per protocol must have been discontinued prior to the protocol specified periods. Patients are not allowed to enter the study if they receive any prohibited concomitant medication or medication in a dosage not allowed and which cannot be discontinued or reduced. These medications should only be discontinued if the Investigator decides that discontinuing patients from therapy is the best course of action for the patient. These prohibited medications and therapies should not be discontinued for the sole purpose of making a patient eligible for enrollment into the study.

## 8.1 PROHIBITED CONCOMITANT MEDICATIONS

The medications listed in **Table 8-1** are not allowed or are restricted during this study (Part 1 and Part 2).

**Table 8-1. Prohibited Medications (Part 1 and Part 2)**

| Type of medication | Washout period before the screening visit (visit 1) and throughout the study (unless otherwise specified) |
|---|---|
| **Prohibited** | |
| Depot steroids | 90 days |
| Immunologically active biologic medications (eg, anti-tumor necrosis factor alpha, abatacept) | 90 days |
| Any other investigational drugs | 30 days or 5 half-lives, whichever comes first |
| Strong CYP3A4 inhibitors (eg, azole antifungals, ritonavir, clarithromycin) | 30 days |
| Immunosuppressive therapy (eg, methotrexate, gold, azathioprine) | 30 days |
| Marijuana (via smoking) | 30 days |
| Oral or systemic corticosteroids | 30 days |

| **Type of medication** | **Washout period before the screening visit (visit 1) and throughout the study (unless otherwise specified)** |
|---|---|
| ICS (monotherapy) or ICS/LABA combination therapy | 30 days |
| LAMA or LAMA/LABA combination therapy | 21 days |
| Beta-adrenergic receptor blocking agents[a] | 14 days |
| Cromones | 14 days |
| Leukotriene modifiers | 14 days |
| Monoamine oxidase inhibitors | 14 days |
| Polycyclic antidepressants | 14 days |
| Once or twice daily LABA monotherapy (eg, indacaterol) | 7 days |
| Oral β2-agonists (tablets, syrup) | 48 hours for long and 12 hours for short |
| $H_2$ antagonists (eg, cimetidine) | 24 hours |
| Drugs of abuse (cannabinoids, amphetamines, barbiturates, cocaine, benzodiazepines, methadone, and opiates)[b] | A negative test is required at the screening visit and use is prohibited throughout the study. |

a. Cardioselective beta blockers are permitted as long as therapy was initiated at least 7 days before the screening visit (visit 1) and is expected to remain at a stable dose throughout the study.

b. If a patient has a positive urine drug screen for a class of drug which is consistent with a medication that the patient is currently prescribed (excluding inhaled marijuana), the patient can be considered eligible for the study after the prescription is confirmed by the Investigator. Inhaled marijuana is not permitted even if prescribed.

CYP=cytochrome P450; ICS=inhaled corticosteroid; LAMA=long-acting anti-muscarinic agent; LABA=long-acting β2 agonist.

### 8.1.1 Washout Restrictions during Part 1 of the Study Only

The washout period for LAMA or LABA is as follows:

- LAMA medications (including mono products and combination products containing LAMAs [eg, LAMA/LABA]) will not be permitted within 21 days of the screening visit (visit 1) and throughout the study (except for the study medication provided at each treatment period). Any patients taking LAMA medications will need to discontinue these medications, and at the Investigator's discretion, the LAMA may be replaced with ipratropium bromide (SAMA), adhering to the washout restrictions below.
- LABA mono products will need to be discontinued 7 days before the screening visit (visit 1) and throughout the study. Any patients taking LABAs will need to discontinue these medications, and at the discretion of the Investigator, the LABA may be replaced with ipratropium bromide (SAMA), adhering to the washout restrictions below.
- ICS/LABA combination products will need to be discontinued 30 days before the screening visit (visit 1) and throughout the study. Any patients taking

ICS/LABAs will need to discontinue these medications, and at the discretion of the Investigator, the ICS/LABA may be replaced with ipratropium bromide (SAMA), adhering to the washout restrictions below

Patients should refrain from taking the following medications from the specified time points below prior to spirometry assessments at each clinic visit (both days of each inpatient visit) during Part 1 of the study:

- SABAs 6 hours
- SAMAs: 8 hours
- short-acting forms of theophylline: 12 hours
- twice-a-day controlled-release forms of theophylline: 24 hours
- once-a-day controlled-release forms of theophylline: 36 hours
- caffeine-containing medications (eg, MIDOL®, EXCEDRIN®) 6 hours

If a patient requires the use of a SABA for rescue during the serial spirometry, the administration of the rescue medication should be recorded as a protocol deviation and the patient should continue with the pulmonary function testing as scheduled for that day.

### 8.1.2 Permitted Medication with Restrictions during Part 1 of the Study Only

The following medications (**Table 8-2**) are also permitted during the study if the noted conditions are met. Note: If patients are taking these restricted medications on an as needed (PRN) basis, then a start/stop date must be entered in the eCRF prior to the screening visit (visit 1) and for each instance thereafter, as applicable.

**Table 8-2. Permitted Medications with Restrictions**

| Type of medication | Washout period before the screening visit (visit 1), unless otherwise specified |
|---|---|
| Nasal corticosteroids | Chronic stable doses at least 14 days duration before the screening visit (visit 1) and stable throughout the study duration allowed throughout the study |
| Theophyllines | Permitted if without a significant adjustment of dosage, formulation, dosing interval for the duration of the study, and judged able by the Investigator to withhold them for the time intervals prior to each clinic visit<br>-short-acting forms: 12 hrs<br>-twice a day controlled-release forms: 24 hrs<br>-once a day controlled-release forms: 36 hrs. |
| PDE4 inhibitors | Permitted if without a significant adjustment of dosage, formulation, and dosing interval for the duration of the study |
| Oral or nasal antihistamines (eg, loratadine, diphenhydramine, cetirizine) | Discontinue 24 hours before each visit and may resume after the visit |

### 8.1.3 Permitted Concomitant Medication/Therapy during Part 2 of the Study Only

In Part 2 of the study, patients will be supplied with Lupin Tiotropium Bromide Inhalation Powder for once daily administration over 72 days.

Patients will also be permitted to resume other non-study medications and albuterol/salbutamol MDI as long as the medications do not contravene the prohibited medications in **Table 8-1**, excluding the use of the LAMA study medication.

## 8.2 GENERAL AND DIETARY RESTRICTIONS

For Part 1, patients will be required to comply with the following restricted activities:

- Patients are not to engage in strenuous exercise on the mornings of any scheduled visit (visit 1 through visit 4).
- If possible, patients should avoid cold air exposure on the mornings prior to spirometry testing at any scheduled visit (visit 1 through visit 4). Patients who experience bronchial symptoms related to exposure to cold air should be adequately stabilized at room temperature before any study-related pulmonary function tests (PFTs) are conducted.
- Patients should not smoke or be in a smoky atmosphere for at least 1 hour prior to spirometry assessments at any scheduled visit (visit 1 through visit 4).
- Patients should avoid intake of caffeinated beverages for at least 6 hours prior to spirometry testing on the mornings of any scheduled visit (visit 1 through visit 4).

Note: If the patient has failed to comply with any of the general and dietary restrictions above, the visit/spirometry should be postponed until the condition is met (see section **9.3.6**).

For Part 2, there are no activity or dietary restrictions.

# 9 STUDY PROCEDURES

## 9.1 SCHEDULE OF EVENTS

The schedule of events is provided in **Table 9-1**.

**Table 9-1. Schedule of Events**

| | **Screening period** | **Single-blind run-in period** | **Part 1 Double-blind treatment period** | | | | | | | **Part 2 Open-label extension** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study visit** | **Visit 1** | **NA** | **TP1 (Visit 2)** | | **TP2 (Visit 3)** | | **TP3 (Visit 4)** | | **F/U[1]** | **Visit 5** | **Visit 6** | **Visit 7** | **Visit 8** | **Visit 9** | **Visit 10** | **F/U[2]** | **ET[3]** |
| **Study days[4]** | **-44 to -14[5]** | **14-16 day period before day 0** | **0** | **1** | **21 (+3)** | **22** | **42 (+3)** | **43** | **50 (±3)** | **43[6]** | **57 (±2)** | **71 (±2)** | **85 (±2)** | **99 (±2)** | **115 (+3)** | **122 (±3)** | **NA** |
| Clinic visit[7] | X | | X | X | X | X | X | X | Tele-phone only | X | Tele-phone only | X | Tele-phone only | X | X | Tele-phone only | X |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Assign patient via IRT | X | | | | | | | | | | | | | | | | |
| Assess inclusion/ exclusion criteria | X | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | |
| Physical examination | X[8] | | | | | | | X | | | | | | | X | | X |
| Height and weight | X | | | | | | | | | | | | | | | | |
| HEENT and chest examination | | | X | | X | | X | | | | | X | | X | | | |
| Medical history including prior concomitant medications | X | | | | | | | | | | | | | | | | |
| 12-lead ECG | X | | X | | X | | X | | | | | X | | X | X | | |
| Clinical laboratory tests (hematology, biochemistry, and urinalysis) | X | | | | | | | | | | | | | | | | |
| Serum pregnancy test (female patients of | X | | | | | | | X[9] | | | | | | | X[9] | | X |

| | **Screening period** | **Single-blind run-in period** | **Part 1 Double-blind treatment period** | | | | | | | **Part 2 Open-label extension** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study visit** | **Visit 1** | **NA** | **TP1 (Visit 2)** | | **TP2 (Visit 3)** | | **TP3 (Visit 4)** | | **F/U[1]** | **Visit 5** | **Visit 6** | **Visit 7** | **Visit 8** | **Visit 9** | **Visit 10** | **F/U[2]** | **ET[3]** |
| **Study days[4]** | **-44 to -14[5]** | **14-16 day period before day 0** | **0** | **1** | **21 (+3)** | **22** | **42 (+3)** | **43** | **50 (±3)** | **43[6]** | **57 (±2)** | **71 (±2)** | **85 (±2)** | **99 (±2)** | **115 (+3)** | **122 (±3)** | **NA** |
| Clinic visit[7] | X | | X | X | X | X | X | X | Tele-phone only | X | Tele-phone only | X | Tele-phone only | X | X | Tele-phone only | X |
| childbearing potential only) | | | | | | | | | | | | | | | | | |
| Urine pregnancy test (female patients of childbearing potential only) | | | X | | | | | | | | | | | | | | |
| Urine drug screen | X | | | | | | | | | | | | | | | | |
| Vital signs measurements[10] | X | | X[11] | X | X[11] | X | X[11] | X | | | | X | | X | X | | X |
| Demonstrate study medication inhalation technique | X | | X | | X | | X | | | X | | X | | X | | | |
| Demonstrate albuterol/salbutamol MDI inhalation technique | X | | X | | X | | X | | | X | | X | | X | | | |
| Dispense single-blind run-in medication | | X[12] | | | | | | | | | | | | | | | |
| Assess inspiratory flow rate via In-Check DIAL device | X | | X | | X | | X | | | | | | | | | | |
| Ipratropium reversibility[13] | X | | | | | | | | | | | | | | | | |
| Study qualifying $FEV_1$ | X | | | | | | | | | | | | | | | | |
| Determine $FEV_1$ baseline/stability limits | X[14] | | X[15] | | | | | | | | | | | | | | |
| Administer single-blind run-in medication | | X | | | | | | | | | | | | | | | |

| | **Screening period** | **Single-blind run-in period** | **Part 1 Double-blind treatment period** | | | | | | | **Part 2 Open-label extension** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study visit** | **Visit 1** | **NA** | **TP1 (Visit 2)** | | **TP2 (Visit 3)** | | **TP3 (Visit 4)** | | **F/U[1]** | **Visit 5** | **Visit 6** | **Visit 7** | **Visit 8** | **Visit 9** | **Visit 10** | **F/U[2]** | **ET[3]** |
| **Study days[4]** | **-44 to -14[5]** | **14-16 day period before day 0** | **0** | **1** | **21 (+3)** | **22** | **42 (+3)** | **43** | **50 (±3)** | **43[6]** | **57 (±2)** | **71 (±2)** | **85 (±2)** | **99 (±2)** | **115 (+3)** | **122 (±3)** | **NA** |
| Clinic visit[7] | X | | X | X | X | X | X | X | Tele-phone only | X | Tele-phone only | X | Tele-phone only | X | X | Tele-phone only | X |
| Collect single-blind run-in medication | | | X | | | | | | | | | | | | | | X |
| Review randomization criteria | | | X | | | | | | | | | | | | | | |
| Randomization via IRT | | | X | | | | | | | | | | | | | | |
| Review continuation criteria | | | | | X | | X | | | X | X | X | X | X | | | |
| Administer study medication at clinic | | | X | | X | | X | | | X | | | | | | | |
| Enroll in open-label extension via IRT[16] | | | | | | | | | | X | | | | | | | |
| Predose and serial $FEV_1$ measurements[17] | | | X | X | X | X | X | X | | | | | | | | | |
| Dispense ediary/ electronic flow meter | X[18] | | | | | | | | | X | | | | | | | |
| Review ediary/ electronic flow meter instructions | X | | X | | X | | X | | | X | | | | | | | |
| Dispense albuterol/salbutamol MDI, as applicable | X[19] | X | X | | X | | X | | | X | | X | | X | | | |
| Dispense/collect placebo trainer | X | | X | | X | | X | | | | | | | | | | |
| Dispense study medication[20] | | | X | | X | | X | | | X | | | | | | | |
| Assess ediary data | X | | X | | X | | X | X | | | X | X | X | X | X | | X |
| Collect ediary/ | X | | X | | | | | X | | | | | | | X | | X |

| | **Screening period** | **Single-blind run-in period** | **Part 1 Double-blind treatment period** | | | | | | | **Part 2 Open-label extension** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study visit** | **Visit 1** | **NA** | **TP1 (Visit 2)** | | **TP2 (Visit 3)** | | **TP3 (Visit 4)** | | **F/U[1]** | **Visit 5** | **Visit 6** | **Visit 7** | **Visit 8** | **Visit 9** | **Visit 10** | **F/U[2]** | **ET[3]** |
| **Study days[4]** | **-44 to -14[5]** | **14-16 day period before day 0** | **0** | **1** | **21 (+3)** | **22** | **42 (+3)** | **43** | **50 (±3)** | **43[6]** | **57 (±2)** | **71 (±2)** | **85 (±2)** | **99 (±2)** | **115 (+3)** | **122 (±3)** | **NA** |
| Clinic visit[7] | X | | X | X | X | X | X | X | Tele-phone only | X | Tele-phone only | X | Tele-phone only | X | X | Tele-phone only | X |
| electronic flow meter, as applicable | | | | | | | | | | | | | | | | | |
| Check for issues with study inhalers | | X | X | | X | | X | | | X | X | X | X | X | X | | X[21] |
| Collect COPD exacerbation data | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Record AEs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Record concomitant medication/therapies | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Collect study medication | | | X | | X | | X | | | | | | | | X | | X |
| Collect albuterol/salbutamol MDI, as applicable | X | | X | | X | | X | X | | | | X | | X | X | | X |
| Schedule next visit | X | | | X | | X | | X | | X | X | X | X | X | X | | |
| Discuss COPD treatment options | X | | | | | | | X | X | | | | | | X | X | X |
| Discharge patient via IRT | | | | | | | | | X | | | | | | | X | X |
| Home-based $FEV_1$ measurements | Record morning predose in ediary/electronic flow meter[22] | | | | | | | | | Record morning predose and 2 hours postdose in ediary/electronic flow meter | | | | | | | |
| Assess EXACT symptom scores | Record once daily in the evening before bedtime via ediary | | | | | | | | | Record once daily in evening before bedtime via ediary | | | | | | | |
| Albuterol/salbutamol MDI medication use | Record daily in ediary | | | | | | | | | Record daily in ediary | | | | | | | |

1) For patients participating in Part 1 only, a follow-up visit will occur via phone contact by investigational center personnel 7 days (±3 days) after completing visit 4.

2) This follow-up visit will only be required for patients participating in Part 2 of the study, and will occur via phone contact by investigational center personnel 7 ±3days after the final treatment visit (visit 10).
3) Regardless if patient is participating in Part 1 or Part 2, the assessments listed for ET will be performed for any patient who is withdrawn prematurely from the study.
4) As there is only the potential to extend visit intervals with permitted visit windows, the terminology of study days will not necessarily represent the exact day of the visit.
5) The screening visit (visit 1) may take place over several days beginning on day -44 to -14 dependent on the patient's washout. If a patient is washing out of ICS (monotherapy) or ICS/LABA combination therapy, an additional 3 days is permitted to complete the assessments for the screening visit (visit 1). All results, with the exception of the clinical laboratory assessments, must be available and evaluated prior to commencing the run-in period. The clinical laboratory results must be available and evaluated prior to randomization. The procedures for the screening visit (visit 1), with the exception of signing of the ICF, performing a pre-washout physical examination, and dispensing/completing the ediary, cannot occur until appropriate medication washouts have been completed in accordance with the protocol. Once the washout requirements have been met, the screening visit (visit 1) should immediately precede the start of the run-in period. If a patient does not require washout, and the patient passes all entry criteria at the screening visit (visit 1), the patient will be eligible to enter the run-in period on the same day as the screening visit (visit 1). The patient must successfully complete the visit 1 procedures/assessments prior to entering the run-in period.
6) After completion of visit 4 (days 42 and 43), patients will either be discharged from the study after completing all double-blind study assessments at visit 4 or a subset of patients (approximately 120 patients) will be eligible for enrollment into a 12-week open-label extension, which will begin on the same day as the final visit in the double blind treatment period.
7) All visits for Part 1 should be scheduled in the mornings between 0600 and 1000 and spirometry testing should begin at ±1 hour of the start of visit 1 testing time.
8) If washout of baseline therapy is needed, then 2 physical examinations are required: one before a patient commences the washout period and one after the washout period ends, prior to enrolling into the run-in period.
9) The visit 4 end of study serum pregnancy test will be performed for women of childbearing potential who are only participating in Part 1 of the study. For women of childbearing potential who are participating in both Part 1 and Part 2, the end of study serum pregnancy test will be performed at visit 10.
10) Vital signs measurements include blood pressure, heart rate, respiration rate, and temperature.
11) Vital signs will be collected within 60 minutes of measuring the predose $FEV_1$ on days 0, 21, and 42.
12) Single blind run-in must be dispensed 14 to 16 days prior to randomization. Patients will administer the single-blind placebo LUPINHALER one daily in the morning for 14 (+2) days after completing the $FEV_1$ measurements.
13) Patient has demonstrated ≥15% reversibility of $FEV_1$ within 30 or 60 minutes following 68 mcg of ipratropium bromide inhalation (pMDI). If required, spacers are permitted for use during reversibility testing for ipratropium bromide administration. Patients who do not demonstrate a positive improvement of at least 15% in $FEV_1$ measured at 30 or 60 minutes (±5 minutes) post inhalation will not be eligible to participate in the study. However, based on Investigator judgment, patients will be allowed to retest once no sooner than 24 hours and no later than 2 weeks after initial failure to meet the reversibility criteria. Reversibility values of 14.50-14.99 will be rounded to 15.
14) A stability limit will be established at the screening visit (visit 1) to determine alert criteria for worsening COPD during the screening and run-in periods, and will be calculated by selecting the best pre-bronchodilator qualifying $FEV_1$ measurement at the screening visit using the onsite spirometer x 80%.

15) Two stability limits (at home and investigational center) will be re-established at the randomization visit (visit 2) for use during the double-blind and open-label treatment periods. The at home limit will be calculated by taking the mean of the best predose $FEV_1$ measurements on the last 3 days before randomization on the electronic flow meter (home device) x 80%, and the investigational center limit will be the mean $FEV_1$ of the predose pre-bronchodilator qualifying $FEV_1$ measurements (-30 and -15 minutes) using the onsite spirometer × 80%.
16) A subset of patients (approximately 120 patients) at select investigational centers who successfully completed Part 1 will be eligible for enrollment into the open-label extension (Part 2).
17) Predose $FEV_1$ will be measured at 30 and 15 minutes before administration of study medication. Serial $FEV_1$ spirometry measured at 0 hours (within 30 and 15 minutes prior to study medication administration [equivalent to the predose $FEV_1$]), and at 5 and 30 minutes postdose, and at 1, 2, 4, 6, 8, 10, 12, 23, and 24 hours postdose. The following windows are permitted: +5 minutes for predose measurements (-30 and -5 minutes) and 5 minute postdose measurement; ±5 minutes for 0.5-6 hours, and ±15 minutes for 8-24 hours.
18) Diary collection begins at the time of signing the ICF, and then continues throughout Part 1 and Part 2, per the randomization scheme.
19) Dispensation of the albuterol/salbutamol MDI is not required during the screening period if the patient is taking this medication as part of their current COPD therapy. Once the patient is enrolled in the run-in period, dispensation/administration of the study albuterol/salbutamol MDI is required and the patient will discontinue the use of their own albuterol/salbutamol MDI.
20) Administration of study medication at the investigational center will occur in the presence of the unblinded and blinded staff members.
21) For patients participating in Part 2.
22) Home based $FEV_1$ measurements will not be performed on the mornings of visit 2 (both day 0 and day 1), visit 3 (both day 21 and day 22), and visit 4 (both day 42 and day 43).

# 9.2 STUDY PROCEDURES

## 9.2.1 Efficacy Procedures

### 9.2.1.1 Spirometry (Part 1 Only)

$FEV_1$

The spirometry endpoint data will be captured using standardized equipment supplied by a central spirometry vendor. This equipment will meet or exceed the ATS/ERS recommendations for forced spirometry testing equipment, and spirometry measurements will be performed according to ATS guidance document recommendations to ensure both technical acceptability and repeatability of test data (**Miller 2005**). The test data will be overread by the central spirometry provider and any discrepancies in relation to the best test effort will be communicated back to the investigational center.

Spirometry testing will be performed by experienced research staff who have passed a proficiency process to ensure understanding of the equipment used and forced spirometry technique. To collect data in a consistent manner, the same staff member will conduct all spirometry assessments for the same patient whenever possible. The same spirometer should be used on a patient throughout the study. Onsite spirometry assessments (baseline/study qualifying/reversibility) must occur after washout of the protocol prohibited and restricted medications.

Patients should be at rest for approximately 15 minutes prior to testing and should be comfortable. Tight clothes should be loosened to allow the thorax to move freely; the patient should be seated in an upright posture and with a nose clip in place. The patient should not smoke or have been in a smoky atmosphere for at least 1 hour prior to each $FEV_1$ assessment, should have avoided highly caffeinated drinks for at least 6 hours, and should have adhered to the restricted medication criteria for the appropriate time as outlined in section **8**. If these criteria have not been met, the patient should have the visit rescheduled.

All visits to the investigational center for Part 1 must be scheduled in the mornings between 0600 and 1000 and spirometry testing should begin at ±1 hour of the start of visit 1 study qualifying spirometry testing time. Predose $FEV_1$ measurements will be recorded at 0 hours (-30 and -15 minutes before administration of study medication) at the investigational center at visits 1 through 4; serial $FEV_1$ measurements will be recorded postdose at 5 and 30 minutes, and at 1, 2, 4, 6, 8, 10, 12, 23, and 24 hours.

The following windows are permitted: +5 minutes for predose measurements (-30 and -15 minutes) and 5 minute postdose measurement, ±5 minutes for 0.5-6 hours, and ±15 minutes for 8-24 hours.

Spirometry procedures are described in the spirometry manual.

Reversibility Testing

For reversibility testing, patients will receive 68 mcg of ipratropium bromide inhalation pMDI as 4 actuations of 17 mcg/actuation (ex-mouthpiece); given at approximately 30 second intervals. If required, spacers are permitted for use during reversibility testing

for ipratropium bromide administration. All actuations are to be completed within 3 minutes of the 1st actuation. The ATS/ERS criteria will be followed for spirometry measures. Patients who do not demonstrate a positive improvement of at least 15% in $FEV_1$ measured at 30 or 60 minutes (±5 minutes) post inhalation will not be eligible to participate in the study (except as permitted per the retest specified below). Reversibility values of 14.50-14.99 will be rounded to 15.

Refer to the spirometry manual for additional information related to reversibility testing.

Patients failing to meet the reversibility requirement will be permitted to retest once, based on Investigator judgment (for only those patients who would normally achieve this level of reversibility) no sooner than 24 hours and no later than 2 weeks after the initial failure, as per the retest criteria in section **9.3.6**.

$FEV_1$ Stability Limits

$FEV_1$ stability limits will be calculated for each patient at the screening visit (visit 1) using the onsite spirometer and the randomization visit (visit 2), using both the home device and onsite spirometer.

Screening Visit:

The stability limit established at the screening visit will be used to determine alert criteria for worsening COPD during the screening and run-in periods. The $FEV_1$ stability limit at the screening visit will be calculated as follows:

Best pre-bronchodilator qualifying $FEV_1$ measurement at the screening visit (visit 1) using the onsite spirometer × 80%.

Randomization Visit

Two stability limits will be re-established at the randomization visit (visit 2) for use during the double-blind and open-label treatment periods using the following equations:

- Investigational Center Stability Limits (for use with onsite spirometer at the double-blind visits only):

  mean $FEV_1$ of the predose pre-bronchodilator qualifying $FEV_1$ measurements (-30 and -15 min) using the onsite spirometer × 80%

- At Home Stability Limits (for use with the electronic flow meter [home device]):

  mean of the best predose $FEV_1$ measurements on the last 3 days before randomization on the home device × 80%

If a patient falls below any of the above $FEV_1$ stability limits, an alert will be triggered to the patient and investigational center personnel.

Note: If the reschedule icon on the site spirometer is chosen for the screening visit (visit 1) or visit 2, and therefore, visit 1 or visit 2 is performed again, the $FEV_1$ stability limit will be updated accordingly. If V1_RETEST on the site spirometer is performed, the stability limit will not be updated.

Refer to the spirometry manual for these instructions and further details regarding general spirometry procedures.

### 9.2.2 Safety Procedures

#### 9.2.2.1 Physical and HEENT/Chest Examinations (Part 1 and Part 2)

Physical and HEENT/Chest examinations will be performed as indicated in **Schedule of Events, Table 9-1** by a qualified healthcare provider, Investigator, or sub-Investigator. Height and weight measurements will also be performed at the screening visit (visit 1).

An assessment of normal, abnormal but not clinically significant, or abnormal and clinically significant will be recorded in the eCRF for each required body system. The Investigator or designee will be required to provide a comment regarding any finding of abnormal but not clinically significant and abnormal and clinically significant.

#### 9.2.2.2 Vital Signs (Part 1 and Part 2)

Vital signs measurements (blood pressure, heart rate, respiration rate, and body temperature) will be performed as indicated in **Schedule of Events, Table 9-1** by a qualified healthcare provider, Investigator, or sub-Investigator. A window of within 60 minutes of measuring the predose $FEV_1$ is permitted on days 0, 21, and 42. The patient must be in a seated position and resting for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given patient. For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the Investigator as a clinically significant change (worsening) from a baseline value will be considered an AE.

#### 9.2.2.3 Spirometry (Part 1 and 2)

Patients enrolled in Part 1 and Part 2 of the study will be issued with an ediary/electronic flow meter to assess their lung function ($FEV_1$). $FEV_1$ collection begins at the time of signing the ICF, and then continues throughout Part 1 and Part 2, per the randomization scheme.

For Part 1, $FEV_1$ will be measured once daily: prior to dosing in the morning (if applicable) at approximately the same time each day. On days of the investigational center visits, spirometry will be performed using the equipment at the investigational center.

For Part 2, $FEV_1$ will be measured twice daily at home: upon awakening in the morning immediately prior to dosing with study medication and at 2 (+2) hours after study medication administration. Three (3) $FEV_1$ measures should be taken at each time point; the highest effort will be used.

#### 9.2.2.4 Adverse Events (Part 1 and Part 2)

All AE/SAEs (including treatment-emergent AEs) will be assessed throughout the study visits and followed to resolution/satisfaction. Adverse events (AEs) will be recorded after the patient has signed the informed consent form (ICF) and captured via patient interview during the onsite or telephone visits.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), the most current version (19.0 or later), for system organ class (SOC), preferred term (PT), and lowest level term (LLT), respectively.

#### 9.2.2.5 Monitoring of COPD Exacerbations (Part 1 and Part 2)

A COPD exacerbation is defined as worsening of symptoms of COPD for at least 2 consecutive days and classified as mild when patients do not require treatment with systemic corticosteroids and/or antibiotics; moderate when treatment with systemic corticosteroids and/or antibiotics are required; or severe when hospitalization or visit to the emergency care/acute care unit is required. A separate exacerbation is considered when an interval of clinical improvement of at least 7 days is observed.

Any moderate or severe COPD exacerbation occurring during Part 1 will result in withdrawal (see section **6.5**).

COPD exacerbations are not considered AEs unless they meet the definition of an SAE.

COPD exacerbations will be documented separately from AEs on a COPD exacerbation log in the eCRF, unless the exacerbation meets the definition of an SAE as described above. In this instance, the exacerbation will be recorded on both the AE and COPD exacerbation pages of the eCRF.

Collection of COPD exacerbations will begin at the time of consent and will continue through the final visits in Part 1 and Part 2 of the study. COPD exacerbations will be captured via patient interview during the onsite or telephone visits.

#### 9.2.2.6 COPD Symptom Scores (Part 1 and Part 2)

During Part 1 (commencing at the time of consent) and Part 2 of the study, as indicated in, **Schedule of Events, Table 9-1,** patients will assess and record their COPD symptoms scores once daily in the evening before bedtime using the EXACT.

The EXACT is a 14-item daily diary designed to provide a direct measure of patient-reported symptoms of COPD exacerbation. The EXACT Total score is computed across the 14 items and has a theoretical range of 0 to 100, with higher values indicating a more severe condition. The total score is used in the determination of exacerbation frequency, severity, and duration of exacerbation.

**All 14 items of the EXACT are to be completed by the patient each evening prior to bedtime, reflecting back on their experiences "today."**

The ER-S: COPD is a derivative instrument of the EXACT designed to address the need for standardized daily diary to assess respiratory symptoms in patients with COPD.

The ER-S: COPD is comprised of 11 respiratory symptom items contained in the 14-item EXACT. A daily Total score (RS-Total score) representing respiratory symptom severity, overall and 3 subscale scores (RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms) can be computed from the E-RS. The daily RS-Total score is computed by summing the raw score assigned to each of the 11 items and has a theoretical range of 0 to 40, with higher values indicating more severe respiratory symptoms. The same simple summation procedure is used for obtaining the 3 daily domain scores of the E-RS: RS-Breathlessness is the sum of items 7, 8, 9, 10, and 11 (score range 0-17); RS-Cough and Sputum is the sum of items 2, 3, 4 (score range 0-11); and RS-Chest Symptoms is the sum of items 1, 5, 6 (score range 0-12).

The ER-S: COPD (derived from the EXACT score) will be used to assess disease stability throughout the study. A baseline score will be obtained from the first available evening session after signing the ICF for use during the screening and run-in periods and from the latest available evening session before the randomization visit (visit 2) for use during the double-blind and open-label treatment periods. If at any time, there is increase in the ERS-COPD daily RS-Total score of ≥2 from baseline, the ediary will alert the patient to notify the investigational center personnel to discuss the patient's current health status. The Investigator will need to determine if the patient is able to continue participating in the study as per the withdrawal criteria in section **6.5**.

Refer to **Appendix C** for additional details.

#### 9.2.2.7 Electrocardiography

A 12-lead ECG will be performed for Part 1 and Part 2 as indicated in **Schedule of Events, Table 9-1**. For Part 1, the ECGs will be collected prior to lung function assessments. Procedures for conducting ECGs are described in the ECG manual. The patient should be in a supine position and resting for at least 5 minutes. A qualified physician at a central diagnostic center will be responsible for interpreting the ECG. However, at the screening visit (visit 1), the Investigator will preliminarily interpret the ECG to determine if the patient is eligible to proceed with screening assessments; final interpretation of the ECG will the responsibility of the central ECG reader. The Investigator is responsible for determining whether an abnormality is clinically relevant.

Patients should have an ECG that is normal or free of clinically significant findings at the screening visit (visit 1) and visit 2.

### 9.2.3 Other Procedures

#### 9.2.3.1 Medical History

A complete medical history will be recorded and evaluated as indicated in **Schedule of Events, Table 9-1**.

#### 9.2.3.2 Clinical Laboratory Assessments

Standard clinical laboratory tests will be performed as indicated in **Schedule of Events, Table 9-1** using a central laboratory as indicated in the study procedures manual.

#### 9.2.3.3 Pregnancy Testing

Serum and urine pregnancy testing will be performed as indicated in **Schedule of Events, Table 9-1** or as indicated by the patient's condition. The urine pregnancy test will be completed by dipstick evaluation at the investigational center on all female patients of childbearing potential. The dipstick testing is based on the detection of beta-HCG and will be carried out as per manufacturer's instructions.

A positive finding during the screening visit (visit 1) will prevent the patient from participating in the study and a positive finding at or after visit 2 will require immediate Sponsor notification, discontinuation of study medication, and withdrawal from the study.

#### 9.2.3.4 Urine Drug Screening

Urine drug screening will be performed via a urine dipstick at the investigational center as indicated in **Schedule of Events, Table 9-1** or at any time during the study should the Investigator deem it is warranted. A positive finding during the screening visit (visit 1) will prevent the patient from participating in the study, and a positive finding after the screening visit will require immediate Sponsor notification, and may result in discontinuation of study medication and termination from the study (if not related to a currently prescribed medication as described below).

If a patient has a positive urine drug screen for a class of drug which is consistent with a medication that the patient is currently prescribed (excluding inhaled marijuana), the patient can be considered eligible for the study after the prescription is confirmed by the Investigator. Inhaled marijuana is not permitted even if prescribed.

Additional details are provided in the laboratory instruction manual.

#### 9.2.3.5 In-Check DIAL Training

For Part 1 of the study, patients will be trained on inspiratory flow rate using the In-Check DIAL, a hand held inspiratory flow measurement device (see **Appendix B**). Training will be performed as indicated in **Schedule of Events, Table 9-1**. Patients must achieve an inspiratory flow rate of ≥40 L/min at the screening visit. Although this criterion is not required for visits 2-4, it is expected that each patient will achieve an inspiratory flow rate of ≥40 L/min for these visits, as this was a requirement for study entry.

## 9.3 STUDY VISITS

The study consists of 2 parts. Part 1 (double-blind treatment period) consists of a screening period, 3 double-blind treatment periods at the investigational center, and a follow-up telephone call at the end of the double-blind treatment period for only those patients participating in Part 1. All visits for Part 1 must be scheduled in the mornings between 0600 and 1000 and spirometry testing should begin at ±1 hour of the start of visit 1 testing time. Part 2 (open-label extension) consists of 7 visits (visit 5 through visit 10, and follow-up), which will begin on the last day of visit 4 (Part 1). Visit 6 and visit 8 will be conducted via telephone contact. The final safety follow-up for those patients

participating in Part 2 will be conducted via telephone 7 days (±3 days) after the last active treatment of the open-label extension (ie, visit 10).

A screening failure is defined as any patient that signed an ICF and was either not enrolled in the study or failed to meet the inclusion/exclusion criteria during the screening period.

A randomization failure is defined as any patient that signed an ICF, underwent all screening assessments, was dispensed single-blind run-in medication, but failed to meet the randomization criteria listed in section **6.3**, Randomization Criteria, at visit 2.

The patient number and information regarding screening/randomization failures will be documented in the study database.

Note: As there is only the potential to extend visit intervals with permitted visit windows, the terminology of study day will not necessarily represent the exact day of the visit. Study day 0 of treatment period 1 will be used as baseline when scheduling study days/visits.

See section **9.3.6** and **9.3.7** for retesting and rescreening parameters, respectively.

### 9.3.1 Screening Period

During the screening period, a signed and dated ICF will be obtained first before screening procedures commence. The screening period may be conducted up to 30 days (day -44 to day -14) before the start of the run-in period. The screening period begins once the ICF is signed, and ends at the start of the run-in period. The screening period may take place over several days beginning on day –44 to day –14 dependent on the patient's washout. If a patient is washing out of ICS (monotherapy) or ICS/LABA combination therapy, an additional 3 days is permitted to complete the assessments for the screening visit (visit 1). The screening visit (visit 1) should immediately precede the start of the run-in period. If a patient does not require washout, and the patient passes all entry criteria at the screening visit (visit 1), the patient will be eligible to enter the run-in period on the same day as the screening visit (visit 1). The patient must successfully complete the visit 1 procedures/assessments prior to entering the run-in period.

The procedures for the screening visit (visit 1), with the exception of signing of the ICF, assigning a patient number, performing a pre-washout physical examination, and dispensing/completing the ediary, cannot occur until appropriate medication washouts have been completed in accordance with the protocol. Once the washout requirements have been met, the screening visit (visit 1) should immediately precede the start of the run-in period.

The following procedures and assessments will be conducted at the screening visit (visit 1) with the exception of the procedures listed above if medication washout is required:

- obtain informed consent
- assign patient identification number via IRT
- review inclusion/exclusion criteria
- collect demographic information

- perform physical examination

  Note: If washout of baseline therapy is needed, then 2 physical examinations are required: one before a patient commences the washout period and one after the washout period ends, prior to enrolling into the run-in period.
- perform height and weight measurements
- collect medical history, including COPD history and prior and concomitant medications
- discuss COPD treatment options for patient
- perform 12-lead ECG, prior to measuring study qualifying spirometry
- perform clinical laboratory tests (serum chemistry, hematology, urinalysis)
- perform serum pregnancy test for all female patients of childbearing potential
- perform urine drug screen
- perform vital signs measurements (blood pressure, heart rate, respiration rate, and body temperature) prior to measuring study qualifying spirometry
- demonstration of albuterol/salbutamol MDI and study medication inhaler technique
- assess inspiratory flow rate via In-Check DIAL device
- perform study qualifying spirometry measurements
- perform reversibility to ipratropium bromide
- determine screening/run-in $FEV_1$ stability limits using the onsite spirometer
- dispense albuterol/salbutamol MDI, as applicable

  Note: Dispensation of the albuterol/salbutamol MDI is not required during the screening period if the patient is taking this medication as part of their current COPD therapy. Once the patient qualifies for the run-in period, dispensation/administration of the study albuterol/salbutamol MDI is required and the patient will discontinue the use of their own albuterol/salbutamol MDI.
- dispense/collect placebo trainer
- dispense ediary/electronic flow meter

  Note: Diary collection begins at the time of signing the ICF until the conclusion of the run-in period, and then continues throughout Part 1 and Part 2, per the randomization scheme.
- review ediary/electronic flow meter instructions
- assess ediary data
- collect ediary/electronic flow meter, as applicable
- collect albuterol/salbutamol MDI (as needed)
- record AEs
- record COPD exacerbations
- schedule next visit

The patient will begin using an ediary/electronic flow meter for use throughout the screening period, if applicable and asked to measure their lung function ($FEV_1$) in the

morning prior to dosing with COPD medication (as applicable) at approximately the same time each day. Patients will be asked to record EXACT symptom scores (see **Appendix C**) and albuterol/salbutamol MDI use in their ediary during the screening period, if applicable.

### 9.3.2 Run-in Period

The run-in period will occur over a period of 14 to 16 days before randomization (day 0). The following activities will occur at the investigational center at the start of the run-in period.

- dispense/administer single-blind run-in medication 14 to 16 days before randomization to patients who meet all selection criteria (perform after spirometry/reversibility are conducted)
- dispense albuterol/salbutamol MDI, as applicable
- record AEs
- record concomitant medications/therapies
- record COPD exacerbations
- check for issues with study inhaler

The patient will continue using an ediary/electronic flow meter for use throughout the run-in period and asked to measure their lung function ($FEV_1$) in the morning prior to dosing with placebo LUPINHALER at approximately the same time each day. Patients will be asked to record EXACT symptom scores (see **Appendix C**) once daily in the evening before bedtime, and albuterol/salbutamol MDI/study medication use in their ediary.

Patients are to withhold their morning dose of placebo run-in medication on the morning of visit 2. Patients will be reminded to follow restrictions on diet and medication use prior to visit 2. Patients should not perform $FEV_1$ measurements on the home device prior to visit 2 (both day 0 and day 1).

### 9.3.3 Double-blind Treatment Period (Part 1)

#### 9.3.3.1 Visit 2

Visit 2 is the beginning of the double-blind treatment period and will be conducted as day 0 and day 1.

The following procedures and assessments will be conducted at visit 2:

**Day 0**

- perform HEENT and chest examination
- perform 12-lead ECG, prior to measuring predose $FEV_1$
- perform urine pregnancy test for all female patients of childbearing potential
- perform vital signs measurements (blood pressure, heart rate, respiration rate, and body temperature) prior to measuring predose $FEV_1$

- perform predose $FEV_1$ measurements at 0 hours (30 and 15 minutes before administration of study medication); see permitted spirometry windows in section **9.2.1.1**
- Re-establish stability limits
  - Two stability limits (at home and investigational center) will be re-established (see section **9.2.1.1**).
- demonstration of albuterol/salbutamol MDI and study medication inhaler technique
- assess inspiratory flow rate via In-Check DIAL device
- dispense/collect study medication
- review randomization criteria
- randomization via IRT
- administration of study medication at the investigational center
- check for issues with study inhaler
- perform serial $FEV_1$ measurements at the following time points: 5 and 30 minutes postdose, and at 1, 2, 4, 6, 8, 10, and 12 hours postdose; see permitted spirometry windows in section **9.2.1.1**
- dispense/collect albuterol/salbutamol MDI (as needed)
- dispense/collect placebo trainer
- review ediary/electronic flow meter instructions
- assess ediary data
- collect ediary/electronic flow meter, as applicable
- record AEs
- record COPD exacerbations
- record concomitant medications/therapies

The patient will continue using the ediary/electronic flow meter throughout the remainder of Part 1 and asked to measure their lung function ($FEV_1$) in the morning prior to administering COPD medication at approximately the same time each day. Patients should not perform $FEV_1$ measurements on the home device prior to day 1, visit 3 (both day 21 and day 22) and visit 4 (both day 42 and 43). Patients will be asked to record EXACT symptom scores (see **Appendix C**) and albuterol/salbutamol MDI in their ediary.

Patient will be instructed to return for day 1 of visit 2 with adequate time to complete the serial spirometry measurements at the time points listed below. Patients will be reminded to conform to the smoking, dietary, and medication restrictions prior to day 1 visit.

**Day 1**

- perform vital signs measurements (blood pressure, heart rate, respiration rate, and body temperature)
- perform serial $FEV_1$ measurements at 23 and 24 hours after study medication administration on day 0; see permitted spirometry windows in section **9.2.1.1**

- record AEs
- record COPD exacerbations
- record concomitant medications/therapies
- schedule next visit

#### 9.3.3.2 Visit 3

**Day 21 (+3 days)**

The following procedures and assessments will be conducted on day 21:

- perform HEENT and chest examination
- perform 12-lead ECG, prior to measuring predose $FEV_1$
- perform vital signs measurements (blood pressure, heart rate, respiration rate, and body temperature) prior to measuring predose $FEV_1$
- demonstration of albuterol/salbutamol MDI and study medication inhaler technique
- assess inspiratory flow rate via In-Check DIAL device
- perform predose $FEV_1$ measurements at 0 hours (30 and 15 minutes before administration of study medication); see permitted spirometry windows in section **9.2.1.1**
- perform serial $FEV_1$ measurements at the following time points: 5 and 30 minutes postdose, and at 1, 2, 4, 6, 8, 10, and 12 hours postdose; see permitted spirometry windows in section **9.2.1.1**
- dispense/collect study medication
- dispense/collect albuterol/salbutamol MDI (as needed)
- review continuation criteria
- dispense/collect placebo trainer
- administration of study medication at the investigational center
- check for issues with study inhaler
- assess ediary data
- review ediary/electronic flow meter instructions
- record AEs
- record COPD exacerbations
- record concomitant medications/therapies

**Day 22**

The patient will be instructed to return for the second day of the study visit (day 22) and the following procedures and assessments will be conducted:

- perform vital signs measurements (blood pressure, heart rate, respiration rate, and body temperature)
- perform serial $FEV_1$ measurements at 23 and 24 hours after study medication administration; see permitted spirometry windows in section **9.2.1.1**

- record AEs
- record COPD exacerbations
- record concomitant medications/therapies
- schedule next visit

#### 9.3.3.3 Visit 4

**Day 42 (+3 days)**

The following procedures and assessments will be conducted on day 42:

- perform HEENT and chest examination
- perform 12-lead ECG, prior to measuring predose $FEV_1$
- perform vital signs measurements (blood pressure, heart rate, respiration rate, and body temperature) prior to measuring predose $FEV_1$
- demonstration of albuterol/salbutamol MDI and study medication inhaler technique
- assess inspiratory flow rate via In-Check DIAL device
- perform predose $FEV_1$ measurements at 0 hours (30 and 15 minutes before administration of study medication); see permitted spirometry windows in section **9.2.1.1**
- perform serial $FEV_1$ measurements at the following time points: 5 and 30 minutes postdose, and at 1, 2, 4, 6, 8, 10, and 12 postdose; see permitted spirometry windows in section **9.2.1.1**
- dispense/collect study medication
- dispense/collect albuterol/salbutamol MDI (as needed)
- review continuation criteria
- dispense/collect placebo trainer
- administration of study medication at the investigational center
- check for issues with study inhaler
- assess ediary data
- review ediary/electronic flow meter instructions
- record AEs
- record COPD exacerbations
- record concomitant medications/therapies

**Day 43 for Visit 4**

The patient will be instructed to return for the second day of the study visit (day 43) and the following procedures and assessments will be conducted:

- perform physical examination
- perform serum pregnancy test for all female patients of childbearing potential (for those patients only participating in Part 1)

- perform vital signs measurements (blood pressure, heart rate, respiration rate, and body temperature)
- perform serial $FEV_1$ measurements at 23 and 24 hours after study medication administration; see permitted spirometry windows in section **9.2.1.1**
- assess diary data
- collect ediary/electronic flow meter
- collect albuterol/salbutamol MDI (as needed)
- record AEs
- record COPD exacerbations
- record concomitant medications/therapies
- discuss COPD treatment options for patient (for those patients only participating in Part 1)
- schedule next visit

See section **9.3.3.4** for patients only participating in Part 1 of the study and section **9.3.4** for patients enrolling into Part 2, the open-label extension.

#### 9.3.3.4 Follow-up Part 1 (Telephone Follow-up)

Patients who are not continuing into Part 2 will be contacted via telephone by investigational center personnel on day 50 ±3 days to ensure that there are no lasting issues related to study participation.

The following assessments will be performed:

- record AEs
- record COPD exacerbations
- record concomitant medications/therapies
- discuss COPD treatment options for patient
- end patient participation via IRT

The patient will be deemed to have completed Part 1 if they have completed the screening visit, single-blind run-in period, and all double-blind treatment visits.

### 9.3.4 Open-Label Treatment Period (Part 2)

#### 9.3.4.1 Visit 5 (Day 43)

Patients participating in the open-label extension will begin study activities on the same day as the final clinic visit in the double-blind treatment period (visit 4, day 43) and will be considered the first day of the open-label extension (visit 5).

The following procedures and assessments will be conducted:

- register/enroll patient in IRT
- demonstration of albuterol/salbutamol MDI and study medication inhaler technique
- dispense ediary/electronic flow meter

- dispense albuterol/salbutamol MDI, as applicable
- review continuation criteria
- dispense study medication and patient to administer 1st dose in the investigational center under supervision of site personnel (after all visit 4 procedures are completed in Part 1, and patient is enrolled in Part 2)
- check for issues with study inhaler
- review ediary/electronic flow meter instructions
- record AEs
- record COPD exacerbations
- record concomitant medications/therapies
- schedule next visit

The patient will be issued with a 90-day supply of Lupin Tiotropium Bromide Inhalation Powder. The daily administration of study medication should be taken at approximately the same time each morning for 72 days.

The patient will also continue using the ediary/electronic flow meter throughout Part 2 and asked to measure their lung function ($FEV_1$) twice daily: upon awakening in the morning immediately prior to dosing with the study medication and at 2 (+2) hours after study medication administration. Patients will be asked to record EXACT symptom scores (see **Appendix C**) and albuterol/salbutamol MDI/study medication use in their edairy.

If at any time patients experience an actual or perceived issue with their inhaler, the ediary/IRT system will alert the investigational center who will arrange the necessary corrective action, if required. The investigational center should endeavor to complete the eCRF within 24 hours of notification of an issue.

#### 9.3.4.2 Visit 6 and 8 Telephone Contact

Visit 6 (day 57 [±2 days]) and visit 8 (day 85 [±2 days]) will be conducted via telephone by investigational center personnel.

The following assessments will be conducted:

- assess diary data
- review continuation criteria
- check for issues with study inhaler
- record AEs
- record COPD exacerbations
- record concomitant medications/therapies

The patient will be reminded about the date of their next clinic visit. Patients will continue to administer study medication once daily and record $FEV_1$ twice daily, EXACT symptom scores, and albuterol/salbutamol MDI/study medication usage in the ediary/electronic flow meter.

#### 9.3.4.3 Visit 7 and 9 Clinic Visits

Visit 7 (day 71 [±2 days]) and visit 9 (day 99 [±2 days]) will occur at the investigational center. The following procedures and assessments will be conducted:

- perform HEENT and chest examination
- perform vital signs measurements (blood pressure, heart rate, respiration rate, and body temperature)
- perform 12-lead ECG
- demonstration of albuterol/salbutamol MDI and study medication inhaler technique
- review continuation criteria
- dispense/collect albuterol/salbutamol MDI, as needed
- assess diary data
- check for issues with study inhaler
- record AEs
- record COPD exacerbations
- record concomitant medications/therapies

The patient will be reminded about the date of their next clinic visit. Patients will continue administering study medication once daily and to record $FEV_1$ twice daily, EXACT scores and albuterol/salbutamol MDI/study/rescue medication usage, in the ediary/electronic flow meter.

#### 9.3.4.4 Visit 10

Visit 10 will occur on day 115 (+3 days) at the investigational center. The following procedures and assessments will be conducted:

- perform physical examination
- perform serum pregnancy test for all female patients of childbearing potential
- perform vital signs measurements (blood pressure, heart rate, respiration rate, and body temperature)
- perform 12-lead ECG
- assess diary data
- collect ediary/electronic flow meter (patient will discontinue recording in diary and taking $FEV_1$ measurements)
- check for issues with study inhaler
- collect albuterol/salbutamol MDI and study medication
- record AEs
- record COPD exacerbations
- record concomitant medications/therapies
- discuss COPD treatment options for patient
- schedule next visit

#### 9.3.4.5 Part 2 (Telephone Follow-up call)

Patients who have completed therapy up to visit 10 (72 days of dosing) will be contacted via telephone by investigational center personnel on day 122 (±3 days) to ensure there are no lasting issues related to study participation.

The following assessments will be performed:

- record AEs
- record COPD exacerbations
- record concomitant medications/therapies
- discuss COPD treatment options for patient
- end patient study participation via IRT

The patient will be deemed to have completed Part 2 if they have completed open-label therapy up to visit 10 (72 days of dosing) and have returned the open-label study medication.

### 9.3.5 Early Termination (ET) Visit

Regardless of participation in Part 1 or Part 2 of the study, patients who prematurely withdraw or who are withdrawn from the study will have the following procedures and assessments performed:

- perform physical examination
- perform serum pregnancy test for all female patients of childbearing potential
- perform vital signs measurement (blood pressure, heart rate, respiration rate, and body temperature)
- assess diary data
- collect diary/electronic flow meter
- check for issues with study inhaler (Part 2 study only)
- collect albuterol/salbutamol MDI or study medication
- record AEs
- record COPD exacerbations
- record concomitant medications/therapies
- discuss COPD treatment options for patient
- end patient/study participation via IRT

### 9.3.6 Retest Visits

Pre-randomization (includes the assessments conducted at the screening visit (visit 1) and visit 2 prior to the patient being randomized):

Only 1 retest for spirometry quality/baseline spirometry/stability or reversibility will be permitted for each patient.

Patients who have failed screening for $FEV_1$ or reversibility may retest once no sooner than 24 hours and no later than 2 weeks later provided that they have met all selection criteria.

Post-randomization:

During Part 1, patients may retest for $FEV_1$ if the value varies by more than ±10% from the predose $FEV_1$ at visit 2 up to 3 times. If 3 retests have been conducted, the patient may need to be withdrawn at the discretion of the Investigator.

Note: Postponing/rescheduling for failure to meet the general and dietary restrictions (section **8.2**) is permitted and is not considered a retest per the criteria above.

### 9.3.7 Rescreening

Only 1 rescreen will be permitted.

Patients may rescreen for the following reason:

- Patients who develop symptoms of a URI/LRI during the screening/single-blind run-in period may rescreen once no sooner than 6 weeks after resolution of symptoms, and within the discretion of the Investigator.

The decision to rescreen patients will be based on the Investigator's judgment. In the case of rescreening, the Sponsor or designee should be notified of the pending rescreening.

Patients who undergo rescreening will need to repeat all screening procedures and evaluations, and be assigned a new patient number via IRT.

# 10 SAFETY AND PHARMACOVIGILANCE

## 10.1 DEFINITION OF AN ADVERSE EVENT

An AE is defined as any untoward medical occurrence in a clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

A new medical condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic medical conditions such as arthritis that are present prior to study entry and do not worsen during the study will not be considered AEs. Worsening of the disease under study should only be recorded as an AE if the outcome is more serious than would normally be expected from the normal course of the disease in a particular patient.

## 10.2 INTENSITY OF ADVERSE EVENTS

The intensity or severity of the AE will be characterized as:

- **Mild**: AE which is easily tolerated
- **Moderate**: AE sufficiently discomforting to interfere with daily activity
- **Severe**: AE which prevents normal daily activities

The maximum severity for the event should be listed when the intensity changes during the course of an AE. If the change in severity represents distinct events rather than a single event, this should be recorded as separate AEs.

## 10.3 RELATIONSHIP OF ADVERSE EVENTS TO STUDY MEDICATION

The causal relationship of the investigational product to the AE(s) should be characterized as:

Not Related: There is *no reasonable possibility* that the AE was caused by or attributed to the investigational product.

Related: There is a *reasonable possibility* that the AE was caused by or attributed to the investigational product. A causal relationship cannot be ruled out.

### 10.3.1 Definition of "No Reasonable Possibility"

The assessment term, "*no reasonable possibility*", can only be applied to those AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those AEs which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.

An AE may be considered as being meeting the definition of "no reasonable possibility" if data are available to identify a clear alternative cause for the AE other than study drug; such as the patient's clinical state, concomitant therapy, and/or other interventions or the AE/SAE has no plausible temporal relationship to administration of study drug.

### 10.3.2 Definition of "Reasonable Possibility"

The assessment term, "*reasonable possibility*", can only be applied to those AEs which, after careful medical consideration at the time they are evaluated, a connection with the study drug administration cannot be ruled out with certainty or is felt with a high degree of certainty to be related to the study drug.

An AE may be considered as meeting the definition of "reasonable possibility" if there is a plausible temporal relationship between the onset of the AE/SAE and study drug administration and the AE/SAE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE/SAE follows a known pattern of response to study drug; and/or the AE/SAE abates or resolves upon discontinuation of study drug or dose reduction and, if applicable, reappears upon re-challenge.

## 10.4 RECORDING OF ADVERSE EVENTS

AEs are illnesses or signs/symptoms that appear or worsen during the testing of a drug whether or not considered related to the investigational product (synonyms = medicinal or pharmaceutical product, study medication, clinical trial materials, etc.), including side effects, injury, toxicity, or hypersensitivity reactions.

All AEs, including observed, elicited, or volunteered problems, complaints or symptoms, are to be recorded on the AE page in the patient's eCRF.

The need to capture this information is not dependent upon whether adverse events are associated with use of the investigational product.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications progression of disease states should also be recorded. In order to avoid vague, ambiguous or colloquial expressions, AEs should be recorded in standard medical terminology rather than the patient's own words. Signs and symptoms should be reported individually unless, in the judgment of the Investigator, they can be grouped under an inclusive term (e.g., gastroenteritis in lieu of abdominal pain, nausea, vomiting, and diarrhea).

Each AE is to be evaluated for date/time of onset, duration, intensity, and causal relationship with the investigational product or other factors.

At every study visit, including the prescreening/screening visit (visit 1), the Investigator must document new AEs and the outcome of ongoing AEs. Any patient with an AE (including SAEs) or any clinically significant abnormal laboratory result or physical finding reported as an AE will be followed by the Investigator until the AE resolves, resolves with sequalae, is otherwise explained by a medical condition, follow-up is not possible (document), or the patient dies. All attempts to follow-up will be documented.

### 10.4.1 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AE:

Clinically significant abnormal laboratory findings or clinically significant abnormal findings from other assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs. Abnormal laboratory findings or other assessments deemed as abnormal will not be reported as AEs if they are determined to be clinically insignificant.

If an abnormal laboratory value or other assessment is clearly related to a medically-defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE form, not the individual laboratory values or assessment.

Clinically significant abnormal laboratory results or other clinically significant assessments will be followed until they resolve (return to normal or baseline values) or stabilize, or until they are judged by the Investigator to be no longer clinically significant.

Clinically significant abnormal laboratory findings or abnormal findings from other assessments that are present at baseline will be recorded as medical history.

#### 10.4.1.1 Clinical Laboratory Abnormalities

It is the responsibility of the Investigator to assess the clinical significance of all abnormal laboratory values as defined by the appropriate reference range(s).

An abnormal laboratory value is considered to be an AE if the abnormality meets any of the following conditions below:

- results in discontinuation from the study
- requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention
- is judged to be of significant clinical importance

Laboratory abnormalities that fulfill a seriousness criterion need to be documented as a SAE.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error, either by laboratory or by Investigator does not require reporting as an AE.

#### 10.4.1.2 Other Safety Assessments:

Any abnormal finding determined from physical examinations or from other safety assessments (eg, vital signs, ECGs, diagnostic imaging, or any other potential safety assessment required or not required by protocol) should be assessed for clinical significance by the Investigator. Only clinically significant abnormal findings should be recorded as an AE.

## 10.5 DEFINITION OF A SERIOUS ADVERSE EVENT

An SAE is defined as an AE that results in any of the following:

- **death**
- **life-threatening**

- **requires hospitalization or prolongs existing hospitalization**
- **results in persistent or significant disability or incapacity**
- **results in a congenital abnormality or birth defect**
- **an important medical event which requires medical intervention to prevent any of the above outcomes**

**Important medical events** are those which may not be immediately life-threatening, but may jeopardize the patient and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm or paradoxical bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; resulting in an adverse event will normally be considered serious by this criterion.

Inpatient **hospitalization** or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event. It does not refer to pre-planned elective hospital admission for treatment of a pre-existing condition that has not significantly worsened, or to diagnostic procedures.

The term **"life-threatening"** in the definition of "serious" refers to an event in which the patient 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.

The term "**disability"** in the definition of "serious" refers to an event in which the patient's ability to conduct normal life functions was substantially disrupted.

**Severe vs. Serious AEs:** The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe headache). This is not the same as "serious", which is based on patient/event outcome or reaction criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Any new SAE that occurs after the study period and is considered to be related (possibly/probably) to the study drug or study participation should be recorded and reported immediately (Section **10.6**). The study period for the purpose of SAE reporting is defined as the period from the patient's signature on the informed consent form until the end of the protocol-defined follow-up visit/period.

## 10.6 SERIOUS ADVERSE EVENT REPORTING

In order to satisfy regulatory requirements, any SAE, whether deemed study drug-related or not, must be reported to the Sponsor's Local Clinical Management (LCM) or designee as soon as possible after the Investigator or site coordinator has become aware of its occurrence. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact.

The LCM contact for this study is the CRO, [redacted].

[redacted]

The SAE should be submitted within 24 hours of becoming aware of the event to the Sponsor's LCM or designee. LCM or designee will forward the SAE report to the following Sponsor pharmacovigilance unit.

Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site within 24 hours of the information becoming available to the LCM or designee.

For both initial and follow-up SAE reports, the LCM or designee will forward this information to the appropriate pharmacovigilance unit at the Sponsor within 24 hours. The Sponsor pharmacovigilance units will submit a summary of the clinical course of the SAEs back to the LCM or designee for local submission to the institutional review board/independent ethics committee (IRB/IEC) and Investigators according to regulations. All other investigators will be notified as per Safety Monitoring Plan.

The Lupin Medical Monitor for this study is:

The following information should be provided by the Investigator or designee to accurately and completely record the event:

- Investigator name and center number
- patient number
- patient initials
- patient demographics
- clinical event
  - description
  - date of onset
  - severity
  - treatment (if blind needs to be broken)
  - relationship to study drug (causality)
  - action taken regarding study drug
  - outcome
  - date of resolution
- if the AE results in death
  - cause of death (whether or not the death was related to study medication)
  - autopsy findings (if available)
- medical history CRF (copy)
- concomitant medication CRF (copy)
- any relevant reports (laboratory, discharge, x-ray, etc)

Patients who have had an SAE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Any newly emergent SAEs after treatment is discontinued or the patient has completed the study and is considered to be related to the study drug or study participation should be recorded and reported immediately. The poststudy period for the purpose of SAE reporting is up to the follow-up visit of the study.

**Pregnancy reports:** Pregnancy reports should be forwarded to the LCM/CRO within 24 hours of the Investigator's knowledge using the Pregnancy Report form who will then submit to Lupin pharmacovigilance unit for data-entry to the global safety database. This includes also normal pregnancies without AE.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities or maternal and newborn complications. Pregnancy follow-up should be recorded on the study specific pregnancy reporting form.

## 10.7 REPORTING TO THE UNITED STATES FOOD AND DRUG ADMINISTRATION (US FDA)

All SAEs observed during the conduct of the study, regardless of whether the event is considered drug related will be reported to US FDA. If the AE is fatal or life-threatening, the Clinical Safety Coordinator in the Center for Drug Evaluation and Research (CDER)'s Office of Generic Drugs will be notified within 7 calendar days after Lupin Inc. or the CRO becoming aware of its occurrence. All other SAEs will be reported within 15 calendar days after Lupin Inc. or the CRO becoming aware of its occurrence. All follow-up reports will be submitted within 15 calendar days of Lupin Inc. or the CRO receiving the information.

# 11 DATA COLLECTION AND ANALYSIS

This section describes the biostatistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the Statistical Analysis Plan (SAP). The SAP will take precedence over the protocol in the case of discrepancy. After finalization of the SAP and unblinding, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical trial report.

## 11.1 DATA COLLECTION METHODS

Data will be collected using eCRFs that are specifically designed for this study. The eCRF data will be captured within a clinical data management system (CDMS) that is 21 CFR part 11 compliant. The CDMS will be fully validated prior to use on the study to ensure that it meets the scientific, regulatory, and logistical requirements of the study. All CDMS users will be provided system and study specific training prior to use, then trained users will be provided with individual system access rights.

Data corrections to the CDMS will be performed using the CDMS update function. For each instance of data modification, the system requires a reason for change. The system keeps a full audit trail of the data values, date and time of modification, and an authorized electronic signature approving the change

Data will be extracted from the CDMS to SAS.® The data may be extracted on a scheduled or ad hoc basis to be used for data cleaning, study management, safety monitoring, data analysis, or other study related purposes.

At the conclusion of the study, an electronic copy of each patient's eCRF in PDF format will be supplied to the Investigator, who will maintain these records as described in section **12.8**.

## 11.2 SAMPLE SIZE CALCULATIONS

The sample size estimation was determined based on demonstrating equivalence between the Test (T) product (Lupin Tiotropium Bromide Inhalation Powder) and the Reference (R) product (SPIRIVA HANDIHALER) for the primary endpoint change from baseline in $FEV_1$ $AUC_{0-24}$ on the treatment day, and to demonstrate that both the Test (T) and Reference (R) products are superior to the placebo. Bioequivalence (BE) will be demonstrated if the 90% confidence interval (CI) on the T to R ratio for the endpoint is contained within the interval (0.80, 1.25). Superiority will be demonstrated by showing that each active treatment's response for the endpoint is greater than, and statistically different from ($p<0.05$, two-sided), that of the Placebo (P). For the equivalence evaluation, the results in the PP analysis set will be considered definitive and for the superiority evaluations, those in the Intent-to-Treat (ITT) population will be considered definitive.

A review of the literature did not yield any estimates of within-patient variability of baseline-adjusted $FEV_1$ $AUC_{0-24}$ from a crossover study using a similar patient population with similar objectives. From a review of studies on clinicaltrials.gov, there

were a number of estimates available of between-patient variability for baseline-adjusted $FEV_1$ $AUC_{0-24}$. From the 12 studies reviewed, the mean coefficient of variation (CV) for the variable was 121%. Within-patient variability is generally much less than between-patient variability. As a starting point for the sample size estimation it was assumed that the within-patient variability would be about 50% of the between-patient variability, or a CV of 60%.

The goal of the study is to complete 180 patients per protocol. With a sample size in each of the 6 sequence groups of 30, for a total sample size of 180, a crossover design will have 90% power to reject both the null hypothesis that the ratio of the test mean to the standard mean is below 0.80 and the null hypothesis that the ratio of test mean to the standard mean is above 1.25 (ie, that the test and standard are not equivalent), in favor of the alternative hypothesis that the means of the 2 treatments are equivalent, assuming that the expected ratio of means is 1.00, the between-patient coefficient of variation is 1.21, the intra-patient coefficient of variation is 0.60. In order to allow for a potential 30% premature withdrawal rate or loss from the PP population due to protocol deviations, 240 patients will be randomized in total, 40 to each of the 6 treatment sequences.

As no estimates of within-patient variability were available in the public domain, a blinded interim analysis will be conducted in order to assess the within-patient variability. The blinded interim analysis will be done to ascertain if an increase in sample size is necessary maintain 90% power to complete the study with a 90% CI for the relative bioavailability of the Test (T) to the Reference (R) product inside of the pre-specified interval 0.80-1.25.

## 11.3 POPULATIONS FOR ANALYSIS

### 11.3.1 Intent-to-Treat (ITT) Population

The ITT analysis set will adhere as closely as practically possible to the intention-to-treat (ITT) ideal, and will be based on data from all patients who were randomized, took at least one dose of study medication and contributed sufficient data for at least one efficacy endpoint to be calculated. The ITT analysis set will be the primary analysis set used for the demonstration of the superiority of the active treatments to placebo. In this population, treatment will be assigned based upon the treatment to which patients were randomized regardless of which treatment they actually received.

### 11.3.2 Per-Protocol (PP) Population

The PP analysis set will exclude patients from the ITT population who had major protocol deviations. These patients will be identified before the study blind is broken. The PP analysis set will be the primary analysis set used for the determination of BE.

### 11.3.3 Safety Population

All patients who received at least one dose of any one of the randomized investigational products and for whom data have been collected after randomization will be included in the safety analysis set.

### 11.3.4 Part 2 of the Study (Open-Label)

All patients who begin treatment during the open-label portion of the study will be included in the descriptive statistics provided for the open-label portion.

## 11.4 INTERIM ANALYSIS

A blinded interim look at the data will be made in order to check the assumption about intra-patient variability made when estimating sample size with the possibility of increasing sample size, if necessary, to maintain 90% power. In particular, the sample size estimate is based on an assumed intra-patient variability to which sample size estimates are very sensitive. As no estimates of intra-patient variability were available, the initial assumption was that the intra-patient CV would be approximately half of the inter-patient CV observed on average in a number of studies. A blinded interim review of the data is planned to assess if this reduction is obtained.

Based on this blinded interim look, the sample size may be revised upward if the assumption of the assumed CV is not observed. The sample size will not be revised downward. The interim look is planned when 150 of the planned 240 randomized patients have completed Part 1 of the study.

## 11.5 METHODS OF STATISTICAL ANALYSES

### 11.5.1 Multiplicity

The comparisons of interest are:

1. The superiority comparison between Lupin Tiotropium Bromide Inhalation Powder, 18 mcg (T) and Placebo (P)
2. The superiority comparison between SPIRIVA HANDIHALER, 18 mcg (R) and Placebo (P)
3. The bioequivalence comparison between Lupin Tiotropium Bromide Inhalation Powder, 18 mcg (T) and SPIRIVA HANDIHALER, 18 mcg (R)

As all 3 of these comparisons must be successfully achieved in order to demonstrate BE, no adjustment for multiplicity is required. The order of testing will be according to the list above.

### 11.5.2 Summarization of Data

Aside from the calculation of the $FEV_1$ AUC $_{0\text{-}24}$, summary statistics (mean, SD, median, min, max) will be provided by treatment for data from the serial spirometry measurements including $t_{max}$ (time to maximum bronchodilator response) as well as for all of the individual measurement times. Additionally, a figure illustrating the serial spirometry ($FEV_1$ over time) by treatment group will be provided.

### 11.5.3 Missing Data

For missing serial spirometry measurements:

Linear interpolation between the 2 adjacent $FEV_1$ measurements will be used to estimate missing spirometry measurements occurring between 2 available measurements. The exception to this would be the unlikely event of missing measurements that occur near the peak of the $FEV_1$-time curve. In these cases the average percentage change from the preceding value for patients receiving the same treatment will be used. This makes use of the response of other patients to the same treatment. For analysis, the percentage will be expressed in terms of an $FEV_1$ value.

For missing measurements at the end of the time profile (ie, no available $FEV_1$ value after a point in time):

- For values at the end of the profile that were missing because rescue medication was taken, the minimum observed $FEV_1$ value on that test day, including the predose value, will be used as the estimate. This is similar to assuming that there would be no increase from baseline after the point that rescue medication was required.
- For values at the end of the profile that were missing for reasons unrelated to the patient's response to treatment, the average percentage change from the preceding values for patients receiving the same treatment will be used. This makes use of the response of other patients to the same treatment. For analysis, the percentage will be expressed in terms of an $FEV_1$ value. Two additional sensitivity analyses will be performed based on the following: (a) the AUC calculation will be based on the time interval up to the last non-missing time point and (b) the baseline value will be substituted for the missing values.
- For values at the end of the profile that were missing for unknown reasons, the observed minimum $FEV_1$ value on the day of testing, including the predose value, will be used as an estimate. This conservatively assumes that there would be no increase from baseline after the point that the data were missing.

Additional sensitivity analysis may be performed and will be described in the study SAP.

If a patient contributes data to at least 2 of the crossover legs, data from that patient will be included in the analysis as the patient will have provided data for one of the treatment comparisons. If a patient completes only 1 leg of the crossover, data from the patient will be listed but will not be included in summary statistics or the analysis. There is no reasonable basis for imputing data for a completely missing leg of the crossover.

### 11.5.4 Primary Variable

The primary variable is the adjusted mean change in $FEV_1AUC_{0\ -24h}$ on the single-dose treatment days. Baseline is defined as the average of the $FEV_1$ values recorded at approximately 30 minutes and 15 minutes before dosing with study medication.

This crossover study will follow a Williams design with 6 treatment sequences balanced for first order carryover effects (see **Table 7-1**).

A repeated measures crossover model consisting of effects of treatment, period, and sequence will be carried out.

### 11.5.5 Establishing Superiority of Test (T) and Reference (R) to Placebo

For the comparison of the Test (T) and Reference (R) products, study sensitivity will be demonstrated if the Test (T) and Reference (R) products are shown to be statistically superior to Placebo (P) ($p < 0.05$ [two-tailed]). For these comparisons, the mixed model analysis described in the previous section will be applied to the ITT population.

### 11.5.6 Establishing Bioequivalence between Test (T) and Reference (R) products

The analysis of the primary endpoint for BE will be the mixed model analysis performed on the PP Analysis Set which will include all patients in the ITT population except those who had major protocol deviations.

Bioequivalence (BE) will be declared if the 90% CI of the T/R ratio is entirely contained within the BE interval, 0.80 to 1.25. This is equivalent to meeting the requirements of the two one-sided tests described above. The 90% CI on the ratio of the Test (T) to Reference (R) means will be constructed using Fieller's theorem.

### 11.5.7 Safety Analyses

All randomized patients who receive at least one dose of at least one study treatment and for whom data have been collected after randomization will be included in the safety analysis set.

Descriptive statistics will be provided for safety variables. No formal hypothesis testing of safety data is planned.

Summaries will be provided for the following safety variables: AEs, vital signs, physical examinations, HEENT and chest examinations, COPD exacerbations, and albuterol/salbutamol MDI use.

#### 11.5.7.1 Adverse events

The number and percentage of patients experiencing at least one AE will be summarized by MedDRA, primary SOC, PT and LLT, by treatment and by intensity and relationship to study medication.

In Part 1, the blinded, single dose crossover part of the study, AEs will be tabulated by the following periods:

- double-blind treatment period
- during washout
- during follow-up

Adverse events (AEs) occurring after a study treatment during the treatment day and the day immediate after the treatment will be assigned to the relevant study treatment group.

Adverse events (AEs) that occur before randomization will be summarized separately and will be listed.

Narratives will be provided for SAEs.

Adverse events (AEs) will be tabulated separately for Part 2 of the study. For Part 2 of the study, AEs will be tabulated by the following periods:

- During the open-label study
- During follow-up (more than 24 hours after the last treatment day in the open-label study)

#### 11.5.7.2 Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate and body temperature, will be collected at the screening visit (visit 1) and all subsequent investigational center visits. Descriptive statistics for vital signs at screening and at treatment visits (visits 2 through 4 or ET for Part 1 and visits 7, 9, and 10 or ET for Part 2) will be provided.

For Part 1, the double-blind period, summary statistics will be provided by treatment received on the day of the measurement.

Summary statistics will be provided separately for Part 2, the open label extension.

#### 11.5.7.3 Physical Examination

For Part 1, physical examination findings at screening (visit 1) and visit 4 or ET will be summarized for any clinically significant findings. Significant changes from screening (visit 1) and the end of the double-blind period will be summarized. Changes from screening (visit 1) to the end of the double-blind period will be presented in 3 by 3 shift tables, where the responses are normal, abnormal but clinically non-significant, or abnormal and clinically significant. Each examination area, eg, skin, abdominal, will have a separate table. Some patients may require 2 physical examinations before treatment starts. If they do, the first one is the prescreening value and the one at visit 1 is the screening value. Prescreening results will be listed only.

For Part 2 of the study (open-label extension), findings at visit 10 or ET will be summarized for any clinically significant findings and significant changes from screening (visit 1) and the end of the open-label extension using the 3 by 3 shift tables described above.

#### 11.5.7.4 HEENT, Chest Examination, and Electrocardiograms (ECG)

For Part 1, during the double-blind period, abbreviated physical examination findings (HEENT and chest examinations) and ECG results will be summarized for any clinically significant findings and significant changes from visit 2.

For Part 2 of the study (open label extension), findings will be summarized for any clinically significant findings and significant changes from visit 2.

HEENT and chest examination findings will be summarized by five 3 by 3 shift tables where the shift is from visit 2 to each of the 4 visits during treatment, 2 visits in Part 1 and 2 visits in Part 2.

Electrocardiography (ECG) findings will be summarized by six 3 by 3 shift tables where the shift is from screening (visit 1) to each of the 6 visits during treatment, 3 visits in Part 1 and 3 visits in Part 2.

#### 11.5.7.5 COPD Exacerbations

COPD exacerbations will be summarized and/or listed separately for Part 1 and Part 2 of the study.

### 11.5.8 Safety Spirometry

Patients will be issued an ediary/electronic flow meter to measure $FEV_1$ for monitoring disease stability.

For Part 1 (commencing at the time of signing the ICF), $FEV_1$ will be measured once daily: prior to dosing in the morning at approximately the same time each day.

For Part 2, FEV1 will be measured twice daily at home: upon awakening in the morning immediately prior to dosing with study medication and at 2 (+2) hours after study medication administration.

Values for each patient will be listed.

### 11.5.9 EXACT/ER-S Scores

EXACT scores will be recorded in the patient's ediary once daily each evening before bedtime. Values of the ER-S COPD for each patient will be listed.

### 11.5.10 Albuterol/Salbutamol Usage

Albuterol/Salbutamol usage will be summarized and/or listed separately for Part 1 and Part 2 of the study.

In addition, urine/serum pregnancy test, urine drug screen, clinical laboratory, drug accountability, smoking restriction, DPI training, and In-Check training data will also be listed.

### 11.5.11 Inhaler Robustness (Part 2)

#### 11.5.11.1 Ruggedness of LUPINHALER during In-Patient Use

Patients will be instructed to report any problems that they experience with their LUPINHALER during the open-label extension. The number and percentage of patients who reported at least one issue with the LUPINHALER will be provided.

Additionally, a listing of the individual issues will be provided. The listing will describe the issue in the detail provided by the patient. These will also be summarized according to the following categories:

- misuse episodes (eg, impact [problems with the device after it was dropped], moisture [fell in water, submersed], other)
- issues identified (eg, mechanical problems, COPD worsening/seems ineffective, other)

### 11.5.11.2 In Vitro Pharmaceutical Performance

In vitro pharmaceutical performance of 100 inhalers post 72 days of in-patient use will be assessed. The data resulting from the in vitro evaluation of the pharmaceutical performance will be presented in a separate report.

# 12 STUDY ADMINISTRATION

## 12.1 REGULATORY AND ETHICAL CONSIDERATIONS

### 12.1.1 Regulatory Authority Approval

This study will be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines and all applicable regulations, including current US Code of Federal Regulations (CFR), Title 21, Parts 50, 54, 56, and 312 and Title 45, Part 164. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. This study will also be carried out in accordance with local legal requirements.

### 12.1.2 Ethics Approval

It is the Investigator's responsibility to ensure that, prior to initiating the study, this protocol is reviewed and approved by the appropriate local IRB/IEC. A non-local IRB/IEC may be used if the site of the study is not under the auspices of an IRB/IEC.

The IRB/IEC must also review and approve the site's ICF, other written information provided to the patient, and all advertisements that may be used for patient recruitment. The Investigator will provide Lupin Inc. or designee with copies of these documents and of dated IRB/IEC approval(s) prior to the start of the study.

If it is necessary to amend the protocol or the ICF during the study, the Investigator will be responsible for ensuring that the IRB/IEC reviews and approves these amended documents. An IRB/IEC approval of the amended protocol and/or ICF must be obtained before implementation of the amended procedures and before new patients are consented to participate in the study using the amended version of the ICF. The Investigator will forward copies of the dated IRB/IEC approval of the amended protocol and/or ICF to Lupin Inc. or designee as soon as available.

### 12.1.3 Patient Informed Consent

Before being admitted to the clinical study, all patients must consent to participate. An ICF will be given to each patient, which will contain all US federally required elements, all ICH-required elements, and Health Insurance Portability and Accountability Act Authorization (HIPAA) information in language that is understandable to the patient. The consent should note that the Investigator is receiving compensation for the expenses of conducting the study.

The process of obtaining the informed consent will be in compliance with all federal regulations, ICH requirements, and local laws.

The Investigator or a designee will review the study and the ICF with each patient. The review will include the nature, scope, procedures, and possible consequences of the patient's participation in the study. The consent and review must be in a form understandable to the patient. The Investigator or designee and the patient must both sign

and date the ICF after review and before the patient can participate in the study. The patient will receive a signed and dated form, and the original will be retained in the site's study files. The Investigator or designee must emphasize to the patient that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the patient is otherwise entitled.

### 12.1.4 Investigator Reporting Requirements

In accordance with applicable regulatory requirements, the Investigator is solely and exclusively obligated to keep the IRB/IEC informed of progress on this study, and/or provide periodic safety updates at his/her site, and notify the IRB/IEC of study closure.

The Investigator will provide Lupin Inc. or designee with copies of all correspondence with, or from, the IRB/IEC that relates to study approvals, updates, or changes. Furthermore, the Investigator will be responsible for obtaining all IRB/IEC renewals according to applicable regulations for the duration of the study and to provide copies of any and all approval extensions to Lupin Inc.

## 12.2 PROTOCOL AMENDMENTS

Changes to the protocol can only be made by an approved protocol amendment. Protocol amendments must be approved by Lupin Inc. and IRB/IEC prior to implementation.

## 12.3 DECLARATION OF THE END OF THE CLINICAL TRIAL

For clinical trial sites located in the EU, a declaration of the end of the clinical trial will be made according to the procedures outlined in Directive 2001/20/EC, Article 10(c) and, for those countries outside the EU, local regulations will be followed.

## 12.4 STUDY MONITORING

In accordance with applicable regulations, GCP, and the procedures of Lupin Inc., or its designee, the Study Monitor will periodically contact the site, including conducting on-site visits. The extent, nature, and frequency of on-site visits will be based on study complexity, enrollment rate, and data quality at the site. Through frequent communications (eg, letter, e-mail, and telephone), the Study Monitor will ensure that the investigation is conducted according to protocol and regulatory requirements.

During these contacts, the monitoring activities will include:

- checking and assessing the progress of the study
- reviewing study data collected to date for completeness and accuracy
- conducting source document verification by reviewing each patient's CRF against source documents (eg, medical records, ICF, laboratory results reports, raw data collection forms)
- performing study medication accountability
- identifying any issues and addressing resolutions

These activities will be done in order to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of the patients are being protected.
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The Investigator will allow the Study Monitor direct access to all relevant documents, and allocate his/her time and the time of his/her staff to the Study Monitor to discuss findings and any relevant issues.

In addition to contacts during the study, the Study Monitor will contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel.

## 12.5 QUALITY ASSURANCE

At its discretion, Lupin Inc. or its designee may conduct a quality assurance audit of this study. Auditing procedures of Lupin Inc. and/or its designee will be followed in order to comply with GCP guidelines and ensure acceptability of the study data for registration purposes. If such an audit occurs, the Investigator will give the auditor direct access to all relevant documents, and will allocate his/her time and the time of his/her staff to the auditor as may be required to discuss findings and any relevant issues.

Regulatory agencies (eg, FDA) may conduct an inspection of this study. If such an inspection occurs, the Investigator will allow the inspector direct access to all source documents, CRFs, and other study documentation for source data check and/or on-site audit inspection. The Investigator must allocate his/her time and the time of his/her staff to the inspector to discuss findings of any relevant issues.

## 12.6 STUDY TERMINATION AND SITE CLOSURE

Upon completion of the study, the following activities, when applicable, must be conducted by the Study Monitor in conjunction with the Investigator, as appropriate:

- return all study equipment to Lupin Inc. or designee
- data clarifications and/or resolutions
- accounting, reconciliation, and final disposition of used and unused study medication
- review of site study records for completeness
- shipment of blood samples to the clinical laboratory, if applicable

Lupin Inc. reserves the right to temporarily suspend or prematurely terminate this study for any reason.

If the study is suspended or terminated for safety reason(s), Lupin Inc. will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator is

responsible for promptly informing the IRB/IEC, and providing the reason(s) for the suspension or termination of the study.

If the study is prematurely discontinued, all study data must be returned to Lupin Inc. or its designee. In addition, the site must conduct final disposition of all unused study medication in accordance with Lupin Inc. procedures for the study.

## 12.7 SITE TERMINATION

Lupin Inc. may, in its sole discretion, terminate a single study site for various reasons, including, but not limited to, the following:

- failure of the Investigator to enroll patients into the study at a reasonable rate
- failure of the Investigator to comply with pertinent ICH/GCP/FDA regulations
- submission of knowingly false information from the research facility to Lupin Inc., Study Monitor, or FDA
- insufficient adherence to protocol requirements

If the participation of a study site is terminated for reasons other than safety (eg, uncorrected data acquisition or image quality issues), Lupin Inc. will issue a written notice to the Investigator. The written notice will contain the reasons for taking such action. If a study site is terminated for noncompliance, Lupin Inc. will also notify appropriate regulatory authorities. Study termination and follow up will be performed in compliance with the conditions set forth in 21 CFR 312.50 and 21 CFR 312.56.

## 12.8 RECORDS RETENTION

In accordance with applicable regulatory requirements and following completion or termination of the study, the Investigator will retain a copy of all study records in a safe, secure, and accessible location for a minimum of 2 years after notification by Lupin Inc. that the investigations have been discontinued, or for 2 years after all marketing applications have been approved. For EU submissions, retention of a minimum 5 years though it was post-submission is required. Study records will include at a minimum the following:

- signed ICFs for all patients
- patient identification list
- record of all communications between the Investigator and the IRB/IEC
- record of all communications between the Investigator and Lupin Inc. or its designee
- list of all Sub-Investigators and other key study personnel
- copies of all financial records related to the study including: financial arrangements for the study; financial payments made by Lupin Inc. or its designee to the Investigator; and financial interests held by the Investigator in the product or in Lupin Inc.
- copies of eCRFs for all patients

- all other source documents (eg, patient records, hospital records, laboratory reports, and drug accountability records)

To avoid any possible errors, the Investigator will contact Lupin Inc. prior to the destruction of any study records. The Investigator must immediately notify Lupin Inc. in the event of accidental loss or destruction of any study records.

## 12.9 CONFIDENTIALITY OF INFORMATION

Patient names will remain confidential and will not be supplied to Lupin Inc. or its designee. Only the patient number and year of birth will be recorded in the CRF. If the patient name appears on any other document collected (eg, hospital discharge summary), it must be obliterated from the document before the document is transmitted to Lupin Inc. or its designee. All study findings will be stored in electronic databases. The patients will give explicit written permission for representatives of Lupin Inc., regulatory authorities, and the IRB/IEC to inspect their medical records to verify the information collected. Patients will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with all state, local, and federal data protection/privacy laws, including, without limitation, the HIPAA.

When patients complete the study, all contact information will be purged from all study files, and all patient identifiers (other than an assigned patient number) will be obliterated from documentation confirming a clinical endpoint event.

## 12.10 PAYMENT TO PATIENTS

Patients may be compensated for participating in this study and the amount of payment will be stated in the ICF approved by the IRB/IEC. Patients not completing this study for whatever reason will be paid on a *pro rata* basis.

## 12.11 CLINICAL TRIAL REGISTRATION

This clinical trial will be registered on the "clinicaltrials.gov" clinical trial registry website as required by 42 USC 282(j).

# 13 REFERENCES

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of COPD. Updated 2016. http://www.goldcopd.org

Barr RG, Bourbeau J, Camargo CA, Ram FS. Inhaled tiotropium for stable chronic obstructive pulmonary disease. Cochrane database of systematic reviews 2005:CD002876

Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2013 Sep 16;9:CD00955

Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442

Van den Boom G, van Schayck CP, van Mollen MP, et al. Active detection of chronic obstructive pulmonary disease and asthma in the general population. Results and economic consequences of the DIMCA program. Am J Respir Crit Care Med 1998;158:1730-8.

# 14 APPENDICES

- Appendix A: Study Medication Instructions for Use
- Appendix B: Inhalation Training with In-Check DIAL
- Appendix C: Evaluating Respiratory Symptoms (E-RS) Scale
- Appendix D: Protocol Amendment 1 Summary of Changes

# Appendix A: Study Medication Instructions for Use

## Patient Instructions for Investigational Product Administration of the Dry Powder Inhalers

Two dry powder inhalers will be used in this study (see Figure A1 and Figure A2):

For the run-in period, 1 inhaler (Figure A2) will be used to administer 2 inhalations from 1 capsule of study medication (Lupin 18 mcg tiotropium bromide or placebo) once daily for 14 +2 days.

For Part 1 of the study, 2 inhalers (Figure A1 and Figure A2) will be used to administer a single-dose of study medication (18 mcg tiotropium bromide or placebo) at each treatment period (visits 2, 3, and 4). A single-dose consists of 1 capsule per inhaler administered as 2 inhalations per capsule. Each capsule will be placed into the inhalers by unblinded study personnel as per the randomization schedule.

For Part 2 of the study, 1 inhaler (Figure A2) will be used to administer 2 inhalations from 1 capsule of study medication (Lupin 18 mcg tiotropium bromide) once daily for 72 +3 days.

Placebo training inhalers will also be provided for training purposes during Part 1 of the study.

**YOUR STUDY INHALERS**

Figure A1 represents HANDIHALER and Figure A2 represents LUPINHALER. These inhalers are for oral inhalation only. Both INHALERS will be over-labeled with the appropriate kit/inhaler number.


**Figure A1**
**HANDIHALER**

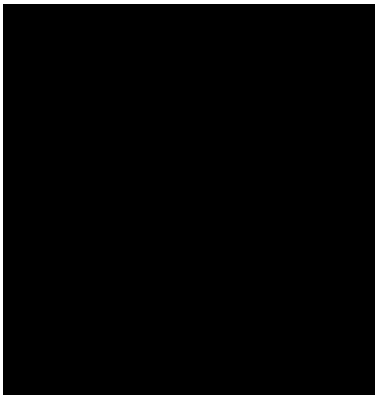


**Figure A2**
**LUPINHALER**

Each INHALER comes with capsules in blister packaging. Use the INHALER provided with the designated capsule(s).

**The parts of each INHALER include:**
(See Figure B1 for HANDIHALER and Figure B2 for LUPINHALER)

1. Dust cap (lid)
2. Mouthpiece
3. Mouthpiece ridge
4. Base
5. Green piercing button
6. Center chamber
7. Air intake vents

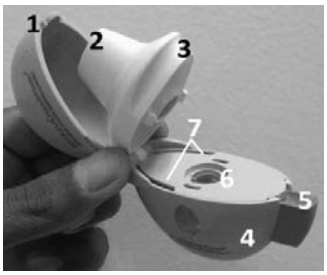



**Figure B1**

**Figure B2**

Each tiotropium capsule is packaged in a blister (See Figure C).

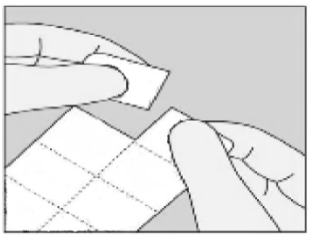


**Figure C**

Each tiotropium capsule contains only a small amount of powder (See Figure D).

Do not open the tiotropium capsule or it may not work.

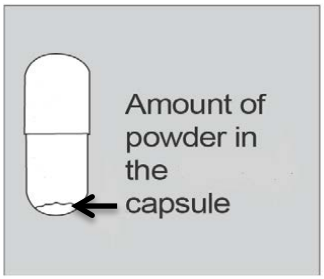



**Figure D**

# FOR PATIENTS PARTICIPATING IN PART 1 DOUBLE-BLIND

## TAKING YOUR DOSE OF STUDY MEDICATION REQUIRES 4 MAIN STEPS.

Note: Some of these steps will be performed by unblinded study personnel prior to you (the patient) receiving the INHALER.

## STEP 1. OPENING YOUR INHALER:

Only unblinded study personnel should open the kits and prepare the INHALERS for the Part 1 double-blind treatment. Opening of the kit and preparation of the INHALERS should be done in a blinded study medication location away from the view of blinded study personnel and you.

After unblinded study personnel has removed your INHALER from the pouch:

- Unblinded study personnel will open the dust cap (lid) by pressing the green piercing button (See Figure E1 for HANDIHALER and Figure E2 for LUPINHALER).

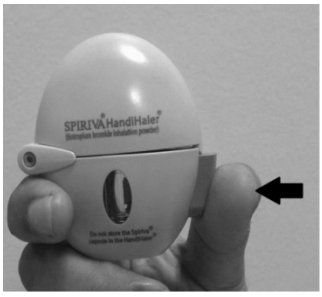



**Figure E1**

**Figure E2**

- Unblinded study personnel will pull the dust cap (lid) upwards away from the base to expose the mouthpiece (See Figure F1 for HANDIHALER and Figure F2 for LUPINHALER).

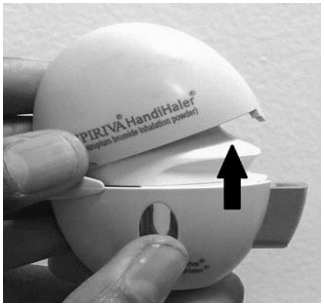



**Figure F1**

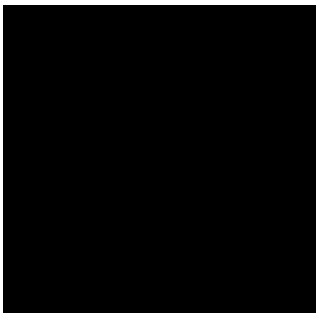


**Figure F2**

- Unblinded study personnel will open the mouthpiece by pulling the mouthpiece ridge up and away from the base so center chamber is showing (See Figure G1 for HANDIHALER and Figure G2 for LUPINHALER).

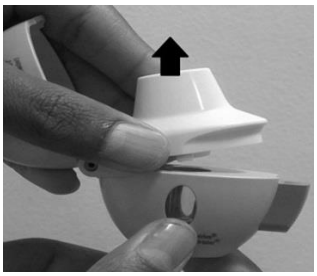


**Figure G1**

**Figure G2**

**STEP 2. INSERTING THE CAPSULE INTO YOUR INHALER:**

Unblinded study personnel will separate the blisters from the blister card by tearing along the perforated line (See Figure H).

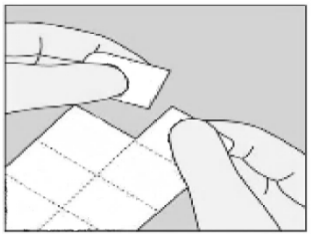


**Figure H**

**Unblinded study personnel will remove the capsule from the blister:**

- Do not cut the foil or use sharp instruments to take out the capsule from the blister.
- Bend one of the blister corners with an arrow and separate the aluminum foil layers.
- Peel back the printed foil until you see the whole capsule (See Figure J).
- If you have opened more than 1 blister to the air, the extra capsule should not be used.

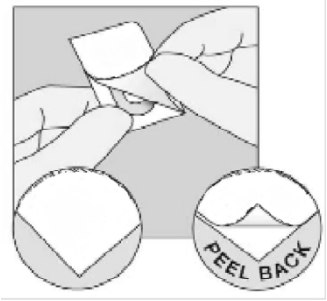



**Figure J**

- Unblinded study personnel will place the capsule in the center chamber of your INHALER (See Figure K1 for HANDIHALER and Figure K2 for LUPINHALER).

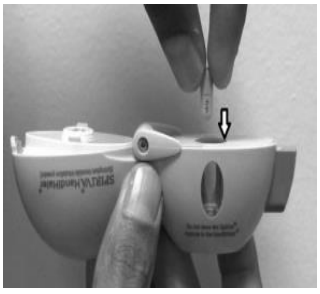


**Figure K1**

**Figure K2**

- Unblinded study personnel will close the mouthpiece firmly against the base until he/she hears a click. Unblinded study personnel will leave the dust cap (lid) open (See Figure L1 for HANDIHALER and Figure L2 for LUPINHALER).

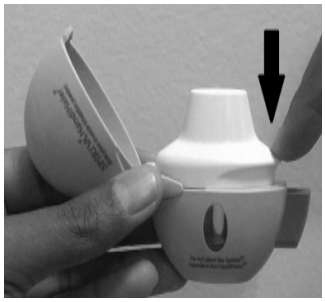


**Figure L1**

**Figure L2**

**STEP 3A. PIERCING THE CAPSULE:**

- Unblinded study personnel will hold your INHALER with the mouthpiece pointed up (See Figure M1 for HANDIHALER and Figure M2 for LUPINHALER).

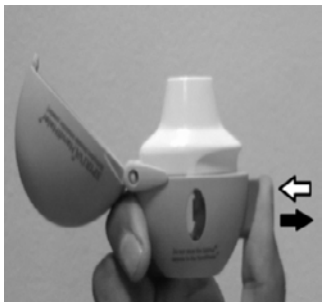


**Figure M1**

**Figure M2**

- Unblinded study personnel will press the green piercing button once until it is flat (flush) against the base, then release. This is how to make holes in the capsule so that you get study medication when you breathe in.
- Do not press the green button more than one time.
- Do not shake the INHALER.
- The piercing of the capsule may produce small pieces of the capsule. Some of these small pieces may pass through the screen of the INHALER into the mouth or throat when you breathe in your medicine. This is normal. The small pieces of the capsule should not harm you.

**STEP 3B. APPLYING TAPE TO MASK THE CHAMBER WINDOW**

- After piercing the capsule, unblinded study personnel will apply an opaque label/tape to cover the chamber window to prevent identification of the capsules, numbering the inhaler dosing order based on even/odd calendar days as described in the pharmacy manual.
- Unblinded study personnel will bring the INHALERS to the patient dosing location leaving the inhaler kit carton, capsule blisters in the blinded study medication location.

**STEP 4. TAKING YOUR DOSE OF STUDY MEDICATION:**

**Blinded study personnel will hand you the INHALER in a horizontal position. Keep the INHALER in the horizontal position.**

**Breathe out completely in 1 breath,** emptying your lungs of any air (See Figure N).

**Important: Do not** breathe into your INHALER.

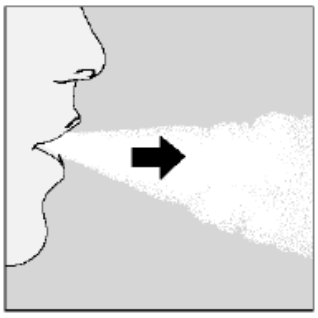


**Figure N**

**With your next breath, take your study medication:**

- **Hold your head in an upright position while you are looking straight ahead** (See Figure P1 for HANDIHALER and Figure P2 for LUPINHALER).
- Raise your INHALER to your mouth in a horizontal position. **Do not** block the air intake vents.
- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the capsule vibrate** (rattle) (See Figure P1 for HANDIHALER and Figure P2 for LUPINHALER).
- Hold your breath for a few seconds and, at the same time, take your INHALER out of your mouth.
- Breathe normally again.

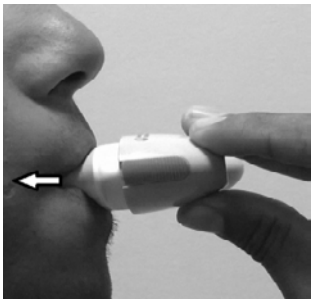


**Figure P1**

**Figure P2**

The rattle tells you that you breathed in correctly. If you do not hear or feel a rattle, see the section, "If you do not hear or feel the capsule rattle as you breathe in your study medication."

**To get the full amount from the capsule, you must again, breathe out completely (See Figure Q)**

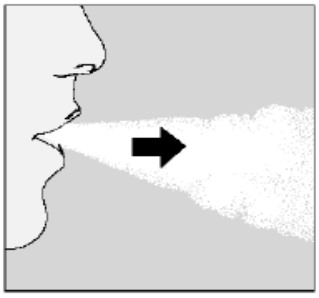


**Figure Q**

**then for a second time, breathe in (See Figure R1 for HANDIHALER and Figure R2 for LUPINHALER) from the same capsule.**

**Important: Do not** press the green piercing button again. **Do not** breathe into your INHALER.

Remember: To get your full amount from the capsule, you must breathe in 2 times from the same capsule. Make sure you breathe out completely each time before you breathe in from your INHALER.

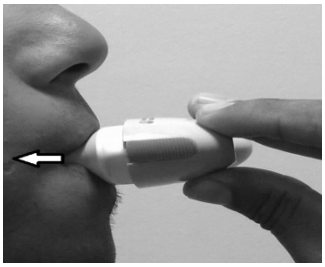


**Figure R1**

**Figure R2**

After completing 2 inhalations from your 1st INHALER, hand the INHALER to unblinded study personnel. Blinded study personnel will collect the INHALER, and close the INHALER.

**Repeat Step 4 with the 2nd INHALER to take your 2nd capsule.**

**Every attempt should be made to administer the powder contents from each of the 2 capsules (2 inhalations/capsule for a total of 4 inhalations) within 2 minutes.**

After you have dosed with both INHALERS, unblinded study personnel will return the INHALERS to the blinded study medication location and deposit each used INHALER containing the used capsule along with unused capsule blisters into the pouch and carton.

**IF YOU DO NOT HEAR OR FEEL THE CAPSULE AS YOU BREATHE IN YOUR STUDY MEDICATION:**

Do not press the green piercing button again.

Blinded study personnel will hold your INHALER with the mouthpiece pointed up and tap your INHALER gently on a table (See Figure S1 for HANDIHALER and Figure S2 for LUPINHALER).

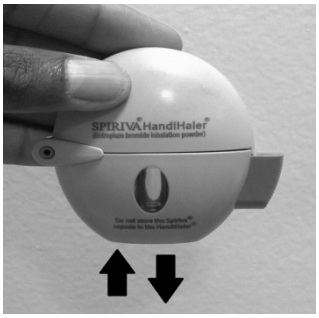



**Figure S1**

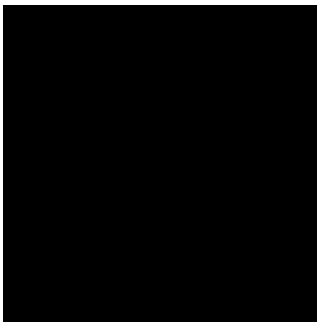


**Figure S2**

Blinded study personnel will check to see that the mouthpiece is completely closed. Breathe out completely before deeply breathing in again with the mouthpiece in your mouth (See Figure R1 for HANDIHALER and Figure R2 for LUPINHALER).

# FOR PATIENTS PARTICIPATING IN TRAINING/RUN-IN/PART 2

## TAKING YOUR DOSE OF STUDY MEDICATION REQUIRES 4 MAIN STEPS.

### STEP 1. OPENING YOUR INHALER:

After study personnel has removed your INHALER from the pouch:

- Open the dust cap (lid) by pressing the green piercing button (See Figure E).

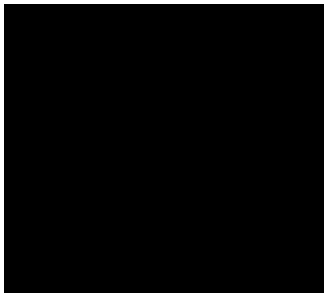


**Figure E**

- Pull the dust cap (lid) upwards away from the base to expose the mouthpiece (See Figure F).

**Figure F**

- Open the mouthpiece by pulling the mouthpiece ridge up and away from the base so center chamber is showing (See Figure G).

**Figure G**

## STEP 2. INSERTING THE CAPSULE INTO YOUR INHALER:

Each day, separate only 1 blister from the blister card by tearing along the perforated line (See Figure H).

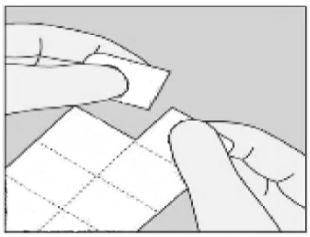


**Figure H**

**Remove the capsule from the blister:**

- Do not cut the foil or use sharp instruments to take out the capsule from the blister.
- Bend one of the blister corners with an arrow and separate the aluminum foil layers.
- Peel back the printed foil until you see the whole capsule (See Figure J).
- If you have opened more than 1 blister to the air, the extra capsule should not be used.

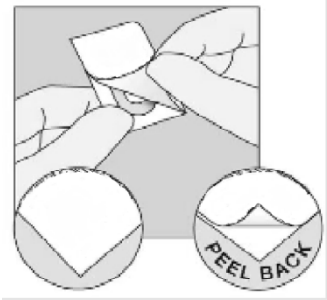



**Figure J**

- Place the capsule in the center chamber of your INHALER (See Figure K).

**Figure K**

- Close the mouthpiece firmly against the base until you hear a click. Leave the dust cap (lid) open (See Figure L).

**Figure L**

**STEP 3. PIERCING THE CAPSULE:**

- Hold your INHALER with the mouthpiece pointed up (See Figure M).

**Figure M**

- Press the green piercing button once until it is flat (flush) against the base, then release. This is how to make holes in the capsule so that you get study medication when you breathe in.
- Do not press the green button more than one time.
- Do not shake the INHALER.
- The piercing of the capsule may produce small pieces of the capsule. Some of these small pieces may pass through the screen of the INHALER into the mouth or throat when you breathe in your study medication. This is normal. The small pieces of the capsule should not harm you.

## STEP 4. TAKING YOUR FULL DAILY DOSE OF STUDY MEDICATION (2 INHALATIONS FROM THE SAME CAPSULE):

**Breathe out completely in 1 breath,** emptying your lungs of any air (See Figure N).

**Important: Do not** breathe into your INHALER.

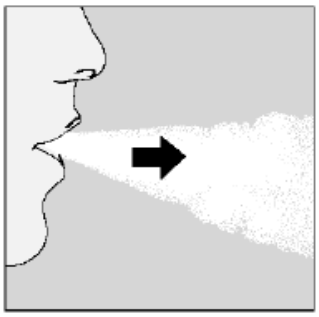


**Figure N**

**With your next breath, take your study medication:**

- **Hold your head in an upright position while you are looking straight ahead** (See Figure P).
- Raise your INHALER to your mouth in a horizontal position. **Do not** block the air intake vents.
- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the capsule vibrate** (rattle) (See Figure P).
- Hold your breath for a few seconds and, at the same time, take your INHALER out of your mouth.
- Breathe normally again.

**Figure P**

The rattle tells you that you breathed in correctly. If you do not hear or feel a rattle, see the section, "If you do not hear or feel the capsule rattle as you breathe in your study medication."

**To get the full amount from the capsule, you must again, breathe out completely (See Figure Q)**

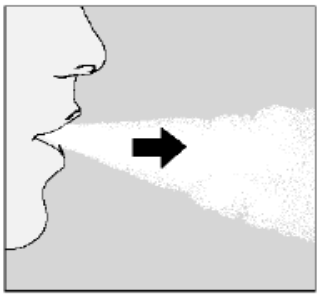


**Figure Q**

**then for a second time, breathe in (See Figure R) from the same capsule.**

**Important: Do not** press the green piercing button again. **Do not** breathe into your INHALER.

Remember: To get your full amount from the capsule, you must breathe in 2 times from the same capsule. Make sure you breathe out completely each time before you breathe in from your INHALER.

**Figure R**

## CARING FOR AND STORING YOUR INHALER:

- After taking your daily dose, open the mouthpiece and tip out the used capsule into your trash can, without touching it.
- Remove any capsule pieces or powder buildup by turning your INHALER upside down and gently, but firmly, tapping it (See Figure S). Then, close the mouthpiece and dustcap for storage.

**Figure S**

- **Do not** store your INHALER and capsules (blisters) in a damp moist place. Always store capsules in the sealed blisters.

## IF YOU DO NOT HEAR OR FEEL THE CAPSULE AS YOU BREATHE IN YOUR STUDY MEDICATION:

- Do not press the green piercing button again.
- Hold your INHALER with the mouthpiece pointed up and tap your INHALER gently on a table (See Figure T).

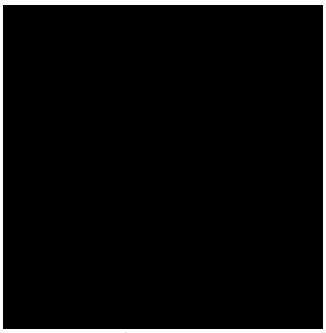


**Figure T**

- Check to see that the mouthpiece is completely closed. Breathe out completely before deeply breathing in again with the mouthpiece in your mouth (See Figure R).
- If you still do not hear or feel the capsule rattle after repeating the above steps:
    - Throw away the used capsule.
    - Open the base by lifting the green piercing button and check the center chamber for pieces of the capsule.
    - Capsule pieces in the center chamber can cause a capsule not to rattle.
    - Turn your INHALER upside down and gently, but firmly, tap to remove the capsule pieces. Call your study doctor for instructions.

## CLEANING YOUR INHALER:

- Clean your INHALER device as needed (See Figure U).
  - **It takes 24 hours to air dry your INHALER** after you clean it.
  - **Do not** use cleaning agents or detergents.
  - **Do not** place your INHALER in the dishwasher for cleaning.

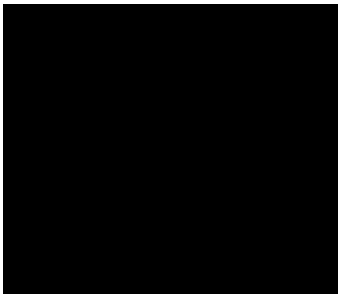


**Figure U**

- **Cleaning Steps:**
  - Open the dust cap and mouthpiece.
  - Open the base by lifting the green piercing button.
  - Look in the center chamber for capsule pieces or powder buildup. If seen, tap out.
  - Rinse your INHALER with warm water, pressing the green piercing button a few times so that the center chamber and the piercing needle are under the running water. Check that any powder buildup or capsule pieces are removed.
  - Dry your INHALER well by tipping the excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open by fully spreading it out so that it dries completely.
  - **Do not** use a hair dryer to dry your INHALER.
  - **Do not** use your INHALER when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.
  - Document in your diary when cleaning of the INHALER has been performed.

## IMPORTANT INFORMATION ABOUT USING YOUR INHALER:

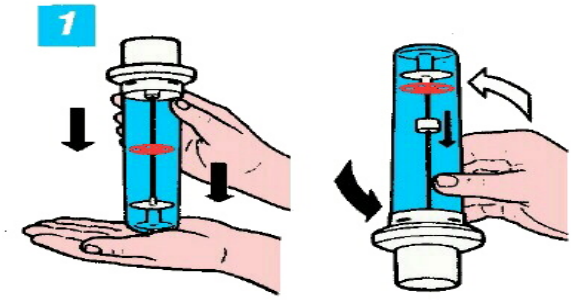
1. Do not swallow capsules.
2. Capsules should only be used with the INHALER and inhaled through your mouth (oral inhalation).
3. Do not use your INHALER to take any other medicine.
4. Do not store capsules in the INHALER.
5. Store capsules in the sealed blister package at room temperature between 68°F to 77°F (20°C to 25°C).
6. Keep capsules away from heat and cold (do not freeze).
7. Store capsules in a dry place. Do not use any unused capsules that have been open to air.
8. Ask your study doctor if you have any questions about storing your capsules.
9. Keep the INHALER and capsules out of the reach of children.
10. Do not let the powder from the capsule get into your eyes.

# Appendix B: Inhalation Training with In-Check DIAL

The In-Check DIAL is an inhalation airflow meter that can help educate and assess patients who use inhaler devices. It simulates the internal resistance of several common inhaler devices, and measures inspiratory flow. Inspiratory flow rate measurements will be obtained at screening and visits 2, 3, and 4 using the In-Check DIAL device.

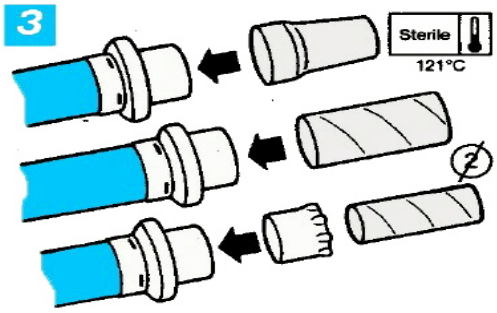
**How to use the In-Check DIAL**

1. Reset the In-Check DIAL. The cursor should be reset to zero through a "tap and turn" maneuver which releases a seated magnet from the top of the DIAL and pushes the cursor back. The DIAL should then be turned upside down to reseat the magnet so as not to get in the way of an accurate measurement.

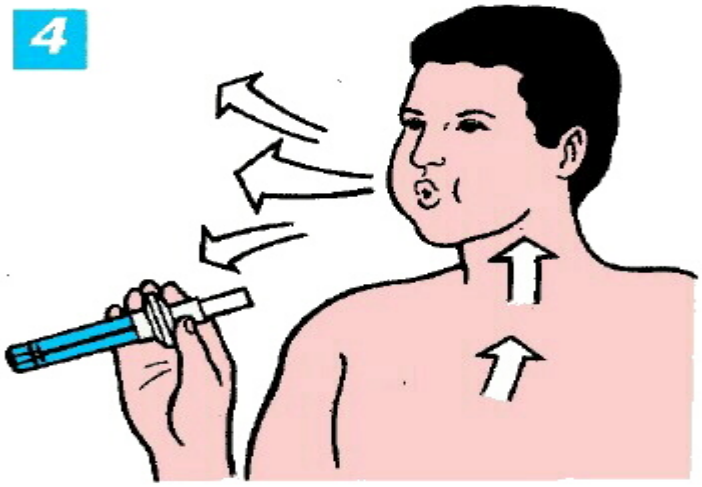



2. Align the scale with the inhaler device. With the triangular pointer on top of the scale, align the "dial" portion of the device for use with HANDIHALER adapter by setting the device to no resistance circle (pMDI) icon - an audible "click" should be heard.

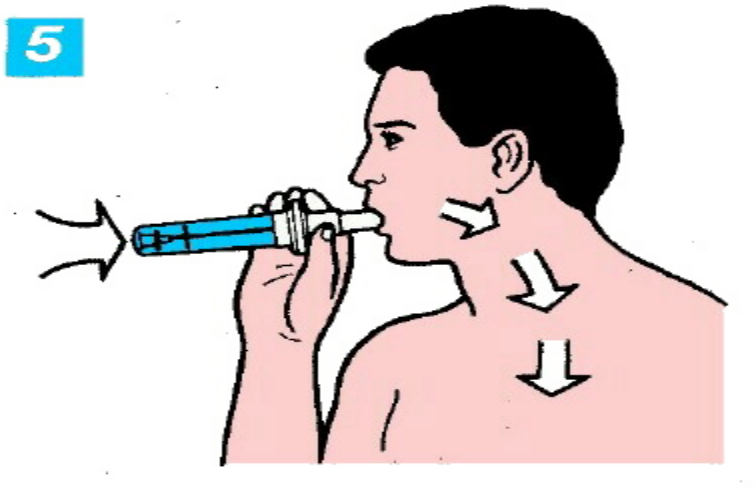
3. Attach a clean mouthpiece. Attach the HANDIHALER resistance adapter (blue transparent cylinder provided separately in a sealed plastic bag) to mimic SPIRIVA HANDIHALER resistance. Insert a disposable one-way valved inspiratory mouthpiece into the wider end of the blue transparent adapter.



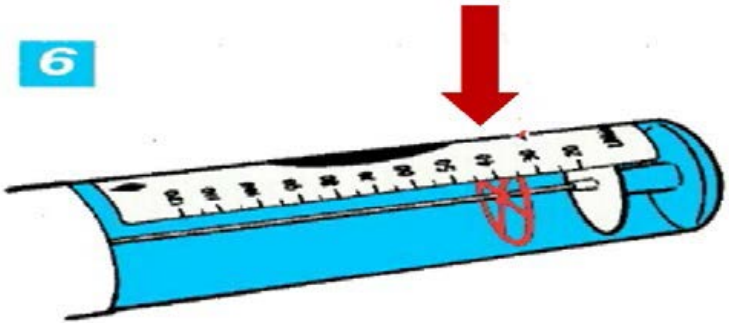

4. Ask the patient to exhale slowly and fully.



5. Seal lips around the mouthpiece. According to the inhaler setting (no resistance circle [pMDI] icon) and HANDIHALER resistance adapter), instruct the patient to inhale deeply.




6. Record the inspiratory flow from the position of the red cursor against the scale. Reset, and repeat until 3 successful inspiratory flow rates (≥40 L/min) are achieved. Record the three (3) inspiratory flow rates on the patient's source.



# Appendix C: EXACT DAILY DIARY

**Instructions:** Please complete your diary every evening, just before you go to bed. As you answer the following questions, please select the option that best describes your experience.

The ediary will be programmed to display your ER-S: COPD daily respiratory symptoms (RS) Total score. A baseline score will be obtained from the first available evening session after the screening visit (visit 1) for use during the screening and run-in periods and from the latest available evening session before the randomization visit (visit 2) for use during the double-blind and open-label treatment periods. If at any time, there is increase in the daily RS Total score of ≥2 from baseline, the ediary will alert you to notify investigational center personnel to discuss your current health status.

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

| | |
|---|---|
| 6. Did your chest feel tight today? | Not at all |
| | Slightly |
| | Moderately |
| | Severely |
| | Extremely |
| 7. Were you breathless today? | Not at all |
| | Slightly |
| | Moderately |
| | Severely |
| | Extremely |
| 8. Describe how breathless you were today: | Unaware of breathlessness |
| | Breathless during strenuous activity |
| | Breathless during light activity |
| | Breathless when washing or dressing |
| | Present when resting |
| 9. Were you short of breath today when performing your usual personal care activities like washing or dressing? | Not at all |
| | Slightly |
| | Moderately |
| | Severely |
| | Extremely |
| | Too breathless to do these |
| 10. Were you short of breath today when performing your usual indoor activities like cleaning or household work? | Not at all |
| | Slightly |
| | Moderately |
| | Severely |
| | Extremely |
| | Too breathless to do these |

| | |
|---|---|
| 11. Were you short of breath today when performing your usual activities outside the home such as yard work or errands? | Not at all |
| | Slightly |
| | Moderately |
| | Severely |
| | Extremely |
| | Too breathless to do these |
| 12. Were you tired or weak today? | Not at all |
| | Slightly |
| | Moderately |
| | Severely |
| | Extremely |
| 13. Last night, was your sleep disturbed? | Not at all |
| | Slightly |
| | Moderately |
| | Severely |
| | Extremely |
| 14. How scared or worried were you about your lung problems today? | Not at all |
| | Slightly |
| | Moderately |
| | Severely |
| | Extremely |
| Copyright | EXACT© 2013, Evidera, Inc. All rights reserved.<br>EXACT version 1.1-English (universal) 9/9/2009 |

*The EXACT instrument and scoring program are owned by Evidera. The questions listed above may be displayed in another format as per the formal licensing agreement with the ediary vendor.

# APPENDIX D: PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES

Protocol Amendment 1 incorporates the following changes. The revisions listed below have been made to the protocol and synopsis as appropriate, and are considered substantial. Revised or new text is presented in bold italics and deletions are struck through. Minor typographical and formatting errors were corrected throughout the protocol.

The primary reasons for this amendment are:

- To incorporate the administrative letter dated 27 Feb 2017, Clarification of the roles of the unblinded/blinded study personnel during study medication administration in Part 1, updates to the study medication and In-Check DIAL instructions for use, and clarification of clinical laboratory results prior to run-in.
  - Roles of the unblinded/blinded study personnel: Unblinded study personnel will prepare double-blind study medication and dispense the inhalers to blinded study personnel and observe dose administration in Part 1. Blinded study personnel will perform study medication training during all parts of the study
  - In-Check DIAL: A new release of the In-Check DIAL device was issued prior to study initiation (ie, new dial top developed to group inhalers by resistance instead of device type); therefore, updated the instructions for use accordingly.
  - Clinical laboratory results: Based on the study visit schedule, the clinical laboratory results may not be available prior to a patient entering run-in; therefore, footnote #5 in the Schedule of Events was updated to state the results must be available and evaluated prior to randomization.
- To incorporate the administrative letter dated 10 Mar 2017, Clarification of the dispensation of the ediary/electronic flow meter and safety monitoring during the screening period.
  - Ediary: Diary collection will begin at the time of signing the ICF. COPD symptom scores (EXACT), albuterol/salbutamol MDI usage, and once daily (morning) $FEV_1$ measurements at home using will be collected using the ediary/electronic flow meter during the screening period.
  - Screening period/screening visit assessments: The screening period may occur up to 30 days prior to the start of the run-in period. Procedures for the screening visit (visit 1), with the exception of signing of the ICF, assigning a patient number, performing a pre-washout physical examination, and dispensing/completing the ediary, cannot occur until appropriate medication washouts have been completed in accordance with the study protocol.
- To prohibit caffeine-containing medication for at least 6 hours prior to spirometry assessments at any scheduled visit (visit 1 through visit 4).

**Study Centers, Synopsis (page 8)**

**Original text:**

The study is planned to be conducted at approximately 60 investigational centers in the United States of America (USA). Additional centers in the USA may be added as needed.

**Revised text:**

The study is planned to be conducted at approximately ~~***60***~~ ***40*** investigational centers in the United States of America (USA). Additional centers in the USA may be added as needed.

**Rationale for change:** *Based on enrollment projections, 40 investigational centers were selected to participate in the study.*

**Study Design Overview, Synopsis (page 9) and Section 5.1.1 Part 1: Double-Blind Treatment Period (page 26)**

**Original text:**

The screening period, of up to 30 days, allows for adequate washout of the following COPD therapies, along with other prohibited medications per protocol:

- long-acting anti-muscarinic agent (LAMA) medications (including mono products and combination products containing LAMAs [eg, LAMA/LABA]) will not be permitted within 21 days of the screening visit (visit 1)
- long-acting beta agonist (LABA) mono products will not be permitted within 7 days of the screening visit (visit 1)
- inhaled corticosteroid (ICS) mono products and ICS/LABA combination products will not be permitted within 30 days of the screening visit (visit 1)

**Revised text:**

The screening period, of up to 30 days, allows for adequate washout of the following COPD therapies, along with other prohibited medications per protocol:

- long-acting anti-muscarinic agent (LAMA) medications (including mono products and combination products containing LAMAs [eg, LAMA/LABA]) will not be permitted within 21 days of the screening visit (visit 1)
- long-acting beta agonist (LABA) mono products will not be permitted within 7 days of the screening visit (visit 1)
- inhaled corticosteroid (ICS) mono products and ICS/LABA combination products will not be permitted within 30 days of the screening visit (visit 1)

***If a patient is washing out of ICS (monotherapy) or ICS/LABA combination therapy as stated above, an additional 3 day window is permitted to complete the assessments for the screening visit (visit 1).***

**Rationale for change:** *For patients on ICS (monotherapy) or ICS/LABA combination therapy additional time may be needed to complete all screening assessments prior to the run-in period; therefore, the window has been extended.*

**Synopsis, Study Design Overview (page 10) and Section 5.1.1 Part 1: Double-Blind Treatment Period (page 27)**

**Original text:**

In order to maintain the patient blind, a specified member of the investigational center (ie, unblinded administrator) will load and dispense the study medication to the patient and instruct the patients to take 2 full inhalations from each of 2 inhalers. The unblinded administrator will also apply an opaque covering to the chamber windows prior to patient administration to obstruct capsule identification in each inhaler. The unblinded administrator will check each inhaler after each dose (2 inhalations) is administered to ensure that the capsule powder has been evacuated. Any instances where the capsule powder is not evacuated should be documented.

**Revised text:**

In order to maintain the patient blind, a specified member of the investigational center (ie, unblinded administrator) will load and dispense the study medication to the patient and instruct the patients to take 2 full inhalations from each of 2 inhalers. The unblinded administrator will also apply an opaque covering to the chamber windows prior to patient administration to obstruct capsule identification in each inhaler. ~~***The unblinded administrator will check each inhaler after each dose (2 inhalations) is administered to ensure that the capsule powder has been evacuated. Any instances where the capsule powder is not evacuated should be documented***~~.

**Rationale for change:** *Because the amount of powder is not visible through the chamber window, it is not feasible to check the remaining powder content via the chamber window through visual inspection. Therefore, this step has been removed.*

**Synopsis, Study Design Overview (page 12), Section 5.1.2 Part 2: Open-Label Extension (page 29), and Section 9.3.4.1 Visit 5 (Day 43) (page 67)**

**Original text:**

If at any time patients experience a perceived issue with their inhaler, the ediary system will alert the investigational center who will arrange the necessary corrective action, if required. The investigational center should endeavor to complete an inhaler report worksheet within 24 hours of notification of an issue.

**Revised text:**

If at any time patients experience a perceived issue with their inhaler, the ediary system will alert the investigational center who will arrange the necessary corrective action, if required. The investigational center should endeavor to complete ~~***an inhaler report worksheet***~~ ***the electronic case report form (eCRF)*** within 24 hours of notification of an issue.

***Rationale for change:*** *Clarification. Any identified issues with study medication will be recorded in the electronic data capture (EDC) system.*

**Synopsis, Study Design Overview (page 12) and Section 5.1.2 Part 2: Open-Label Extension (page 29)**

**Original text:**

Safety will be monitored throughout Part 1 and Part 2 of the study by vital signs measurements, albuterol/salbutamol MDI and concomitant medication usage, physical examinations, head, ears, eyes, nose, throat (HEENT)/chest examinations, spirometry ($FEV_1$) measurements, electrocardiography

(ECGs), ER-S: COPD scores (derived from the EXACT), COPD exacerbations, and adverse events (AEs).

**Revised text:**

Safety will be monitored throughout Part 1 and Part 2 of the study by vital signs measurements, albuterol/salbutamol MDI and concomitant medication usage, physical examinations, head, ears, eyes, nose, throat (HEENT)/chest examinations, spirometry ($FEV_1$) measurements, electrocardiography (ECGs), ER-S: COPD scores (derived from the EXACT), COPD exacerbations, and adverse events (AEs). ***During the screening and run-in periods, safety will be assessed via $FEV_1$ measurements, ER-S: COPD scores, and monitoring of AEs and COPD exacerbations.***

**Rationale for change:** *Clarification. Safety is assessed during the screening and run-periods via $FEV_1$ measurements, COPD symptom scores, and monitoring of AEs and COPD exacerbations.*

**Synopsis, Inclusion criteria (page 13), Section 6.1 Inclusion Criteria (pages 30-31), Schedule of Assessments, footnote 13 (page 52)**

**Original text:**

9. Patient has demonstrated ≥15% reversibility of $FEV_1$ within 30 or 60 minutes following 68 mcg of ipratropium bromide inhalation (pMDI) at the screening visit (visit 1). Patients who do not demonstrate a positive improvement of at least 15% in $FEV_1$ measured at 30 or 60 minutes post inhalation will not be eligible to participate in the study. However, based on Investigator judgment, patients will be allowed to retest once no sooner than 24 hours and no later than 2 weeks after the initial failure (see section 9.3.6). Reversibility values of 14.50-14.99 will be rounded to 15.

**Revised text:**

9. Patient has demonstrated ≥15% reversibility of $FEV_1$ within 30 or 60 minutes following 68 mcg of ipratropium bromide inhalation (pMDI) at the screening visit (visit 1). ***If required, spacers are permitted for use during reversibility testing for ipratropium administration.*** Patients who do not demonstrate a positive improvement of at least 15% in $FEV_1$ measured at 30 or 60 minutes post inhalation will not be eligible to participate in the study. However, based on Investigator judgment, patients will be allowed to retest once no sooner than 24 hours and no later than 2 weeks after the initial failure (see section 9.3.6). Reversibility values of 14.50-14.99 will be rounded to 15.

***Rationale for change:*** *Clarification. Spacers will be permitted for use during reversibility testing.*

**Exclusion criterion #15, Synopsis (page 15) and Section 6.2 Exclusion Criteria (page 33)**

**Original text:**

15. Positive urine drug screen at the screening visit (visit 1). If a patient has a positive urine drug screen for a class of drug which is consistent with a medication that the patient is currently prescribed, the patient can be considered eligible for the study after the prescription is confirmed by the Investigator.

**Revised text:**

15. Positive urine drug screen at the screening visit (visit 1). If a patient has a positive urine drug screen for a class of drug which is consistent with a medication that the patient is currently prescribed ***(excluding inhaled marijuana)***, the patient can be considered eligible for the study after the prescription is confirmed by the Investigator.

**Rationale for change:** *Clarification. Inhaled marijuana has been previously established as a prohibited medication as indicated in Table 8-1; therefore use is prohibited even if prescribed.*

**Synopsis, Randomization Criteria (page 16) and Section 6.3 Randomization Criteria (page 34)**

**Original text:**

5. Patient has withheld all inhaled SABAs for at least 6 hours and SAMAs for at least 8 hours prior to lung function assessments at randomization (visit 2).

**Revised text:**

5. Patient has withheld all inhaled SABAs for at least 6 hours and SAMAs for at least 8 hours prior to lung function assessments at ~~***randomization (***~~visit 2~~***)***~~.

***Rationale for change:*** *Typographical error. At visit 2, patients will withhold SABAs for at least 6 hours and SAMA for at least hours prior to lung function assessments.*

**Randomization criterion #9, Synopsis (page 16) and Section 6.3 Randomization Criteria (page 34)**

**Original text:**

9. Patient has demonstrated compliance to placebo run-in medication within the margins of at least ≥75% and ≤125% of projected use.

**Revised text:**

9. Patient has demonstrated ***ediary*** compliance to placebo run-in medication within the margins of at least ≥75% and ≤125% of projected use.

***Rationale for change:*** *Clarification. Compliance to placebo run-in medication will be calculated and verified via the ediary.*

**Section 3.2 Clinical Experience with Tiotropium Bromide Inhalation Powder Administered by a Dry Powder Inhaler (DPI) (pages 22-23)**

**Original text:**

To date, one clinical study (Study LBC-P-055-15) with Lupin Tiotropium Bromide Inhalation Powder has been conducted.

**Revised text:**

To date, ~~***one***~~ ***2*** clinical ~~***study***~~ ***studies*** (Study LBC-P-055-15 ***and LBC-P-006-15***) with Lupin Tiotropium Bromide Inhalation Powder ~~***has***~~ ***have*** been conducted.

***Study LBC-P-0006-15 was a randomized, open-label, single-dose, 3-period Phase 1, PK crossover study being conducted in healthy male subjects 18-45 years of age under fasting conditions. The primary objective of the study was to assess the systemic levels and relative bioavailability of a single orally-administered dose of tiotropium (18 mcg), from 2 different batches of Lupin tiotropium capsules 18 mcg (×1 capsule) via the LUPINHALER, and 1 batch of SPIRIVA capsules 18 mcg (×1 capsule) via the HANDIHALER.***

***Preliminary safety results from this study indicate that Tiotropium Bromide Inhalation Powder was well tolerated by the healthy subjects, ages 18 to 45 years. No SAEs were reported. The final statistical analyses and PK results are not available at this time.***

***Rationale for change:*** *Informational update. A 2nd PK study was conducted to assess the PK profiles of different batches of Lupin Tiotropium Bromide Inhalation Powder with SPIRIVA HANDIHALER.*

**Section 4.4.3 Other Endpoints (page 25)**

**Original text:**

For a subset of the LUPINHALERs used during the open-label extension (Part 2), the following endpoints will be assessed:

- ruggedness of the LUPINHALER during 72 days of in-patient use
  - percent (%) of overall inhalers with reported problems or malfunctions; comprised of problems/malfunctions encountered with the device (eg, lack of efficacy, mechanical problems, problems with device after it has been dropped) during 72 days of in-patient use
  - in vitro pharmaceutical performance of 100 inhalers post 72 days of in-patient use

    The data resulting from the in vitro evaluation of the pharmaceutical performance will be presented in a separate report.

**Revised text:**

For a subset of the LUPINHALERs used during the open-label extension (Part 2), the following endpoints will be assessed:

- ruggedness of the LUPINHALER during 72 days of in-patient use
  - percent (%) of overall inhalers with reported problems or malfunctions; comprised of ~~***problems/malfunctions encountered with the device (eg, lack of efficacy, mechanical problems, problems with device after it has been dropped)***~~ ***misuse episodes (eg, impact and moisture) and issues identified (eg, mechanical problems and COPD worsening/seems ineffective)*** during 72 days of in-patient use
  - in vitro pharmaceutical performance of 100 inhalers post 72 days of in-patient use

    The data resulting from the in vitro evaluation of the pharmaceutical performance will be presented in a separate report.

***Rationale for change:*** *Clarification. Ruggedness of the LUPINHALER will be summarized into 2 main categories with additional subclassification.*

**Section 6.5 Withdrawal Criteria (pages 35-36)**

**Original text:**

The following alert criteria should be evaluated by the Investigator for consideration of whether the patient should be withdrawn from the study.

These criteria would include the following:

- COPD exacerbation during Part 2 that prohibits the patient from administering their study medication (Lupin Tiotropium Bromide Inhalation Powder) once daily
- use of medication for respiratory symptoms not allowed by the study protocol
- viral or bacterial respiratory infection during Part 1 which results in an increase in the symptoms of COPD from the patient's normal baseline level

- prior to randomization (Part 1): a decrease in $FEV_1$ of more than 20% from the predose $FEV_1$ at the screening visit (visit 1)
- post randomization (Part 1 and Part 2): more than 3 occurrences of a decrease in $FEV_1$ of more than 20% from the predose $FEV_1$ at the randomization visit (visit 2)
- >20% decrease from the mean morning baseline $FEV_1$ on more than 3 of the last 7 (rolling) days during Part 1 or 2
- viral or bacterial respiratory infection during Part 2 which results in an increase in the symptoms of COPD from the patient's normal baseline level
- increase of ≥2 on the ER-S: COPD daily respiratory symptoms (RS) Total Score during Part 1 or 2
- ≥12 or more albuterol/salbutamol puffs per day on more than 2 of the last 7 (rolling) days during Part 1 or 2

**Revised text:**

These criteria would include the following:

- COPD exacerbation during Part 2 that prohibits the patient from administering their study medication (Lupin Tiotropium Bromide Inhalation Powder) once daily
- use of medication for respiratory symptoms not allowed by the study protocol
- viral or bacterial respiratory infection during Part 1 which results in an increase in the symptoms of COPD from the patient's normal baseline level
- prior to randomization (Part 1): a decrease in $FEV_1$ of more than 20% from the predose $FEV_1$ at the screening visit (visit 1)
- post randomization (Part 1 and Part 2): more than 3 occurrences of a decrease in $FEV_1$ of more than 20% from the predose $FEV_1$ at the randomization visit (visit 2)
- >20% decrease from the mean morning baseline $FEV_1$ on more than 3 of the last 7 (rolling) days during Part 1 ***(commencing once the predose pre-bronchodilator study qualifying $FEV_1$ (ie, pre-PFT) is performed at the screening visit [visit 1]))*** or Part 2
- viral or bacterial respiratory infection during Part 2 which results in an increase in the symptoms of COPD from the patient's normal baseline level
- increase of ≥2 on the ER-S: COPD daily respiratory symptoms (RS) Total Score during Part 1 ***(commencing at the start of the screening period)*** or ***Part*** 2
- ≥12 or more albuterol/salbutamol puffs per day on more than 2 of the last 7 (rolling) days during Part 1 ***(commencing at the start of the screening period)*** or ***Part*** 2.

***Rationale for change:*** *Clarification. Diary collection begins at the time of signing the ICF. eDiaries/electronic flow meters will be dispensed on the 1st day of the screening period prior to patients beginning any medication washout, to assist with safety monitoring throughout the screening period. $FEV_1$ monitoring, COPD symptom scores, and rescue use will be recorded in the ediary/electronic flow meter. The $FEV_1$ withdrawal criteria for verifying stability will commence at once the pre-PFT is performed at visit 1.*

**Section 7.4 Ancillary Supplies (page 38)**

**Original text:**

ediary/electronic flow meter

For Part 1 and Part 2 of the study, patients will be issued an ediary/electronic flow meter to record COPD symptom scores (EXACT), albuterol/salbutamol MDI and study medication usage, and $FEV_1$ measurements at home. In addition device robustness data will be tracked via the ediary system.

**Revised text:**

For ***the screening period, run-in period,*** Part 1 and Part 2 of the study, patients will be issued an ediary/electronic flow meter to record COPD symptom scores (EXACT); albuterol/salbutamol MDI ***usage***; ***and*** study medication usage ***(run-in and Part 2 only);*** and $FEV_1$ measurements at home. ***Diary collection begins at the time of signing the ICF. eDiaries/electronic flow meters will be dispensed on the 1st day of the screening period prior to patients beginning any medication washout, to assist with safety monitoring throughout the screening period.***

In addition device robustness data will be tracked via the ediary system.

***Rationale for change:*** *Clarification. Diary collection begins at the time of signing of ICF to assess the safety of patients during the screening period.*

**Section 7.6 Method of Assigning Patients to Treatment Sequences (page 40)**

**Original text:**

Additionally, on each study day, as this is a double-dummy study, the order of administration of the LUPINHALER and HANDIHALER will be randomly assigned via a randomization schedule separate from the main crossover randomization schedule.

**Revised text:**

Additionally, on each study day, as this is a double-dummy study, the order of administration of the LUPINHALER and HANDIHALER will be ~~***randomly***~~ assigned ~~***via a randomization schedule separate from the main crossover randomization schedule***~~ ***based on even/odd calendar days. On odd calendar days (eg, 1, 3, 5, 29, 31), the LUPINHALER will be dosed first. On even calendar days (eg, 2, 4, 6, 28, 30), the HANDIHALER will be dosed first***.

***Rationale for change:*** *Implementing a randomization schedule for the order of inhaler administration for each patient for each day would not be practical. The method described assures that the same inhaler is not administered first on each day of the study for each patient.*

**Section 7.7.1 Blinding Part 1 (pages 40-41)**

**Original text:**

The unblinded administrator will collect the study medication from the pharmacy, remove the capsule from the relevant blister strips and prepare the inhalers out of sight of the patient. The unblinded administrator will then obscure the observation windows in the device with opaque tape and ask the patient to complete dosing as per the instructions for use (Appendix A). After the 2nd inhalation the unblinded administrator will unmask the inhaler, review the capsule to ensure the dose has been properly administered and re-attach the tape to mask the window. The same process will be repeated for the other inhaler until 2 inhalations from each capsule have been completed through both test and reference inhalers.

As indicated in the randomization scheme (Table 7-1), at each treatment visit the patient will receive either:

- one active dose from 1 of the 2 inhalers; other inhaler contain placebo dose
- 2 placebo doses

Training of the patient on inhaler technique and dosing of the study medication and drug accountability should be undertaken exclusively by the unblinded administrator so that the core study team who are responsive for efficacy and safety assessments are unaware of the inhalers administered.

The patient will self-administer the medication at the investigational center on each study day guided by this unblinded study team member. $FEV_1$ testing will continue postdose by the blinded study team.

**Revised text:**

The unblinded administrator will collect the study medication from the pharmacy, remove the capsule from the relevant blister strips and prepare the inhalers out of sight of the patient. The unblinded administrator will then obscure the observation windows in the device with opaque tape and ***~~ask~~ dispense to blinded study personnel, who will assist*** the patient to complete dosing as per the instructions for use (Appendix A). After the 2nd inhalation the unblinded administrator will unmask the inhaler, review the capsule to ensure the dose has been properly administered and re-attach the tape to mask the window. The same process will be repeated for the other inhaler until 2 inhalations from each capsule have been completed through both test and reference inhalers.

As indicated in the randomization scheme (Table 7-1), at each treatment visit the patient will receive either:

- one active dose from 1 of the 2 inhalers; other inhaler contain placebo dose
- 2 placebo doses

Training of the patient on inhaler technique and dosing of the study medication ***~~and drug accountability should be undertaken exclusively by the unblinded administrator~~ will be undertaken by blinded study personnel. The unblinded administrator will acknowledge all shipments, prepare blinded study medication, and dispense the blinded study medication to the blinded study personnel*** so that the core study team who are responsive for efficacy and safety assessments are unaware of the inhalers administered. ***In addition, the unblinded administrator will witness dose administration in the double-blind portion of Part 1.***

The patient will self-administer the medication at the investigational center on each study day guided by this ***~~un~~***blinded study team member. $FEV_1$ testing will continue postdose by the blinded study team.

***Rationale for change:*** *Clarification. To define the roles of the unblinded and blinded study personnel during administration of study mediation in Part 1 Double-Blind. Unblinded study personnel will prepare double-blind study medication and dispense the inhalers to blinded study personnel and observe dose administration in Part 1. Blinded study personnel will perform study medication training during all parts of the study and assist with dosing of the patients in Part 1.*

**Section 7.7.2 Blinding Part 2 (page 41)**

**Original text:**

Part 2 will be conducted via an open-label design; therefore, no blinding is required. Used inhalers and unused/used capsules will be returned to the investigational center.

**Revised text:**

Part 2 will be conducted via an open-label design; therefore, no blinding is required. Used inhalers and unused***~~/used~~*** capsules will be returned to the investigational center.

***Rationale for change:*** *Only the unused capsules in Part 2 will be returned to the investigational center. Used capsules will be discarded in the patient's trash.*

**Section 7.9 Dosing Procedures (page 42)**

**Original text:**

For Part 1, prior to study visits 2 through 4, patients should refrain from using albuterol/salbutamol MDI and other prohibited medication; patients should not smoke at least 1 hour prior to lung function

assessments during the visits; and patients should adhere to the dietary restrictions as per protocol (see section 8.2). Patients will be trained on the correct use of the study medication. Patients will administer 2 inhalations from each of 2 inhalers of the assigned study medication in the morning with the assistance of the unblinded administrator. Dosing at visits 2-4 must be administered by the unblinded site staff member. Patients may stay overnight at the investigational center or at nearby housing facility (eg, hotel) to complete the $FEV_1$ serial measurements over a 24-hour period. In certain cases, the patient may return home after the 12 hour $FEV_1$ measurement and return for the 23 and 24 $FEV_1$ measurements, at the discretion of the Investigator.

After administration of study medication, the patient will enter a washout period of 21 days + 3 days between treatment periods, where the patient may continue to use albuterol/salbutamol MDI and other medications permitted per protocol (see section 8). For visits 2 through 4, patients should present at the investigational center so that the start of lung function testing will be within ±1 hour from the lung function testing at visit 1.

For Part 2 of the study, patients will be trained on the correct use of the DPI by the unblinded administrator. The dose should be taken at home in the morning. Predose $FEV_1$ measurements should be performed upon awakening in the morning immediately prior to dosing with the study medication; postdose $FEV_1$ measurements are to be performed 2 (+2) hours after study medication administration.

**Revised text:**

For Part 1, prior to study visits 2 through 4, patients should refrain from using albuterol/salbutamol MDI and other prohibited medication; patients should not smoke at least 1 hour prior to lung function assessments during the visits; and patients should adhere to the dietary restrictions as per protocol (see section 8.2). Patients will be trained on the correct use of the study medication. Patients will administer 2 inhalations from each of 2 inhalers of the assigned study medication in the morning with the assistance of the ~~***un***~~blinded administrator. ~~***Dosing at visits 2-4 must be administered by the unblinded site staff member.***~~ Patients may stay overnight at the investigational center or at nearby housing facility (eg, hotel) to complete the $FEV_1$ serial measurements over a 24-hour period. In certain cases, the patient may return home after the 12 hour $FEV_1$ measurement and return for the 23 and 24 $FEV_1$ measurements, at the discretion of the Investigator.

After administration of study medication, the patient will enter a washout period of 21 days + 3 days between treatment periods, where the patient may continue to use albuterol/salbutamol MDI and other medications permitted per protocol (see section 8). For visits 2 through 4, patients should present at the investigational center so that the start of lung function testing will be within ±1 hour from the lung function testing at visit 1.

For Part 2 of the study, patients will be trained on the correct use of the DPI by the ~~***un***~~blinded ~~***administrator***~~ ***study personnel***. The dose should be taken at home in the morning. Predose $FEV_1$ measurements should be performed upon awakening in the morning immediately prior to dosing with the study medication; postdose $FEV_1$ measurements are to be performed 2 (+2) hours after study medication administration.

***Rationale for change:*** *Clarification. To define the roles of the unblinded and blinded study personnel during administration of study mediation in Part 1 Double-Blind. Unblinded study personnel will prepare double-blind study medication and dispense the inhalers to blinded study personnel and observe dose administration in Part 1. Blinded study personnel will perform study medication training during all parts of the study and assist with dosing of the patients in Part 1.*

**Section 7.10 Study Medication Accountability (page 42)**

**Original text:**

At study conclusion, all used and unused study medication, albuterol/salbutamol medication, and placebo trainers must be returned to the Sponsor or Sponsor's designee. Documented evidence of destruction should be made available to the Sponsor.

**Revised text:**

At study conclusion, all used and unused study medication ***(with the exception of used capsules during the run-in period and open-label extension)***, albuterol/salbutamol medication, and placebo trainers must be returned to the Sponsor or Sponsor's designee. Documented evidence of destruction should be made available to the Sponsor.

***Rationale for change:*** *Only the unused capsules in the run-in period and Part 2 will be returned to the investigational center. Used capsules will be discarded in the patient's trash.*

**Table 8-1 Prohibited Concomitant Medications (page 45)**

**Original text:**

| **Type of medication** | **Washout period before the screening visit (visit 1) and throughout the study (unless otherwise specified)** |
|---|---|
| **Prohibited** | |
| Beta-adrenergic receptor blocking agents | 14 days |
| Drugs of abuse (cannabinoids, amphetamines, barbiturates, cocaine, benzodiazepines, methadone, and opiates)[a] | A negative test is required at the screening visit and use is prohibited throughout the study. |

a. If a patient has a positive urine drug screen for a class of drug which is consistent with a medication that the patient is currently prescribed, the patient can be considered eligible for the study after the prescription is confirmed by the Investigator.

**Revised text:**

| **Type of medication** | **Washout period before the screening visit (visit 1) and throughout the study (unless otherwise specified)** |
|---|---|
| **Prohibited** | |
| Beta-adrenergic receptor blocking agents[a] | 14 days |
| Drugs of abuse (cannabinoids, amphetamines, barbiturates, cocaine, benzodiazepines, methadone, and opiates)[a b] | A negative test is required at the screening visit and use is prohibited throughout the study. |

a. ***Cardioselective beta blockers are permitted as long as therapy was initiated at least 7 days before the screening visit (visit 1) and is expected to remain at a stable dose throughout the study.***

b. If a patient has a positive urine drug screen for a class of drug which is consistent with a medication that the patient is currently prescribed ***(excluding inhaled marijuana)***, the patient can be considered eligible for the study after the prescription is confirmed by the Investigator. ***Inhaled marijuana is not permitted even if prescribed.***

***Rationale for change:*** *Cardioselective beta blockers are permitted if therapy initiated at least 7 days prior to the screening visit (visit 1) and the patient remains on a stable dose throughout the study. Inhaled marijuana has been previously established as a prohibited medication as indicated in Table 8-1; therefore use is prohibited even if prescribed.*

## Section 8.1.1 Washout Restrictions during Part 1 of the Study Only (page 46)

**Original text:**

Patients should refrain from taking the following medications from the specified time points below prior to spirometry assessments at each clinic visit (both days of each inpatient visit) during Part 1 of the study:

- SABAs 6 hours
- SAMAs: 8 hours
- short-acting forms of theophylline: 12 hours
- twice-a-day controlled-release forms of theophylline: 24 hours
- once-a-day controlled-release forms of theophylline: 36 hours

**Revised text:**

Patients should refrain from taking the following medications from the specified time points below prior to spirometry assessments at each clinic visit (both days of each inpatient visit) during Part 1 of the study:

- SABAs 6 hours
- SAMAs: 8 hours
- short-acting forms of theophylline: 12 hours
- twice-a-day controlled-release forms of theophylline: 24 hours
- once-a-day controlled-release forms of theophylline: 36 hours
- ***caffeine-containing medications (eg, MIDOL®, EXCEDRIN®) 6 hours***

***Rationale for change:*** *Caffeine could impact lung function and is therefore restricted with appropriate washout.*

**Schedule of Events (page 52)**

**Original text:**

5) The screening visit (visit 1) may take place over several days beginning on day -44 to -14 dependent on the patient's washout. All results must be available and evaluated prior to commencing the run-in period.

**Revised text:**

5) The screening visit (visit 1) may take place over several days beginning on day -44 to -14 dependent on the patient's washout. ***If a patient is washing out of ICS (monotherapy) or ICS/LABA combination therapy, an additional 3 days is permitted to complete the assessments for the screening visit (visit 1)***. All results***, with the exception of the clinical laboratory assessments,*** must be available and evaluated prior to commencing the run-in period. ***The clinical laboratory results must be available and evaluated prior to randomization. The procedures for the screening visit (visit 1), with the exception of signing of the ICF, performing a pre-washout physical examination, and dispensing/completing the ediary, cannot occur until appropriate medication washouts have been completed in accordance with the protocol. Once the washout requirements have been met, the screening visit (visit 1) should immediately precede the start of the run-in period. If a patient does not require washout, and the patient passes all entry criteria at the screening visit (visit 1), the patient will be eligible to enter the run-in period on the same day as the screening visit (visit 1). The patient must successfully complete the visit 1 procedures/assessments prior to entering the run-in period.***

***Rationale for change:*** *Clarification. Clinical laboratory results may not be available prior to a patient entering run-in; however, the results must be reviewed and evaluated for clinical significance prior to patient randomization. Diary collection begins at the time of signing of ICF to assess the safety of patients during the screening period. For patients on ICS (monotherapy) or ICS/LABA combination therapy additional time may be needed to complete all screening assessments prior to the run-in period; therefore, the window has been extended.*

**Schedule of Events (page 52)**

**Original text:**

14) A stability limit will be established at the screening visit to determine alert criteria for worsening COPD during the screening and run-in periods, and will be calculated by selecting the best pre-bronchodilator qualifying $FEV_1$ measurement at the screening visit using the onsite spirometer x 80%.

**Revised text:**

14) A stability limit will be established at the screening visit ***(visit 1)*** to determine alert criteria for worsening COPD during the screening and run-in periods, and will be calculated by selecting the best pre-bronchodilator qualifying $FEV_1$ measurement at the screening visit using the onsite spirometer x 80%.

***Rationale for change:*** *Clarification. A stability limit will be established at visit 1 using the onsite spirometry to monitor a patient's COPD status between visit 1 and the run-in period.*

**Schedule of Events (page 53)**

**Original text:**

17) Predose $FEV_1$ will be measured at 30 and 15 minutes before administration of study medication. Serial $FEV_1$ spirometry measured at 0 hours (within 30 and 15 minutes prior to study medication administration [equivalent to the predose $FEV_1$]), and at 5 and 30 minutes postdose, and at 1, 2, 4, 6, 8, 10, 12, 23, and 24 hours postdose. The following windows are permitted: +5 minutes for predose measurements (-30 and -5 minutes); ±5 minutes for 0.5-6 hours, and ±15 minutes for 8-24 hours.

**Revised text:**

17) Predose $FEV_1$ will be measured at 30 and 15 minutes before administration of study medication. Serial $FEV_1$ spirometry measured at 0 hours (within 30 and 15 minutes prior to study medication administration [equivalent to the predose $FEV_1$]), and at 5 and 30 minutes postdose, and at 1, 2, 4, 6, 8, 10, 12, 23, and 24 hours postdose. The following windows are permitted: +5 minutes for predose measurements (-30 and -5 minutes) ***and 5 minute postdose measurement***; ±5 minutes for 0.5-6 hours, and ±15 minutes for 8-24 hours.

***Rationale for change:*** *Added a collection time window of +5 minutes for the 5 minute postpose $FEV_1$ measurement.*

**Schedule of Events (page 53)**

**Original text:**

20) Administration of study medication at the investigational center will occur in the presence of the unblinded a staff member.

**Revised text:**

20) Administration of study medication at the investigational center will occur in the presence of the unblinded ***and blinded*** staff member***s***.

***Rationale for change:*** *Clarification. To define the roles of the unblinded and blinded study personnel during administration of study mediation in Part 1 Double-Blind. Unblinded study personnel will prepare double-blind study medication and dispense the inhalers to blinded study personnel and observe dose administration in Part 1. Blinded study personnel will perform study medication training during all parts of the study and assist with dosing of the patients in Part 1.*

**Section 9.2.1.1 Spirometry (page 54)**

**Original text:**

Spirometry testing will be performed by experienced research staff who have passed a proficiency process to ensure understanding of the equipment used and forced spirometry technique. To collect data in a consistent manner, the same staff member will conduct all spirometry assessments for the same patient whenever possible. The same spirometer should be used on a patient throughout the study

**Revised text:**

Spirometry testing will be performed by experienced research staff who have passed a proficiency process to ensure understanding of the equipment used and forced spirometry technique. To collect data in a consistent manner, the same staff member will conduct all spirometry assessments for the same patient whenever possible. The same spirometer should be used on a patient throughout the study. ***Onsite spirometry assessments (baseline/study qualifying/reversibility) must occur after washout of the protocol prohibited and restricted medications.***

***Rationale for change:*** *Clarification. To emphasize spirometry assessments must occur after washout of prohibited and restricted medications.*

**Section 9.2.1.1 Spirometry (page 54)**

**Original text:**

The following windows are permitted: +5 minutes for predose measurements (-30 and -15 minutes); ±5 minutes for 0.5-6 hours, and ±15 minutes for 8-24 hours.

**Revised text:**

The following windows are permitted: +5 minutes for predose measurements (-30 and -15 minutes) and ***5 minute postdose measurement,*** ±5 minutes for 0.5-6 hours, and ±15 minutes for 8-24 hours.

***Rationale for change:*** *Added a collection time window of +5 minutes for the 5 minute postpose $FEV_1$ measurement.*

**Section 9.2.1.1 Spirometry (pages 54-55)**

**Original text:**

Reversibility Testing

For reversibility testing, patients will receive 68 mcg of ipratropium bromide inhalation pMDI as 4 actuations of 17 mcg/actuation (ex-mouthpiece); given at approximately 30 second intervals. All actuations are to be completed within 3 minutes of the 1st actuation. The ATS/ERS criteria will be followed for spirometry measures. Patients who do not demonstrate a positive improvement of at least

15% in $FEV_1$ measured at 30 or 60 minutes (±5 minutes) post inhalation will not be eligible to participate in the study (except as permitted per the retest specified below). Reversibility values of 14.50-14.99 will be rounded to 15.

**Revised text:**

Reversibility Testing

For reversibility testing, patients will receive 68 mcg of ipratropium bromide inhalation pMDI as 4 actuations of 17 mcg/actuation (ex-mouthpiece); given at approximately 30 second intervals. ***If required, spacers are permitted for use during reversibility testing for ipratropium bromide administration.*** All actuations are to be completed within 3 minutes of the 1st actuation. The ATS/ERS criteria will be followed for spirometry measures. Patients who do not demonstrate a positive improvement of at least 15% in $FEV_1$ measured at 30 or 60 minutes (±5 minutes) post inhalation will not be eligible to participate in the study (except as permitted per the retest specified below). Reversibility values of 14.50-14.99 will be rounded to 15.

***Rationale for change:*** *Clarification. Spacers will be permitted for use during reversibility testing.*

**Section 9.2.1.1 Spirometry (page 55)**

**Original text:**

$FEV_1$ Stability Limits

$FEV_1$ stability limits will be calculated for each patient at the screening visit (visit 1) using the onsite spirometer and the randomization visit (visit 2), using both the home device and onsite spirometer.

Screening Visit:

The stability limit established at the screening visit will be used to determine alert criteria for worsening COPD during the screening and run-in periods. The $FEV_1$ stability limit at the screening visit will be calculated as follows:

Best pre-bronchodilator qualifying $FEV_1$ measurement at the screening visit using the onsite spirometer × 80%.

Randomization Visit

Two stability limits will be re-established at the randomization visit (visit 2) for use during the double-blind and open-label treatment periods using the following equations:

- Investigational Center Stability Limits (for use with onsite spirometer):

  mean $FEV_1$ of the predose pre-bronchodilator qualifying $FEV_1$ measurements (-30 and -15 min) using the onsite spirometer × 80%
- At Home Stability Limits (for use with the electronic flow meter [home device]):

  mean of the best predose $FEV_1$ measurements on the last 3 days before randomization on the home device × 80%

If a patient falls below any of the above $FEV_1$ stability limits, an alert will be triggered to the patient and investigational center personnel.

**Revised text:**

$FEV_1$ stability limits will be calculated for each patient at the screening visit (visit 1) using the onsite spirometer and the randomization visit (visit 2) using both the home device and onsite spirometer.

Screening Visit:

The stability limit established at the screening visit will be used to determine alert criteria for worsening COPD during the screening and run-in periods. The $FEV_1$ stability limit at the screening visit will be calculated as follows:

Best pre-bronchodilator qualifying $FEV_1$ measurement at the screening visit ***(visit 1)*** using the onsite spirometer × 80%.

Randomization Visit

Two stability limits will be re-established at the randomization visit (visit 2) for use during the double-blind and open-label treatment periods using the following equations:

- Investigational Center Stability Limits (for use with onsite spirometer ***at the double-blind visits only***):

  mean $FEV_1$ of the predose pre-bronchodilator qualifying $FEV_1$ measurements (-30 and -15 min) using the onsite spirometer × 80%

- At Home Stability Limits (for use with the electronic flow meter [home device]):

  mean of the best predose $FEV_1$ measurements on the last 3 days before randomization on the home device × 80%

If a patient falls below any of the above $FEV_1$ stability limits, an alert will be triggered to the patient and investigational center personnel.

Note: If the reschedule icon on the site spirometer is chosen for the screening visit (visit 1) or visit 2, and therefore, visit 1 or visit 2 is performed again, the $FEV_1$ stability limit will be updated accordingly. If V1_RETEST on the site spirometer is performed, the stability limit will not be updated.

***Rationale for change:*** *Clarification. To specify that the predose spirometry conducted at the screening visit (visit 1) is used to define the stability limits between visit 1 and the run-in period and the predose spirometry at visit 2 is used to define the stability limits for the double-blind and open-label portions of the study. If the reschedule icon is selected at visit 1 or visit 2, the stability limit will be updated accordingly.*

**Section 9.2.2.3 Spirometry (Part 1 and 2) (page 56)**

**Original text:**

Patients enrolled in Part 1 and Part 2 of the study will be issued with an ediary/electronic flow meter to assess their lung function ($FEV_1$).

**Revised text:**

Patients enrolled in Part 1 and Part 2 of the study will be issued with an ediary/electronic flow meter to assess their lung function ($FEV_1$). ***$FEV_1$ collection begins at the time of signing the ICF, and then continues throughout Part 1 and Part 2, per the randomization scheme.***

***Rationale for change:*** *Clarification. Diary collection, including $FEV_1$ measurements, begins at the time of signing the ICF and continues throughout the study.*

**Section 9.2.2.4 Adverse Events (Part 1 and Part 2) (page 57)**

**Original text:**

All AE/SAEs (including treatment-emergent AEs) will be assessed throughout the study visits and followed to resolution/satisfaction. Adverse events (AEs) will be recorded after the patient has signed the informed consent form (ICF).

**Revised text:**

All AE/SAEs (including treatment-emergent AEs) will be assessed throughout the study visits and followed to resolution/satisfaction. Adverse events (AEs) will be recorded after the patient has signed the informed consent form (ICF) ***and captured via patient interview during the onsite or telephone visits***.

***Rationale for change:*** *Clarification. Adverse events (AEs) experienced in the outpatient portion of the study will be collected via telephone contact or at the investigational center visits.*

**Section 9.2.2.5 Monitoring of COPD Exacerbations (Part 1 and Part 2) (page 57)**

**Original text:**

Collection of COPD exacerbations will begin at the time of consent and will continue through the final visits in Part 1 and Part 2 of the study.

**Revised text:**

Collection of COPD exacerbations will begin at the time of consent and will continue through the final visits in Part 1 and Part 2 of the study. ***COPD exacerbations will be captured via patient interview during the onsite or telephone visits***.

***Rationale for change:*** *Clarification. COPD exacerbations experienced in the outpatient portion of the study will be collected via telephone contact or at the investigational center visits.*

**Section 9.2.2.6 COPD Symptom Scores (Part 1 and 2) (pages 57-58)**

**Original text:**

During Part 1 and Part 2 of the study, as indicated in, **Schedule of Events, Table 9-1,** patients will assess and record their COPD symptoms scores once daily in the evening before bedtime using the EXACT.

The ER-S: COPD (derived from the EXACT score) will be used to assess disease stability throughout the study. A baseline score will be obtained from the first available evening session after the screening visit (visit 1) for use during the screening and run-in periods and from the latest available evening session before the randomization visit (visit 2) for use during the double-blind and open-label treatment periods. If at any time, there is increase in the ERS-COPD daily RS-Total score of ≥2 from baseline, the ediary will alert the patient to notify the investigational center personnel to discuss the patient's current health status. The Investigator will need to determine if the patient is able to continue participating in the study as per the withdrawal criteria in section **6.5**.

**Revised text:**

During Part 1 ***(commencing at the time of consent)*** and Part 2 of the study, as indicated in, **Schedule of Events, Table 9-1,** patients will assess and record their COPD symptoms scores once daily in the evening before bedtime using the EXACT.

The ER-S: COPD (derived from the EXACT score) will be used to assess disease stability throughout the study. A baseline score will be obtained from the first available evening session after ~~***the screening visit (visit 1)***~~ ***signing the ICF*** for use during the screening and run-in periods and from the latest available evening session before the randomization visit (visit 2) for use during the double-blind and open-label

treatment periods. If at any time, there is increase in the ERS-COPD daily RS-Total score of ≥2 from baseline, the ediary will alert the patient to notify the investigational center personnel to discuss the patient's current health status. The Investigator will need to determine if the patient is able to continue participating in the study as per the withdrawal criteria in section **6.5**.

***Rationale for change:*** *Clarification. Diary collection, including COPD symptom scores (ie, EXACT), begins at the time of signing the ICF and continues throughout the study.*

**Section 9.2.2.7 Electrocardiography (Part 1 and 2) (page 58)**

**Original text:**

A 12-lead ECG will be performed for Part 1 and Part 2 as indicated in **Schedule of Events, Table 9-1**. For Part 1, the ECGs will be collected prior to lung function assessments. Procedures for conducting ECGs are described in the ECG manual. A qualified physician at a central diagnostic center will be responsible for interpreting the ECG. However, at the screening visit (visit 1), the Investigator will preliminarily interpret the ECG to determine if the patient is eligible to proceed with screening assessments; final interpretation of the ECG will the responsibility of the central ECG reader. The Investigator is responsible for determining whether an abnormality is clinically relevant.

**Revised text:**

A 12-lead ECG will be performed for Part 1 and Part 2 as indicated in **Schedule of Events, Table 9-1**. For Part 1, the ECGs will be collected prior to lung function assessments. Procedures for conducting ECGs are described in the ECG manual. ***The patient should be in a supine position and resting for at least 5 minutes.*** A qualified physician at a central diagnostic center will be responsible for interpreting the ECG. However, at the screening visit (visit 1), the Investigator will preliminarily interpret the ECG to determine if the patient is eligible to proceed with screening assessments; final interpretation of the ECG will the responsibility of the central ECG reader. The Investigator is responsible for determining whether an abnormality is clinically relevant.

***Rationale for change:*** *Clarification. Electrocardiograms should be performed in a supine position after at least 5 minutes of rest.*

**Section 9.2.3.4 Urine Drug Screening (page 59)**

**Original text:**

Urine drug screening will be performed via a urine dipstick at the investigational center as indicated in **Schedule of Events, Table 9-1** or at any time during the study should the Investigator deem it is warranted. A positive finding during the screening visit (visit 1) will prevent the patient from participating in the study, and a positive finding after the screening visit will require immediate Sponsor notification, and may result in discontinuation of study medication and termination from the study (if not related to a currently prescribed medication as described below).

If a patient has a positive urine drug screen for a class of drug which is consistent with a medication that the patient is currently prescribed, the patient can be considered eligible for the study after the prescription is confirmed by the Investigator.

Additional details are provided in the laboratory instruction manual.

**Revised text:**

Urine drug screening will be performed via a urine dipstick at the investigational center as indicated in **Schedule of Events, Table 9-1** or at any time during the study should the Investigator deem it is

warranted. A positive finding during the screening visit (visit 1) will prevent the patient from participating in the study, and a positive finding after the screening visit will require immediate Sponsor notification, and may result in discontinuation of study medication and termination from the study (if not related to a currently prescribed medication as described below).

If a patient has a positive urine drug screen for a class of drug which is consistent with a medication that the patient is currently prescribed ***(excluding inhaled marijuana)***, the patient can be considered eligible for the study after the prescription is confirmed by the Investigator. ***Inhaled marijuana is not permitted even if prescribed.***

Additional details are provided in the laboratory instruction manual.

**Rationale for change:** *Benzodiazepines and barbiturates could impact lung function and are therefore prohibited with appropriate washout. Inhaled marijuana has been previously established as a prohibited medication as indicated in Table 8-1; therefore it was included as a clarification.*

**Section 9.3 STUDY VISITS (page 59)**

**Original text:**

The study consists of 2 parts. Part 1 (double-blind treatment period) consists of a screening visit (visit 1), 3 treatment periods at the investigational center, and a follow-up telephone call at the end of the double-blind treatment period for only those patients participating in Part 1.

**Revised text:**

The study consists of 2 parts. Part 1 (double-blind treatment period) consists of a screening ~~***visit (visit 1)***~~ ***period***, 3 ***double-blind*** treatment periods at the investigational center, and a follow-up telephone call at the end of the double-blind treatment period for only those patients participating in Part 1

***Rationale for change:*** *Clarification. To indicate the study includes a screening period which is 30 days (day -44 to day -14) before the start of the run-in period, which may be used to washout of COPD and other medications per protocol.*

**Section 9.3.1 Screening Period (page 60)**

**Original text:**

At the screening visit (visit 1), a signed and dated ICF will be obtained before screening procedures commence. The screening visit (visit 1) will be conducted up to 30 days (day -44 to day -14) before the start of the run-in period. The following procedures and assessments will be conducted at the screening visit (visit 1):

**Revised text:**

~~***At the screening visit (visit 1)***~~ ***During the screening period***, a signed and dated ICF will be obtained ***first*** before screening procedures commence. The screening ~~***visit (visit 1)***~~ ***period*** may be conducted up to 30 days (day -44 to day -14) before the start of the run-in period. The screening ***period*** begins once the ICF is signed, and ends at the start of the run-in period. ***The screening period may take place over several days beginning on day –44 to day –14 dependent on the patient's washout. If a patient is washing out of ICS (monotherapy) or ICS/LABA combination therapy, an additional 3 days is permitted to complete the assessments for the screening visit (visit 1). The screening visit (visit 1) should immediately precede the start of the run-in period. If a patient does not require washout, and the patient passes all entry criteria at the screening visit (visit 1), the patient will be eligible to enter the run-in period on the***

***same day as the screening visit (visit 1). The patient must successfully complete the visit 1 procedures/assessments prior to entering the run-in period.***

***The procedures for the screening visit (visit 1), with the exception of signing of the ICF, assigning a patient number, performing a pre-washout physical examination, and dispensing/completing the ediary, cannot occur until appropriate medication washouts have been completed in accordance with the protocol. Once the washout requirements have been met, the screening visit (visit 1) should immediately precede the start of the run-in period.***

The following procedures and assessments will be conducted at the screening visit (visit 1) ***with the exception of the procedures listed above if medication washout is required:***

***Rationale for change:*** *Clarification. To differentiate the screening period and the screening visit, and define the procedures to be performed at each of these visits. The screening period may occur up to 30 days (day -44 to day -14) before the start of the run-in period to washout of COPD and other medications per protocol. The screening visit cannot occur until the appropriate washout requirements have been met. For patients on ICS (monotherapy) or ICS/LABA combination therapy additional time may be needed to complete all screening assessments prior to the run-in period; therefore, the window has been extended.*

**Section 9.3.1 Screening Period (pages 61-62)**

**Original text:**

The patient will continue using an ediary/electronic flow meter for use throughout the screening period and asked to measure their lung function ($FEV_1$) in the morning prior to dosing with COPD medication (as applicable) at approximately the same time each day. Patients will be asked to record EXACT symptom scores (see **Appendix C**) and albuterol/salbutamol MDI/study medication use in their ediary.

**Revised text:**

The patient will ~~***continue***~~ ***begin*** using an ediary/electronic flow meter for use throughout the screening period***, if applicable,*** and asked to measure their lung function ($FEV_1$) in the morning prior to dosing with COPD medication (as applicable) at approximately the same time each day. Patients will be asked to record EXACT symptom scores (see **Appendix C**) and albuterol/salbutamol MDI~~***/study medication***~~ use in their ediary ***during the screening period, if applicable***.

***Rationale for change:*** *Clarification. To define the procedures to be conducted during the screening period.*

**Section 9.3.2 Run-in Period (page 62)**

**Original text:**

The patient will continue using an ediary/electronic flow meter for use throughout the run-in period and asked to measure their lung function ($FEV_1$) in the morning prior to dosing with placebo LUPINHALER at approximately the same time each day. Patients will be asked to record EXACT symptom scores (see **Appendix C**), and albuterol/salbutamol MDI/study medication use in their ediary.

**Revised text:**

The patient will continue using an ediary/electronic flow meter for use throughout the run-in period and asked to measure their lung function ($FEV_1$) in the morning prior to dosing with placebo LUPINHALER at approximately the same time each day. Patients will be asked to record EXACT symptom scores (see

**Appendix C**) ***once daily in the evening before bedtime,*** and albuterol/salbutamol MDI/study medication use in their ediary.

***Rationale for change:*** *Clarification. To indicate the EXACT is performed once daily in the evening before bedtime.*

**Section 9.3.3.1 Visit 2, Day 0 (page 63), Section 9.3.3.2 Visit 3, Day 21 (+3 days) (page 64), Section 9.3.3.3 Visit 4, Day 42 (+3 days) (page 65)**

**Original text:**

- administration of study medication at the investigational center under supervision of unblinded study personnel

**Revised text:**

- administration of study medication at the investigational center ***~~under supervision of unblinded study personnel~~***

***Rationale for change:*** *Unblinded study personnel will prepare double-blind study medication and dispense the inhalers to blinded study personnel and observe dose administration in Part 1. Blinded study personnel will perform study medication training during all parts of the study and assist with dosing of the patients in Part 1.*

**Section 9.3.3.1 Visit 2, Day 0 (page 63)**

**Original text:**

The patient will continue using the ediary/electronic flow meter throughout the Part 1 and asked to measure their lung function ($FEV_1$) in the morning prior to administering COPD medication at approximately the same time each day. Patients should not perform $FEV_1$ measurements on the home device prior to day 1, visit 3 (both day 21 and day 22) and visit 4 (both day 42 and 43). Patients will be asked to record EXACT symptom scores (see **Appendix C**) and albuterol/salbutamol MDI in their ediary.

**Revised text:**

The patient will continue using the ediary/electronic flow meter throughout the ***remainder of*** Part 1 and asked to measure their lung function ($FEV_1$) in the morning prior to administering COPD medication at approximately the same time each day. Patients should not perform $FEV_1$ measurements on the home device prior to day 1, visit 3 (both day 21 and day 22) and visit 4 (both day 42 and 43). Patients will be asked to record EXACT symptom scores (see **Appendix C**) and albuterol/salbutamol MDI in their ediary.

***Rationale for change:*** *Clarification.*

**Section 9.3.6 Retest Visits (page 70)**

**Original text:**

Post-randomization:

During Part 1, patients may retest for $FEV_1$ if the value varies by more than ±10% from the predose $FEV_1$ at the screening visit (visit 1) up to 3 times. If 3 retests have been conducted, the patient may need to be withdrawn at the discretion of the Investigator.

**Revised text:**

Post-randomization:

During Part 1, patients may retest for $FEV_1$ if the value varies by more than ±10% from the predose $FEV_1$ at ***~~the screening visit (visit 1)~~ visit 2*** up to 3 times. If 3 retests have been conducted, the patient may need to be withdrawn at the discretion of the Investigator.

***Rationale for change:*** *Typographical error. Patients may retest if the post-randomization $FEV_1$ value varies by more than ±10% from the predose $FEV_1$ at visit 2.*

**Section 10.6 Serious Adverse Event Reporting (page 75)**

**Original text**

The Lupin Medical Monitor for this study is:

[redacted]

**Revised text:**

The Lupin Medical Monitor for this study is:

[redacted]

***Rationale for change:*** *Administrative update. The Medical Monitor's title and phone number have been updated.*

**Section 11.5.4 Primary Variable (page 81)**

**Original text:**

A mixed model analysis consisting of fixed effects of treatment, visit, and sequence, and the random effect of patient will be carried out.

**Revised text:**

***A repeated measures crossover model consisting of effects of treatment, period, and sequence will be carried out.***

***Rationale for change:*** *Clarification of the statistical model to be used to allow unstructured covariance.*

**Section 11.5.7.1 Adverse events (page 81)**

**Original text:**

In Part 1, the blinded, single dose crossover part of the study, AEs will be tabulated by the following periods:

- pre-randomization
- on or within 24 hours after a study treatment day

- during washout
- during follow-up (more than 24 hours after the last treatment day)

Adverse events (AEs) occurring on or within 24 hours after a study treatment day will be assigned to the relevant study treatment

**Revised text:**

In Part 1, the blinded, single dose crossover part of the study, AEs will be tabulated by the following periods:

- ~~***pre-randomization***~~
- ~~***on or within 24 hours after a study treatment day***~~ ***double-blind treatment period***
- during washout
- during follow-up ~~***(more than 24 hours after the last treatment day)***~~

~~***Adverse events (AEs) occurring on or within 24 hours after a study treatment day will be assigned to the relevant study treatment.***~~

~~***Adverse events (AEs) that occur before randomization for patients who are screen/randomization failures will be listed. Those patients will not be part of the safety population.***~~

***Adverse events (AEs) occurring after a study treatment during the treatment day and the day immediate after the treatment will be assigned to the relevant study treatment group.***

***Adverse events (AEs) that occur before randomization will be summarized separately and will be listed.***

***Rationale for change*****:** *Adverse events (AEs) occurring on the day of treatment and the day immediately after treatment will be summarized by treatment instead of washout. Adverse events (AEs) will be summarized for all patients prior to randomization.*

**Section 11.5.7.3 Physical Examination (page 82)**

**Original text:**

For Part 1, physical examination findings at screening (visit 1) and visit 4 or ET will be summarized for any clinically significant findings. Significant changes from screening (visit 1) and the end of the double-blind period will be summarized. Changes from screening (visit 1) to the end of the double-blind period will be presented in 3 by 3 shift tables, where the responses are normal, abnormal but clinically non-significant, or abnormal and clinically significant. Each examination area, eg, skin, abdominal, will have a separate table.

**Revised text:**

For Part 1, physical examination findings at screening (visit 1) and visit 4 or ET will be summarized for any clinically significant findings. Significant changes from screening (visit 1) and the end of the double-blind period will be summarized. Changes from screening (visit 1) to the end of the double-blind period will be presented in 3 by 3 shift tables, where the responses are normal, abnormal but clinically non-significant, or abnormal and clinically significant. Each examination area, eg, skin, abdominal, will have a separate table. ***Some patients may require 2 physical examinations before treatment starts. If they do, the first one is the prescreening value and the one at visit 1 is the screening value. Pre-screening results will be listed only.***

***Rationale for change:*** *Clarification. If 2 physical exams are conducted prior to double-blind treatment due to required medication washout, the first one will be considered prescreening with results listed, and the one conducted at visit 1 will be used in data analyses.*

**Section 11.5.7.4 HEENT, Chest Examination, and Electrocardiograms (ECG) (pages 82-83)**

**Original text:**

For Part 1, during the double-blind period, abbreviated physical examination findings (HEENT and chest examinations) and ECG results will be summarized for any clinically significant findings and significant changes from screening.

For Part 2 of the study (open label extension), findings will be summarized for any clinically significant findings and significant changes from screening.

Note that the screening data for these variables is captured during the full physical examination at screening (visit 1).

HEENT and chest examination findings will be summarized by five 3 by 3 shift tables where the shift is from screening (visit 1) to each of the 5 visits during treatment, 3 visits in Part 1 and 2 visits in Part 2.

**Revised text:**

For Part 1, during the double-blind period, abbreviated physical examination findings (HEENT and chest examinations) and ECG results will be summarized for any clinically significant findings and significant changes from ~~***screening***~~ ***visit 2***.

For Part 2 of the study (open label extension), findings will be summarized for any clinically significant findings and significant changes from ~~***screening***~~ ***visit 2***.

~~***Note that the screening data for these variables is captured during the full physical examination at screening (visit 1).***~~

HEENT and chest examination findings will be summarized by five 3 by 3 shift tables where the shift is from ~~***screening (visit 1)***~~ ***visit 2*** to each of the ~~***5***~~ ***4*** visits during treatment, ~~***3***~~ ***2*** visits in Part 1 and 2 visits in Part 2.

***Rationale for change:*** *Typographical error. HEENT examinations commence at visit 2; therefore, visit 2 will be the baseline for this assessment with a total of 4 post randomization assessments, 2 in Part 1 and 2 in Part 2.*

**Section 11.5.7.5 COPD Exacerbations (page 83)**

**Original text:**

A listing of COPD exacerbations that occurred will be provided separately for Part 1 and Part 2 of the study.

**Revised text:**

~~***A listing of COPD exacerbations that occurred will be provided separately for Part 1 and Part 2 of the study.***~~

***COPD exacerbations will be summarized and/or listed separately for Part 1 and Part 2 of the study.***

***Rationale for change:*** *Clarification. Part 1 of the study is randomized double-blind while Part 2 of the study is unrandomized and open-label so it would not be appropriate to combine them.*

**Section 11.5.8 Safety Spirometry (page 83)**

**Original text:**

For Part 1, $FEV_1$ will be measured once daily: prior to dosing in the morning at approximately the same time each day.

**Revised text:**

For Part 1 ***(commencing at the time of signing the ICF)***, $FEV_1$ will be measured once daily: prior to dosing in the morning at approximately the same time each day.

***Rationale for change:*** *Clarification. Diary collection begins at the time of signing of ICF to assess the safety of patients during the screening period and throughout the study.*

**Section 11.5.10 Albuterol/Salbutamol Usage (page 83)**

**Added text:**

***Albuterol/Salbutamol usage will be summarized and/or listed separately for Part 1 and Part 2 of the study.***

***In addition, urine/serum pregnancy test, urine drug screen, clinical laboratory, drug accountability, smoking restriction, DPI training, and In-Check training data will also be listed.***

***Rationale for change:*** *Clarification.* Part 1 of the study is randomized double-blind while Part 2 of the study is unrandomized and open-label so it would not be appropriate to combine them.

**Section 11.5.11.1 Ruggedness of LUPINHALER during In-Patient Use (pages 83 -84)**

**Original text:**

Patients will be instructed to report any problems that they experience with their LUPINHALER during the open-label extension. The number and percentage of patients who reported at least one issue with the LUPINHALER will be provided.

Additionally, a listing of the individual issues will be provided. The listing will describe the issue in the detail provided by the patient. These will also be summarized according to the following categories:

- lack of efficacy
- mechanical problems
- problems with the device after it was dropped
- other

**Revised text:**

Patients will be instructed to report any problems that they experience with their LUPINHALER during the open-label extension. The number and percentage of patients who reported at least one issue with the LUPINHALER will be provided.

Additionally, a listing of the individual issues will be provided. The listing will describe the issue in the detail provided by the patient. These will also be summarized according to the following categories:

- ~~***lack of efficacy***~~
- ~~***mechanical problems***~~
- ~~***problems with the device after it was dropped***~~
- ~~***other***~~
- ***misuse episodes (eg, impact [problems with the device after it was dropped], moisture [fell in water, submersed], other)***

- ***issues identified (eg, mechanical problems, COPD worsening/seems ineffective, other)***

***Rationale for change:*** *Clarification. Ruggedness of the LUPINHALER will be summarized into 2 main categories with additional subclassification.*

**Original Text:**

# Appendix A: Study Medication Instructions for Use

### Patient Instructions for Investigational Product Administration of the Dry Powder Inhalers

Two dry powder inhalers will be used in this study (see Figure A1 and Figure A2):

For the run-in period, 1 inhaler (Figure A2) will be used to administer 2 inhalations from 1 capsule of study medication (Lupin 18 mcg tiotropium bromide or placebo) once daily for 14 +2 days.

For Part 1 of the study, 2 inhalers (Figure A1 and Figure A2) will be used to administer a single-dose of study medication (18 mcg tiotropium bromide or placebo) at each treatment period (visits 2, 3, and 4). A single-dose consists of 1 capsule per inhaler administered as 2 inhalations per capsule. Each capsule will be placed into the inhalers by unblinded study personnel as per the randomization schedule.

For Part 2 of the study, 1 inhaler (Figure A2) will be used to administer 2 inhalations from 1 capsule of study medication (Lupin 18 mcg tiotropium bromide) once daily for 72 +3 days.

Placebo training inhalers will also be provided for training purposes during Part 1 of the study.

**YOUR STUDY INHALERS**

Figure A1 represents INHALER 1 and Figure A2 represents INHALER 2. These inhalers are for oral inhalation only. Both INHALERS will be over-labeled with the appropriate kit/inhaler number.


**Figure A1**
**INHALER 1**

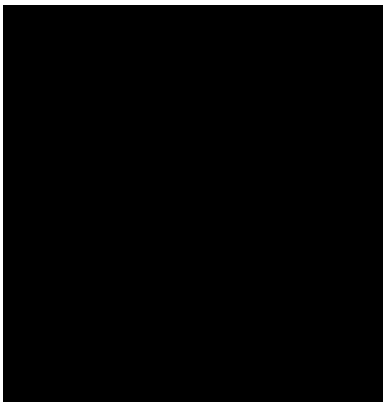


**Figure A2**
**INHALER 2**

Each INHALER comes with capsules in blister packaging. Use the INHALER provided with the designated capsule(s).

**The parts of each INHALER include:**
(See Figure B1 for INHALER 1 and Figure B2 for INHALER 2)

1. Dust cap (lid)
2. Mouthpiece
3. Mouthpiece ridge
4. Base
5. Green piercing button
6. Center chamber
7. Air intake vents

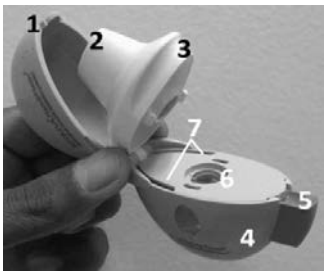



**Figure B1**

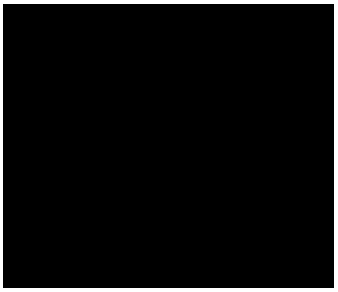


**Figure B2**

Each tiotropium capsule is packaged in a blister (See Figure C).

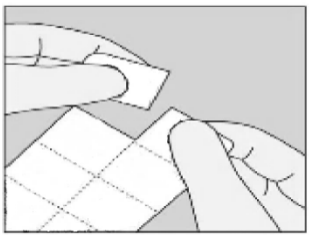


**Figure C**

Each tiotropium capsule contains only a small amount of powder (See Figure D).

Do not open the tiotropium capsule or it may not work.

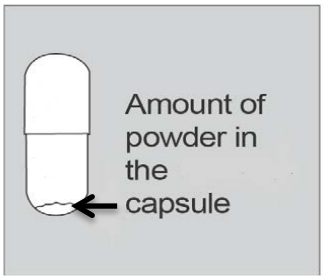



**Figure D**

# FOR PATIENTS PARTICIPATING IN PART 1

## TAKING YOUR DOSE OF STUDY MEDICATION REQUIRES 4 MAIN STEPS.

Note: Some of these steps will be performed by unblinded study personnel prior to you receiving the INHALER.

## STEP 1. OPENING YOUR INHALER:

After unblinded study personnel has removed your INHALER from the pouch:

- Unblinded study personnel will open the dust cap (lid) by pressing the green piercing button (See Figure E1 for INHALER 1 and Figure E2 for INHALER 2).

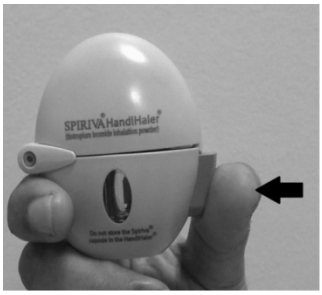



**Figure E1**

**Figure E2**

- Unblinded study personnel will pull the dust cap (lid) upwards away from the base to expose the mouthpiece (See Figure F1 for INHALER 1 and Figure F2 for INHALER 2).

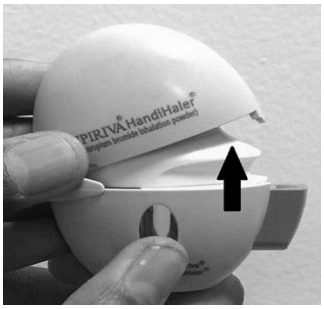



**Figure F1**

**Figure F2**

- Unblinded study personnel will open the mouthpiece by pulling the mouthpiece ridge up and away from the base so center chamber is showing (See Figure G1 for INHALER 1 and Figure G2 for INHALER 2).

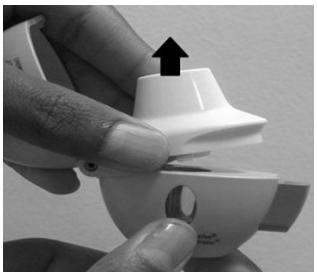


**Figure G1**

**Figure G2**

**STEP 2. INSERTING THE CAPSULE INTO YOUR INHALER:**

Unblinded study personnel will separate the blisters from the blister card by tearing along the perforated line (See Figure H).

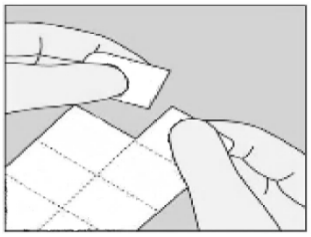


**Figure H**

**Unblinded study personnel will remove the capsule from the blister:**

- Do not cut the foil or use sharp instruments to take out the capsule from the blister.
- Bend one of the blister corners with an arrow and separate the aluminum foil layers.
- Peel back the printed foil until you see the whole capsule (See Figure J).
- If you have opened more than 1 blister to the air, the extra capsule should not be used.

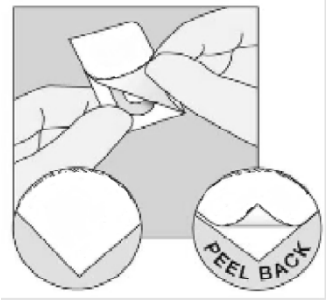



**Figure J**

- Unblinded study personnel will place the capsule in the center chamber of your INHALER (See Figure K1 for INHALER 1 and Figure K2 for INHALER 2).

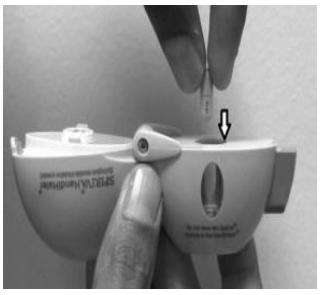


**Figure K1**

**Figure K2**

- Unblinded study personnel will close the mouthpiece firmly against the base until he/she hears a click. Unblinded study personnel will leave the dust cap (lid) open (See Figure L1 for INHALER 1 and Figure L2 for INHALER 2).

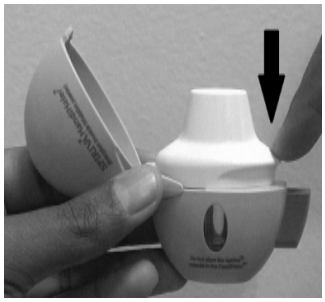


**Figure L1**

**Figure L2**

- Unblinded study personnel will apply an opaque label/tape to cover the chamber window to prevent identification of the capsules.

**STEP 3. PIERCING THE CAPSULE:**

- Unblinded study personnel will hold your INHALER with the mouthpiece pointed up (See Figure M1 for INHALER 1 and Figure M2 for INHALER 2).

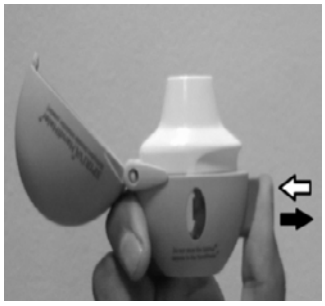


**Figure M1**

**Figure M2**

- Unblinded study personnel will press the green piercing button once until it is flat (flush) against the base, then release. This is how to make holes in the capsule so that you get study medication when you breathe in.
- Do not press the green button more than one time.
- Do not shake the INHALER.
- The piercing of the capsule may produce small pieces of the capsule. Some of these small pieces may pass through the screen of the INHALER into the mouth or throat when you breathe in your medicine. This is normal. The small pieces of the capsule should not harm you.

**STEP 4. TAKING YOUR DOSE OF STUDY MEDICATION:**

**Unblinded study personnel will hand you the INHALER in a horizontal position. Keep the INHALER in the horizontal position.**

**Breathe out completely in 1 breath,** emptying your lungs of any air (See Figure N).

**Important: Do not** breathe into your INHALER.

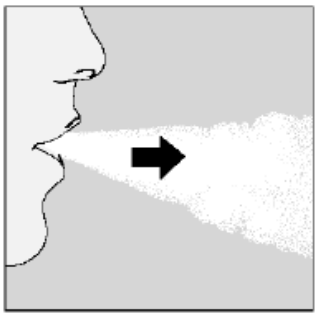


**Figure N**

**With your next breath, take your study medication:**

- **Hold your head in an upright position while you are looking straight ahead** (See Figure P1 for INHALER 1 and Figure P2 for INHALER 2).
- Raise your INHALER to your mouth in a horizontal position. **Do not** block the air intake vents.
- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the capsule vibrate** (rattle) (See Figure P1 for INHALER 1 and Figure P2 for INHALER 2).
- Hold your breath for a few seconds and, at the same time, take your INHALER out of your mouth.
- Breathe normally again.

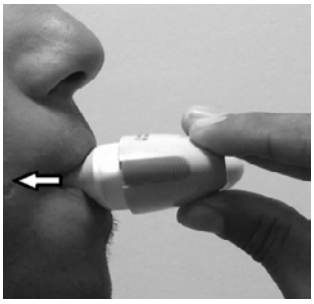


**Figure P1**

**Figure P2**

The rattle tells you that you breathed in correctly. If you do not hear or feel a rattle, see the section, "If you do not hear or feel the capsule rattle as you breathe in your study medication."

**To get the full amount from the capsule, you must again, breathe out completely (See Figure Q)**

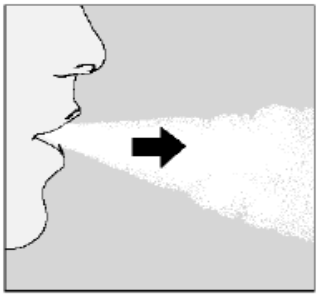


**Figure Q**

**then for a second time, breathe in (See Figure R1 for INHALER 1 and Figure R2 for INHALER 2) from the same capsule.**

**Important: Do not** press the green piercing button again. **Do not** breathe into your INHALER.

Remember: To get your full amount from the capsule, you must breathe in 2 times from the same capsule. Make sure you breathe out completely each time before you breathe in from your INHALER.

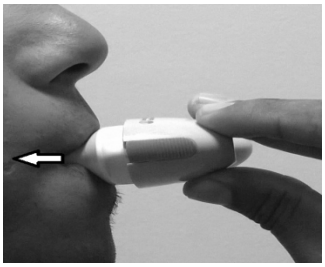


**Figure R1**

**Figure R2**

After completing 2 inhalations from your 1st INHALER, hand the INHALER to unblinded study personnel. Unblinded study personnel will collect the INHALER, visually verify the capsules are empty (no powder contents remaining), and close the INHALER.

**Repeat Step 4 with the 2nd INHALER to take your 2nd capsule.**

**Every attempt should be made to administer the powder contents from each of the 2 capsules (2 inhalations/capsule for a total of 4 inhalations) within 2 minutes.**

**IF YOU DO NOT HEAR OR FEEL THE CAPSULE AS YOU BREATHE IN YOUR STUDY MEDICATION:**

Do not press the green piercing button again.

Unblinded study personnel will hold your INHALER with the mouthpiece pointed up and tap your INHALER gently on a table (See Figure S1 for INHALER 1 and Figure S2 for INHALER 2).

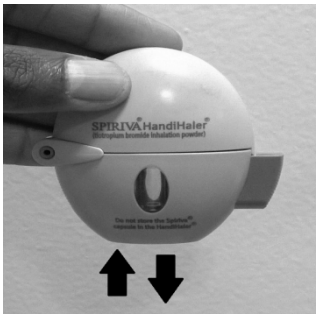



**Figure S1**

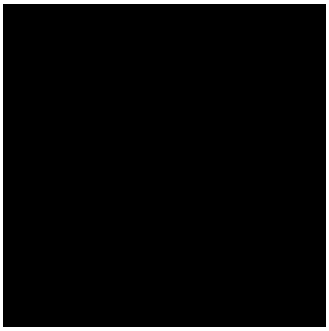


**Figure S2**

Unblinded study personnel will check to see that the mouthpiece is completely closed. Breathe out completely before deeply breathing in again with the mouthpiece in your mouth (See Figure R1 for INHALER 1 and Figure R2 for INHALER 2).

# FOR PATIENTS PARTICIPATING IN TRAINING/RUN-IN/PART 2

## TAKING YOUR DOSE OF STUDY MEDICATION REQUIRES 4 MAIN STEPS.

### STEP 1. OPENING YOUR INHALER:

After study personnel has removed your INHALER from the pouch:

- Open the dust cap (lid) by pressing the green piercing button (See Figure E).

**Figure E**

- Pull the dust cap (lid) upwards away from the base to expose the mouthpiece (See Figure F).

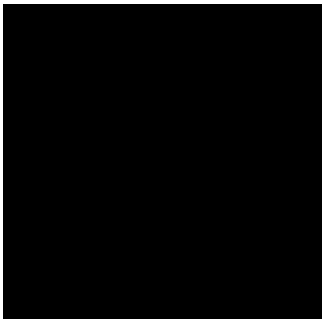


**Figure F**

- Open the mouthpiece by pulling the mouthpiece ridge up and away from the base so center chamber is showing (See Figure G).

**Figure G**

## STEP 2. INSERTING THE CAPSULE INTO YOUR INHALER:

Each day, separate only 1 blister from the blister card by tearing along the perforated line (See Figure H).

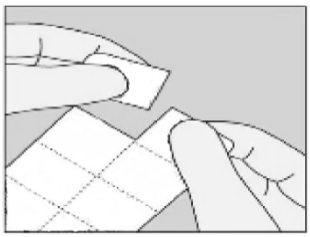


**Figure H**

**Remove the capsule from the blister:**

- Do not cut the foil or use sharp instruments to take out the capsule from the blister.
- Bend one of the blister corners with an arrow and separate the aluminum foil layers.
- Peel back the printed foil until you see the whole capsule (See Figure J).
- If you have opened more than 1 blister to the air, the extra capsule should not be used.

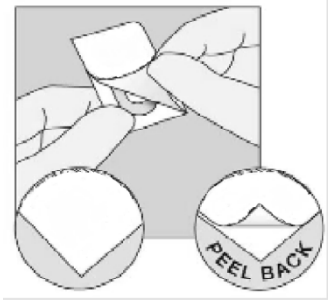



**Figure J**

- Place the capsule in the center chamber of your INHALER (See Figure K).

**Figure K**

- Close the mouthpiece firmly against the base until you hear a click. Leave the dust cap (lid) open (See Figure L).

**Figure L**

**STEP 3. PIERCING THE CAPSULE:**

- Hold your INHALER with the mouthpiece pointed up (See Figure M).

**Figure M**

- Press the green piercing button once until it is flat (flush) against the base, then release. This is how to make holes in the capsule so that you get study medication when you breathe in.
- Do not press the green button more than one time.
- Do not shake the INHALER.
- The piercing of the capsule may produce small pieces of the capsule. Some of these small pieces may pass through the screen of the INHALER into the mouth or throat when you breathe in your study medication. This is normal. The small pieces of the capsule should not harm you.

## STEP 4. TAKING YOUR FULL DAILY DOSE OF STUDY MEDICATION (2 INHALATIONS FROM THE SAME CAPSULE):

**Breathe out completely in 1 breath,** emptying your lungs of any air (See Figure N).

**Important: Do not** breathe into your INHALER.

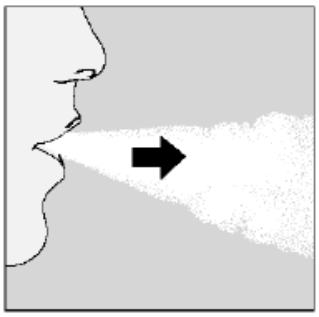


**Figure N**

**With your next breath, take your study medication:**

- **Hold your head in an upright position while you are looking straight ahead** (See Figure P).
- Raise your INHALER to your mouth in a horizontal position. **Do not** block the air intake vents.
- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the capsule vibrate** (rattle) (See Figure P).
- Hold your breath for a few seconds and, at the same time, take your INHALER out of your mouth.
- Breathe normally again.

**Figure P**

The rattle tells you that you breathed in correctly. If you do not hear or feel a rattle, see the section, "If you do not hear or feel the capsule rattle as you breathe in your study medication."

**To get the full amount from the capsule, you must again, breathe out completely (See Figure Q)**

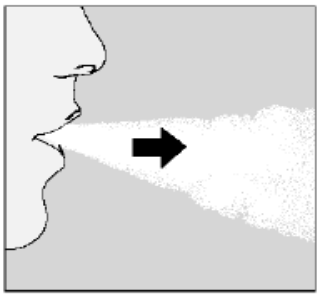


**Figure Q**

**then for a second time, breathe in (See Figure R) from the same capsule.**

**Important: Do not** press the green piercing button again. **Do not** breathe into your INHALER.

Remember: To get your full amount from the capsule, you must breathe in 2 times from the same capsule. Make sure you breathe out completely each time before you breathe in from your INHALER.

**Figure R**

## CARING FOR AND STORING YOUR INHALER:

- After taking your daily dose, open the mouthpiece and tip out the used capsule into your resealable bag, without touching it.
- Remove any capsule pieces or powder buildup by turning your INHALER upside down and gently, but firmly, tapping it (See Figure S). Then, close the mouthpiece and dustcap for storage.

**Figure S**

- **Do not** store your INHALER and capsules (blisters) in a damp moist place. Always store capsules in the sealed blisters.

## IF YOU DO NOT HEAR OR FEEL THE CAPSULE AS YOU BREATHE IN YOUR STUDY MEDICATION:

- Do not press the green piercing button again.
- Hold your INHALER with the mouthpiece pointed up and tap your INHALER gently on a table (See Figure T).

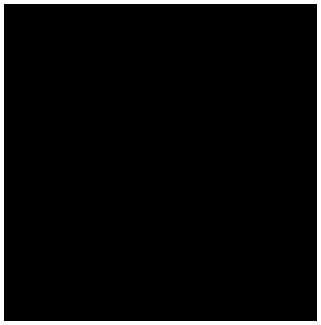


**Figure T**

- Check to see that the mouthpiece is completely closed. Breathe out completely before deeply breathing in again with the mouthpiece in your mouth (See Figure R).
- If you still do not hear or feel the capsule rattle after repeating the above steps:
    - Place the capsule in the resealable bag.
    - Open the base by lifting the green piercing button and check the center chamber for pieces of the capsule.
    - Capsule pieces in the center chamber can cause a capsule not to rattle.
    - Turn your INHALER upside down and gently, but firmly, tap to remove the capsule pieces. Call your study doctor for instructions.

## CLEANING YOUR INHALER:

- Clean your INHALER device as needed (See Figure U).
  - **It takes 24 hours to air dry your INHALER** after you clean it.
  - **Do not** use cleaning agents or detergents.
  - **Do not** place your INHALER in the dishwasher for cleaning.

**Figure U**

- **Cleaning Steps:**
  - Open the dust cap and mouthpiece.
  - Open the base by lifting the green piercing button.
  - Look in the center chamber for capsule pieces or powder buildup. If seen, tap out.
  - Rinse your INHALER with warm water, pressing the green piercing button a few times so that the center chamber and the piercing needle are under the running water. Check that any powder buildup or capsule pieces are removed.
  - Dry your INHALER well by tipping the excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open by fully spreading it out so that it dries completely.
  - **Do not** use a hair dryer to dry your INHALER.
  - **Do not** use your INHALER when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.
  - Document in your diary when cleaning of the INHALER has been performed.

## IMPORTANT INFORMATION ABOUT USING YOUR INHALER:

11. Do not swallow capsules.
12. Capsules should only be used with the INHALER and inhaled through your mouth (oral inhalation).
13. Do not use your INHALER to take any other medicine.
14. Do not store capsules in the INHALER.
15. Store capsules in the sealed blister package at room temperature between 68°F to 77°F (20°C to 25°C).
16. Keep capsules away from heat and cold (do not freeze).
17. Store capsules in a dry place. Do not use any unused capsules that have been open to air.
18. Ask your study doctor if you have any questions about storing your capsules.
19. Keep the INHALER and capsules out of the reach of children.
20. Do not let the powder from the capsule get into your eyes.

**Revised Text:**

# Appendix A: Study Medication Instructions for Use

### Patient Instructions for Investigational Product Administration of the Dry Powder Inhalers

Two dry powder inhalers will be used in this study (see Figure A1 and Figure A2):

For the run-in period, 1 inhaler (Figure A2) will be used to administer 2 inhalations from 1 capsule of study medication (Lupin 18 mcg tiotropium bromide or placebo) once daily for 14 +2 days.

For Part 1 of the study, 2 inhalers (Figure A1 and Figure A2) will be used to administer a single-dose of study medication (18 mcg tiotropium bromide or placebo) at each treatment period (visits 2, 3, and 4). A single-dose consists of 1 capsule per inhaler administered as 2 inhalations per capsule. Each capsule will be placed into the inhalers by unblinded study personnel as per the randomization schedule.

For Part 2 of the study, 1 inhaler (Figure A2) will be used to administer 2 inhalations from 1 capsule of study medication (Lupin 18 mcg tiotropium bromide) once daily for 72 +3 days.

Placebo training inhalers will also be provided for training purposes during Part 1 of the study.

**YOUR STUDY INHALERS**

Figure A1 represents ***HANDIHALER ~~INHALER 1~~*** and Figure A2 represents ***LUPINHALER ~~INHALER 2.~~*** These inhalers are for oral inhalation only. Both INHALERS will be over-labeled with the appropriate kit/inhaler number.


**Figure A1**
***HANDIHALER ~~INHALER 1~~***

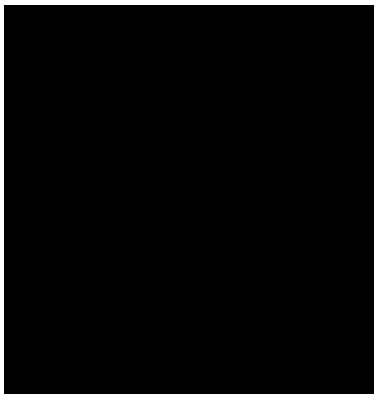


**Figure A2**
***LUPINHALER ~~INHALER 2~~***

Each INHALER comes with capsules in blister packaging. Use the INHALER provided with the designated capsule(s).

**The parts of each INHALER include:**
(See Figure B1 for ***HANDIHALER ~~INHALER 1~~*** and Figure B2 for ***LUPINHALER ~~INHALER 2~~***)

1. Dust cap (lid)
2. Mouthpiece
3. Mouthpiece ridge
4. Base
5. Green piercing button
6. Center chamber
7. Air intake vents

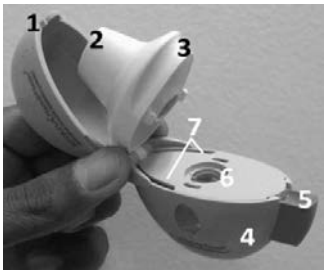



**Figure B1**

**Figure B2**

Each tiotropium capsule is packaged in a blister (See Figure C).

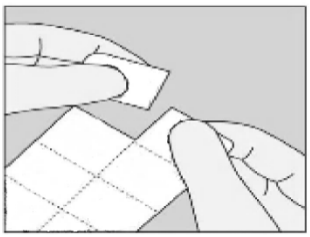


**Figure C**

Each tiotropium capsule contains only a small amount of powder (See Figure D).

Do not open the tiotropium capsule or it may not work.

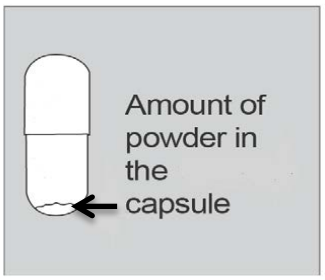



**Figure D**

# FOR PATIENTS PARTICIPATING IN PART 1 *DOUBLE-BLIND*

**TAKING YOUR DOSE OF STUDY MEDICATION REQUIRES 4 MAIN STEPS.**

Note: Some of these steps will be performed by unblinded study personnel prior to you (the patient) receiving the INHALER.

**STEP 1. OPENING YOUR INHALER:**

***Only unblinded study personnel should open the kits and prepare the INHALERS for the Part 1 double-blind treatment. Opening of the kit and preparation of the INHALERS should be done in a blinded study medication location away from the view of blinded study personnel and you.***

After unblinded study personnel has removed your INHALER from the pouch:

- Unblinded study personnel will open the dust cap (lid) by pressing the green piercing button (See Figure E1 for ***HANDIHALER ~~INHALER 1~~*** and Figure E2 for ***LUPINHALER ~~INHALER 2~~***).

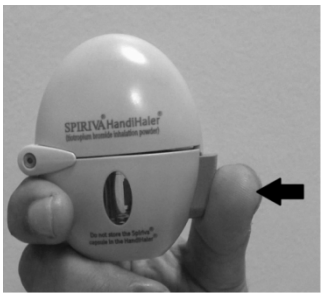



**Figure E1**

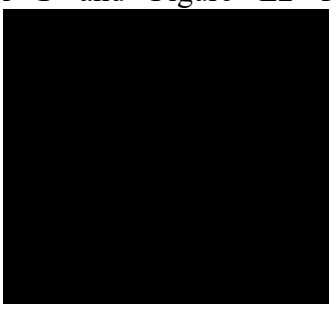


**Figure E2**

- Unblinded study personnel will pull the dust cap (lid) upwards away from the base to expose the mouthpiece (See Figure F1 for ***HANDIHALER ~~INHALER 1~~*** and Figure F2 for ***LUPINHALER ~~INHALER 2~~***)

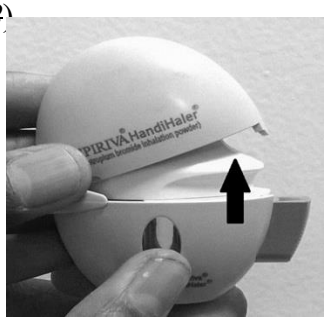



**Figure F1**

**Figure F2**

- Unblinded study personnel will open the mouthpiece by pulling the mouthpiece ridge up and away from the base so center chamber is showing (See Figure G1 for ***HANDIHALER ~~INHALER 1~~*** and Figure G2 for ***LUPINHALE***

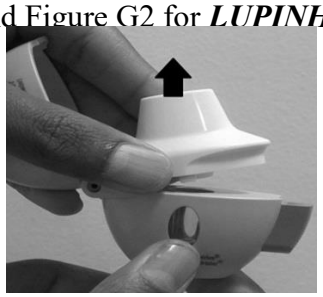


**Figure G1**

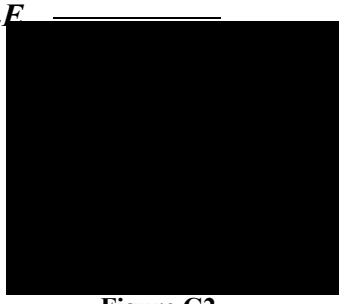


**Figure G2**

**STEP 2. INSERTING THE CAPSULE INTO YOUR INHALER:**

Unblinded study personnel will separate the blisters from the blister card by tearing along the perforated line (See Figure H).

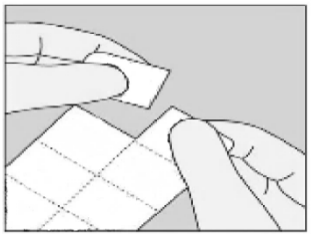


**Figure H**

**Unblinded study personnel will remove the capsule from the blister:**

- Do not cut the foil or use sharp instruments to take out the capsule from the blister.
- Bend one of the blister corners with an arrow and separate the aluminum foil layers.
- Peel back the printed foil until you see the whole capsule (See Figure J).
- If you have opened more than 1 blister to the air, the extra capsule should not be used.

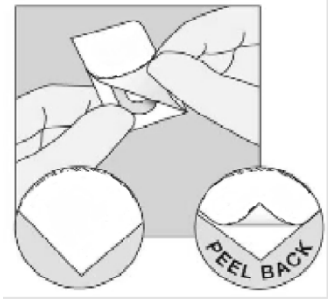



**Figure J**

- Unblinded study personnel will place the capsule in the center chamber of your INHALER (See Figure K1 for ***HANDIHALER ~~INHALER 1~~*** and Figure K2 for ***LUPINHALER ~~INHALER 2~~)***.

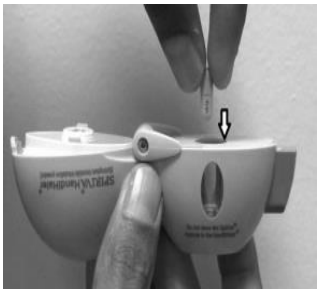


**Figure K1**

**Figure K2**

- Unblinded study personnel will close the mouthpiece firmly against the base until he/she hears a click. Unblinded study personnel will leave the dust cap (lid) open (See Figure L1 for ***HANDIHALER ~~INHALER 1~~*** and Figure L2 for ***LUPINHALER ~~INHALER 2~~***).

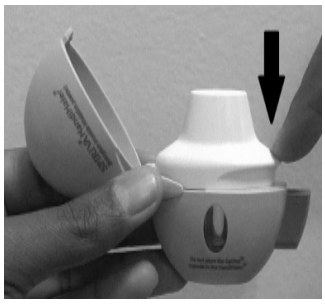


**Figure L1**

**Figure L2**

- ***~~Unblinded study personnel will apply an opaque label/tape to cover the chamber window to prevent identification of the capsules.~~***

**STEP 3*A*. PIERCING THE CAPSULE:**

- Unblinded study personnel will hold your INHALER with the mouthpiece pointed up (See Figure M1 for ***HANDIHALER ~~INHALER 1~~*** and Figure M2 for ***LUPINHALER ~~INHALER 2~~***).

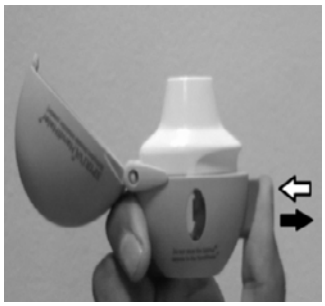


**Figure M1**

**Figure M2**

- Unblinded study personnel will press the green piercing button once until it is flat (flush) against the base, then release. This is how to make holes in the capsule so that you get study medication when you breathe in.
- Do not press the green button more than one time.
- Do not shake the INHALER.
- The piercing of the capsule may produce small pieces of the capsule. Some of these small pieces may pass through the screen of the INHALER into the mouth or throat when you breathe in your medicine. This is normal. The small pieces of the capsule should not harm you.

***STEP 3B. APPLYING TAPE TO MASK THE CHAMBER WINDOW***

- ***After piercing the capsule, unblinded study personnel will apply an opaque label/tape to cover the chamber window to prevent identification of the capsules, numbering the inhaler dosing order based on even/odd calendar days as described in the pharmacy manual.***
- ***Unblinded study personnel will bring the INHALERS to the patient dosing location leaving the inhaler kit carton, capsule blisters in the blinded study medication location.***

**STEP 4. TAKING YOUR DOSE OF STUDY MEDICATION:**

***~~UnB~~*linded study personnel will hand you the INHALER in a horizontal position. Keep the INHALER in the horizontal position.**

**Breathe out completely in 1 breath,** emptying your lungs of any air (See Figure N).

**Important: Do not** breathe into your INHALER.

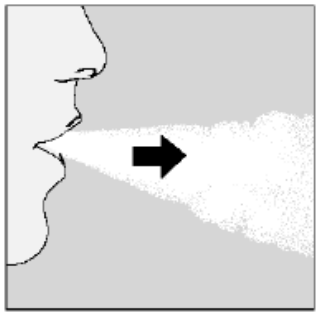


**Figure N**

**With your next breath, take your study medication:**

- **Hold your head in an upright position while you are looking straight ahead** (See Figure P1 for ***HANDIHALER ~~INHALER 1~~*** and Figure P2 for ***LUPINHALER ~~INHALER 2~~***).
- Raise your INHALER to your mouth in a horizontal position. **Do not** block the air intake vents.
- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the capsule vibrate** (rattle) (See Figure P1 for ***HANDIHALER ~~INHALER 1~~*** and Figure P2 for ***LUPINHALER ~~INHALER 2~~***).
- Hold your breath for a few seconds and, at the same time, take your INHALER out of your mouth.
- Breathe normally again.

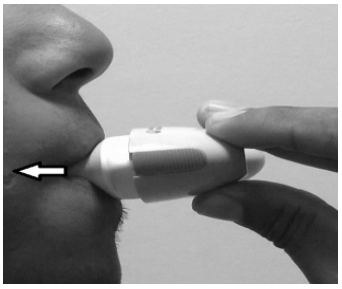


**Figure P1**

**Figure P2**

The rattle tells you that you breathed in correctly. If you do not hear or feel a rattle, see the section, "If you do not hear or feel the capsule rattle as you breathe in your study medication."

**To get the full amount from the capsule, you must again, breathe out completely (See Figure Q)**

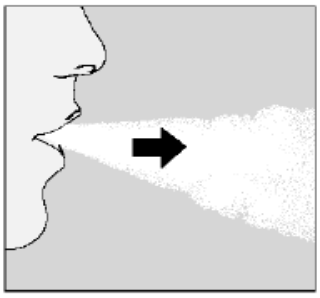


**Figure Q**

**then for a second time, breathe in (See Figure R1 for *HANDIHALER* ~~*INHALER 1*~~ and Figure R2 for *LUPINHALER* ~~*INHALER 2*~~) from the same capsule.**

**Important: Do not** press the green piercing button again. **Do not** breathe into your INHALER.

Remember: To get your full amount from the capsule, you must breathe in 2 times from the same capsule. Make sure you breathe out completely each time before you breathe in from your INHALER.

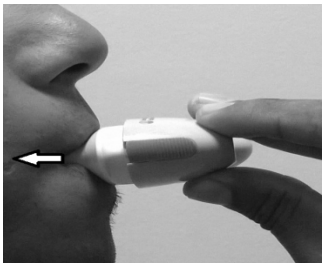


**Figure R1**

**Figure R2**

After completing 2 inhalations from your 1st INHALER, hand the INHALER to ~~un~~blinded study personnel. ~~***Un***~~***B***linded study personnel will collect the INHALER, ~~visually verify the capsules are empty (no powder contents remaining),~~ and close the INHALER.

**Repeat Step 4 with the 2nd INHALER to take your 2nd capsule.**

**Every attempt should be made to administer the powder contents from each of the 2 capsules (2 inhalations/capsule for a total of 4 inhalations) within 2 minutes.**

***After you have dosed with both INHALERS, unblinded study personnel will return the INHALERS to the blinded study medication location and deposit each used INHALER containing the used capsule along with unused capsule blisters into the pouch and carton.***

**IF YOU DO NOT HEAR OR FEEL THE CAPSULE AS YOU BREATHE IN YOUR STUDY MEDICATION:**

Do not press the green piercing button again.

***~~UnB~~***linded study personnel will hold your INHALER with the mouthpiece pointed up and tap your INHALER gently on a table (See Figure S1 for ***HANDIHALER ~~INHALER 1~~*** and Figure S2 for ***LUPINHALER ~~INHALER 2~~***).

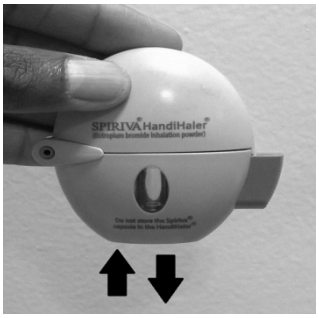



**Figure S1**

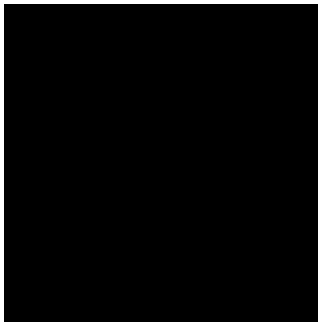


**Figure S2**

***~~UnB~~***linded study personnel will check to see that the mouthpiece is completely closed. Breathe out completely before deeply breathing in again with the mouthpiece in your mouth (See Figure R1 for ***HANDIHALER ~~INHALER 1~~*** and Figure R2 for ***LUPINHALER ~~INHALER 2~~***).

# FOR PATIENTS PARTICIPATING IN TRAINING/RUN-IN/PART 2

## TAKING YOUR DOSE OF STUDY MEDICATION REQUIRES 4 MAIN STEPS.

### STEP 1. OPENING YOUR INHALER:

After study personnel has removed your INHALER from the pouch:

- Open the dust cap (lid) by pressing the green piercing button (See Figure E).

**Figure E**

- Pull the dust cap (lid) upwards away from the base to expose the mouthpiece (See Figure F).

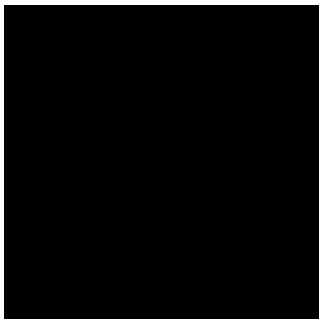


**Figure F**

- Open the mouthpiece by pulling the mouthpiece ridge up and away from the base so center chamber is showing (See Figure G).

**Figure G**

## STEP 2. INSERTING THE CAPSULE INTO YOUR INHALER:

Each day, separate only 1 blister from the blister card by tearing along the perforated line (See Figure H).

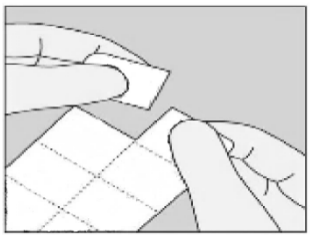


**Figure H**

**Remove the capsule from the blister:**

- Do not cut the foil or use sharp instruments to take out the capsule from the blister.
- Bend one of the blister corners with an arrow and separate the aluminum foil layers.
- Peel back the printed foil until you see the whole capsule (See Figure J).
- If you have opened more than 1 blister to the air, the extra capsule should not be used.

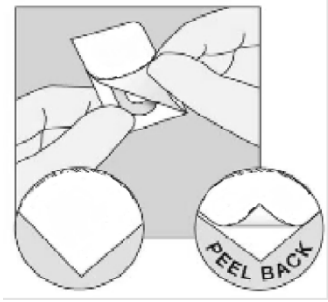



**Figure J**

- Place the capsule in the center chamber of your INHALER (See Figure K).

**Figure K**

- Close the mouthpiece firmly against the base until you hear a click. Leave the dust cap (lid) open (See Figure L).

**Figure L**

**STEP 3. PIERCING THE CAPSULE:**

- Hold your INHALER with the mouthpiece pointed up (See Figure M).

**Figure M**

- Press the green piercing button once until it is flat (flush) against the base, then release. This is how to make holes in the capsule so that you get study medication when you breathe in.
- Do not press the green button more than one time.
- Do not shake the INHALER.
- The piercing of the capsule may produce small pieces of the capsule. Some of these small pieces may pass through the screen of the INHALER into the mouth or throat when you breathe in your study medication. This is normal. The small pieces of the capsule should not harm you.

## STEP 4. TAKING YOUR FULL DAILY DOSE OF STUDY MEDICATION (2 INHALATIONS FROM THE SAME CAPSULE):

**Breathe out completely in 1 breath,** emptying your lungs of any air (See Figure N).

**Important: Do not** breathe into your INHALER.

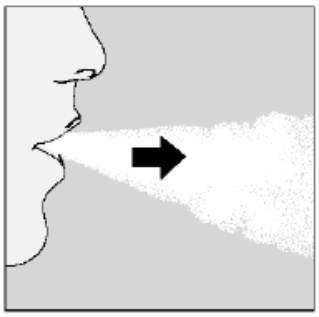


**Figure N**

**With your next breath, take your study medication:**

- **Hold your head in an upright position while you are looking straight ahead** (See Figure P).
- Raise your INHALER to your mouth in a horizontal position. **Do not** block the air intake vents.
- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the capsule vibrate** (rattle) (See Figure P).
- Hold your breath for a few seconds and, at the same time, take your INHALER out of your mouth.
- Breathe normally again.

**Figure P**

The rattle tells you that you breathed in correctly. If you do not hear or feel a rattle, see the section, "If you do not hear or feel the capsule rattle as you breathe in your study medication."

**To get the full amount from the capsule, you must again, breathe out completely (See Figure Q)**

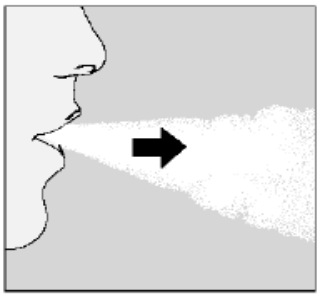


**Figure Q**

**then for a second time, breathe in (See Figure R) from the same capsule.**

**Important: Do not** press the green piercing button again. **Do not** breathe into your INHALER.

Remember: To get your full amount from the capsule, you must breathe in 2 times from the same capsule. Make sure you breathe out completely each time before you breathe in from your INHALER.

**Figure R**

## CARING FOR AND STORING YOUR INHALER:

- After taking your daily dose, open the mouthpiece and tip out the used capsule into your ~~***resealable bag***~~ ***trash can,*** without touching it.
- Remove any capsule pieces or powder buildup by turning your INHALER upside down and gently, but firmly, tapping it (See Figure S). Then, close the mouthpiece and dustcap for storage.

**Figure S**

- **Do not** store your INHALER and capsules (blisters) in a damp moist place. Always store capsules in the sealed blisters.

## IF YOU DO NOT HEAR OR FEEL THE CAPSULE AS YOU BREATHE IN YOUR STUDY MEDICATION:

- Do not press the green piercing button again.
- Hold your INHALER with the mouthpiece pointed up and tap your INHALER gently on a table (See Figure T).

**Figure T**

- Check to see that the mouthpiece is completely closed. Breathe out completely before deeply breathing in again with the mouthpiece in your mouth (See Figure R).
- If you still do not hear or feel the capsule rattle after repeating the above steps:
  - ~~***Place the capsule in the resealable bag.***~~ ***Throw away the used capsule.***
  - Open the base by lifting the green piercing button and check the center chamber for pieces of the capsule.
  - Capsule pieces in the center chamber can cause a capsule not to rattle.
  - Turn your INHALER upside down and gently, but firmly, tap to remove the capsule pieces. Call your study doctor for instructions.

## CLEANING YOUR INHALER:

- Clean your INHALER device as needed (See Figure U).
  - **It takes 24 hours to air dry your INHALER** after you clean it.
  - **Do not** use cleaning agents or detergents.
  - **Do not** place your INHALER in the dishwasher for cleaning.

**Figure U**

- **Cleaning Steps:**
  - Open the dust cap and mouthpiece.
  - Open the base by lifting the green piercing button.
  - Look in the center chamber for capsule pieces or powder buildup. If seen, tap out.
  - Rinse your INHALER with warm water, pressing the green piercing button a few times so that the center chamber and the piercing needle are under the running water. Check that any powder buildup or capsule pieces are removed.
  - Dry your INHALER well by tipping the excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open by fully spreading it out so that it dries completely.
  - **Do not** use a hair dryer to dry your INHALER.
  - **Do not** use your INHALER when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.
  - Document in your diary when cleaning of the INHALER has been performed.

## IMPORTANT INFORMATION ABOUT USING YOUR INHALER:

21. Do not swallow capsules.
22. Capsules should only be used with the INHALER and inhaled through your mouth (oral inhalation).
23. Do not use your INHALER to take any other medicine.
24. Do not store capsules in the INHALER.
25. Store capsules in the sealed blister package at room temperature between 68°F to 77°F (20°C to 25°C).
26. Keep capsules away from heat and cold (do not freeze).
27. Store capsules in a dry place. Do not use any unused capsules that have been open to air.
28. Ask your study doctor if you have any questions about storing your capsules.
29. Keep the INHALER and capsules out of the reach of children.
30. Do not let the powder from the capsule get into your eyes.

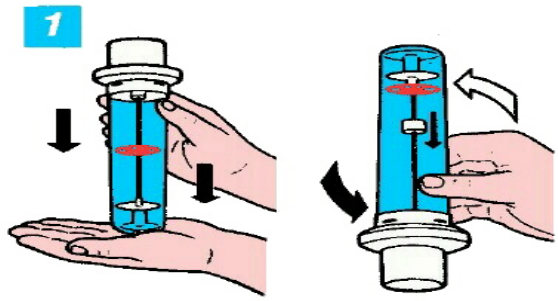
## Original Text:

## Appendix B: Inhalation Training with In-Check DIAL

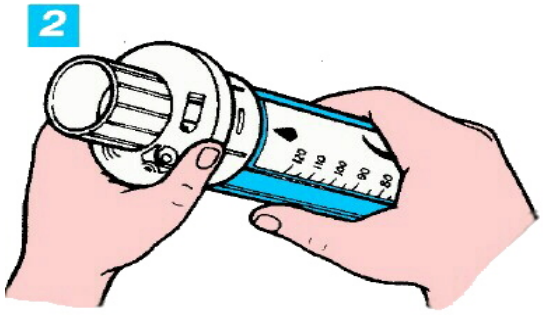
The In-Check DIAL is an inhalation airflow meter that can help educate and assess patients who use inhaler devices. It simulates the internal resistance of several common inhaler devices, and measures inspiratory flow. Inspiratory flow rate measurements will be obtained at screening and visits 2, 3, and 4 using the In-Check DIAL device and will be recorded in the eCRF.

**How to use the In-Check DIAL**

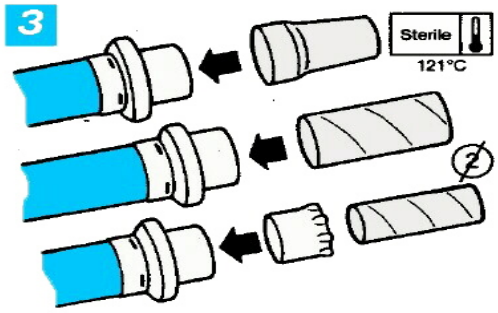
1. Reset the In-Check DIAL. The cursor should be reset to zero through a "tap and turn" maneuver which releases a seated magnet from the top of the DIAL and pushes the cursor back. The DIAL should then be turned upside down to reseat the magnet so as not to get in the way of an accurate measurement.



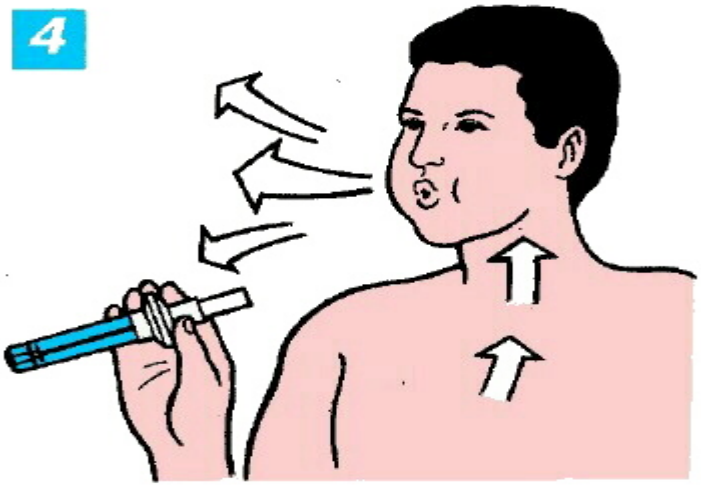

2. Align the scale with the inhaler device. With the triangular pointer on top of the scale, align the "dial" portion of the device for use with HANDIHALER adapter by setting the device to **"free flow"** (wavy flag icon) - an audible "click" should be heard.



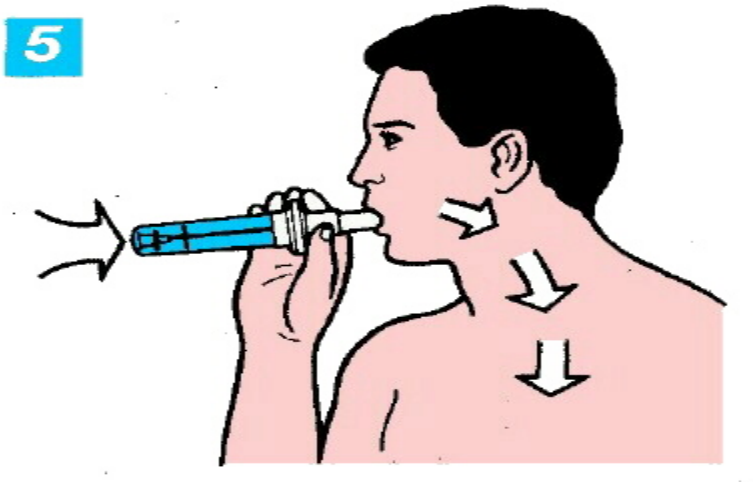
3. Attach a clean mouthpiece. Attach the HANDIHALER resistance adapter (blue transparent cylinder provided separately in a sealed plastic bag) to mimic SPIRIVA HANDIHALER resistance. Insert a disposable one-way valved inspiratory mouthpiece into the wider end of the blue transparent adapter.



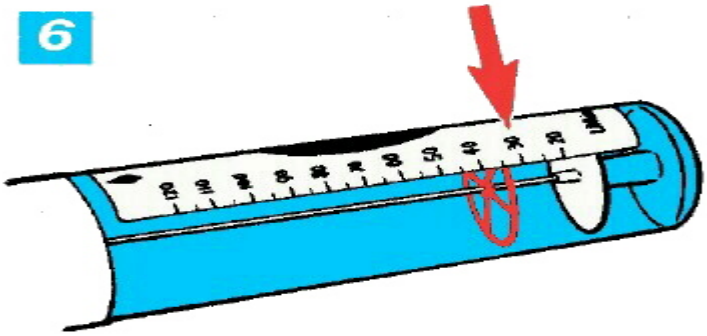

4. Ask the patient to exhale slowly and fully.



5. Seal lips around the mouthpiece. According to the inhaler setting (wavy flow icon and HANDIHALER resistance adapter), instruct the patient to inhale deeply.




6. Record the inspiratory flow from the position of the red cursor against the scale. Reset, and repeat until 3 successful inspiratory flow rates (≥40 L/min) are achieved. Record the three (3) inspiratory flow rates on the patient's source and eCRF.



## Revised Text:

## Appendix B: Inhalation Training with In-Check DIAL

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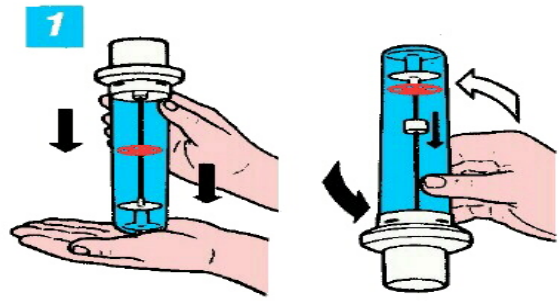
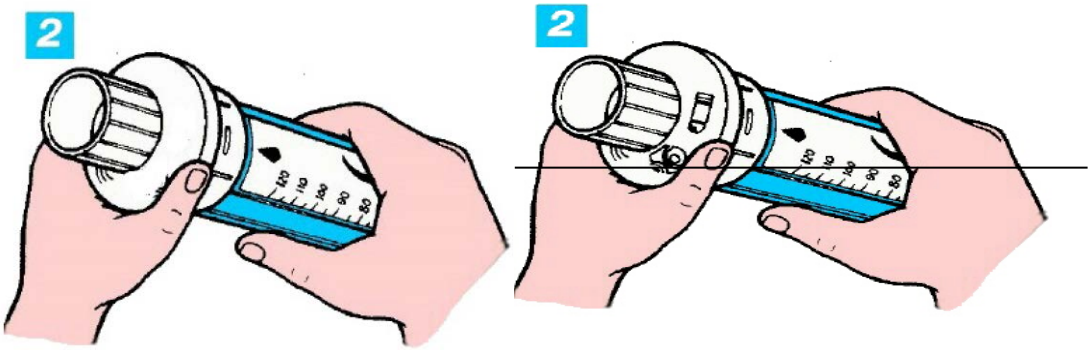



2. Align the scale with the inhaler device. With the triangular pointer on top of the scale, align the "dial" portion of the device for use with HANDIHALER adapter by setting the device to ~~***"free flow" (wavy flag icon)***~~ ***no resistance circle (pMDI) icon*** - an audible "click" should be heard.



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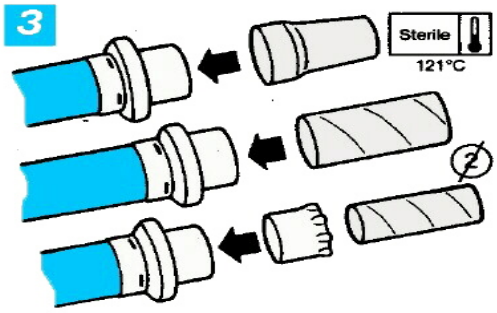


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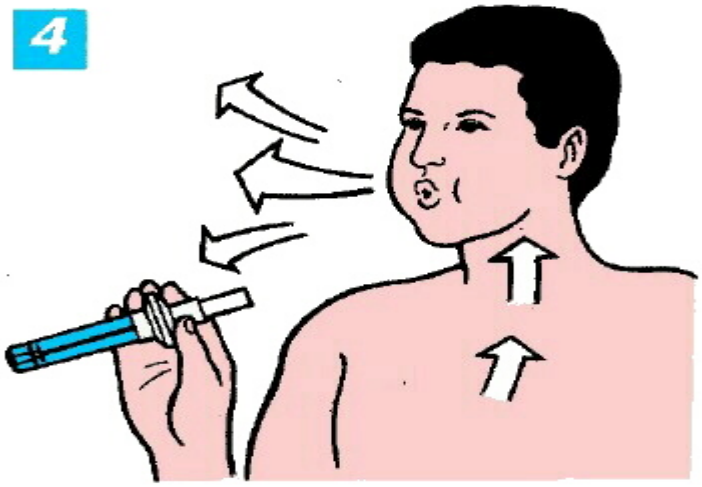

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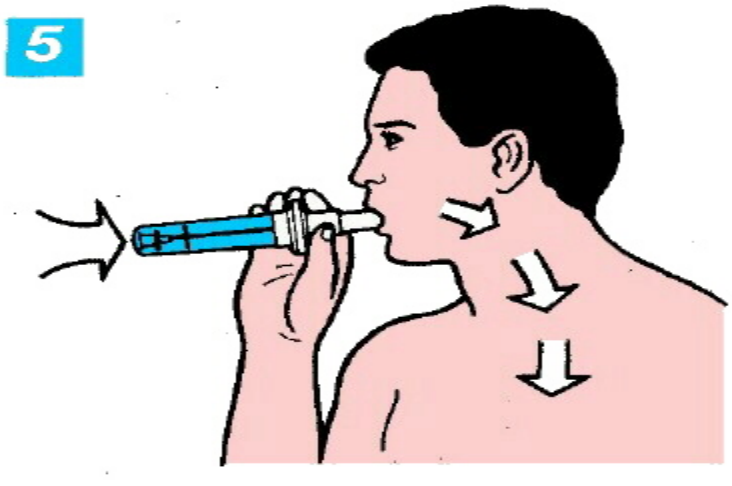


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