Statistical Analysis Plan

Sponsor:	Lupin Inc.
Protocol No:	TB-DPI-301
PRA Project Id:	LPBTB301-TB301X
Protocol Version Dates:	11-May-2017
Version No.:	Amendment 1
Title:	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
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1.0 Approvals

Sponsor: Lupin Inc.

Representative/ Title: [redacted] VP, Global Clinical Development Inhalation, Complex Generics, and Brands

Signature /Date: [redacted] 08Feb2018

Representative/ Title: [redacted]

Signature /Date: [redacted] 8th Feb 2018

PRA

Project Manager/Title: [redacted]

Signature /Date: [redacted] 09 Feb 2018

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2.0 Table of Contents

3.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Lupin Inc. Protocol TB-DPI-301.

4.0 Scope

This plan is a living document that will be created during the trial start-up. Statistical Analysis Plan (SAP) 1 will be drafted within three months of the final case report form (CRF), and maintained throughout the lifecycle of the trial. The Statistical Analysis Plan 2 will be finalized prior to database lock. SAP 1 and SAP 2 will require sign off from the Project Manager and the sponsor.

The Statistical Analysis Plan outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Interim Analysis
- Statistical methods regarding subject disposition, important protocol deviations, study drug exposure, prior and concomitant medications, demographic and baseline characteristics, medical history, efficacy analysis, adverse events handling, and other safety data examinations

The Table, Listing and Figure Shells will be provided in a separate document.

5.0 Introduction

This SAP describes the statistical methods to be used during the reporting and analyses of data collected under Lupin Inc. Protocol TB-DPI-301.

This SAP should be read in conjunction with the study protocol and CRF. This version of the plan has been developed using the protocol Amendment version 1 dated 11May2017 and CRF dated 14Mar2017. Any further changes to the protocol or CRF may necessitate updates to the SAP.

The SAP is to be developed in two stages. The purpose is to "finalize" a SAP so that PRA can start programming earlier in the process. Versions of the SAP up to initial sponsor approval will be known as SAP1. Changes following approval of SAP1 will be tracked in the SAP Change Log and a final version of the SAP, known as SAP2, will be issued for sponsor approval prior to database lock.

6.0 Study Objectives

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 baseline-adjusted 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 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.

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

7.0 Study Design

This is a Phase 3 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. 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.

This clinical study includes two parts. 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.

Part 1 (14 weeks)

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 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).

Screening period: up to 30 days

The screening period allows for adequate washout of the COPD therapies including long-acting anti-muscarinic agent (LAMA), long-acting beta agonist (LABA), or inhaled corticosteroid (ICS)/LABA therapy, along with other prohibited medications per protocol. 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 (e.g., 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

Single-blind placebo run-in period: 14 (+2) days

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.

Three single-dose, double-blind treatment periods (visits 2-4) each separated by a 21-day (+3 days) washout period

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 as described in Table 1:

Table 1 Randomization Design

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
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 (i.e., 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 FEV1 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 FEV1 measurements at 5 and 30 minutes post-dose, and at 1, 2, 4, 6, 8, 10, 12, 23, and 24 hours post-dose. 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).

Follow-up period: 7 days (±3 days)
Patients who successfully complete 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.

Part 2 (12 weeks)
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 successfully completed Part 1 of the study and continue to meet the continuation criteria, to assess robustness of the LUPINHALER over 72 days of treatment.

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 FEV1 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.

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.

The schedule of events for this study is provided in Table 2 Schedule of Events.

Table 2 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																

	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
Study qualifying FEV_1	X																
Determine FEV_1 baseline/stability limits	X[14]		X[15]														
Administer single-blind run-in medication		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							

	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
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/ electronic flow meter, as applicable	X		X					X							X		X
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		

	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
Discuss COPD treatment options	X							X	X						X	X	X
Discharge patient via IRT									X							X	X
Home-based FEV_1 measurements	Record morning pre-dose in eDiary/electronic flow meter[22]									Record morning pre-dose and 2 hours post-dose 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) Pre-dose 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 pre-dose FEV_1]), and at 5 and 30 minutes post-dose, and at 1, 2, 4, 6, 8, 10, 12, 23, and 24 hours post-dose. 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 until the conclusion of the run-in period, 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 oftheir 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).

7.1 Sample Size Considerations

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 CV is 1.21, the intra-patient CV 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. The blinded interim analysis will be discussed in Section 11.0.

7.2 Randomization

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). Y-Prime Inc. will be responsible for generating the randomization schedule.

The randomization scheme utilized in TB-DPI-301 will be central. A total of 240 patients will be randomized in a ratio of 1:1:1:1:1:1 to the 6 treatment sequences based on a Williams design Latin square in the cross-over design shown in Table 1.

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.

8.0 Study Variables

8.1 Primary Efficacy Variable

The primary variable is the baseline-adjusted FEV_1 $AUC_{0\text{-}24h}$ 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.

8.2 Safety Variables

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)
- Laboratory (screening only)
- ER-S: COPD Scores
- Safety Spirometry

8.3 Other Variables

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 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.

9.0 Definitions

9.1 Baseline and Change from Baseline

Baseline is defined as the last observation prior to dosing. Generally, baseline in Part 2 of the study will be the same as baseline in Part 1 of the study unless otherwise specified. For the primary variable (FEV_1 $AUC_{0\text{-}24h}$), baseline is defined as the average of the FEV_1 values recorded at approximately 30 minutes and 15 minutes before dosing with study medication.

Change from baseline = post-baseline value – baseline value.

9.2 Baseline-adjusted FEV_1 $AUC_{0\text{-}24h}$

The baseline-adjusted FEV_1 $AUC_{0\text{-}24h}$ is defined as the baseline-adjusted area under the curve for forced expiratory volume in 1 second from time zero to 24 hours postdose using the trapezoidal rule based on actual time of measurement.

The baseline FEV_1 will be the average of the 2 predose FEV_1 measurements (30 minutes and 15 minutes pre-dose) at the clinic visit. If one of the predose FEV_1 measurements is missing, or excluded due to poor quality spirometry effort, the other non-missing measurement will be used as baseline. If both predose FEV_1 measurements are missing or excluded, baseline will be treated as missing.

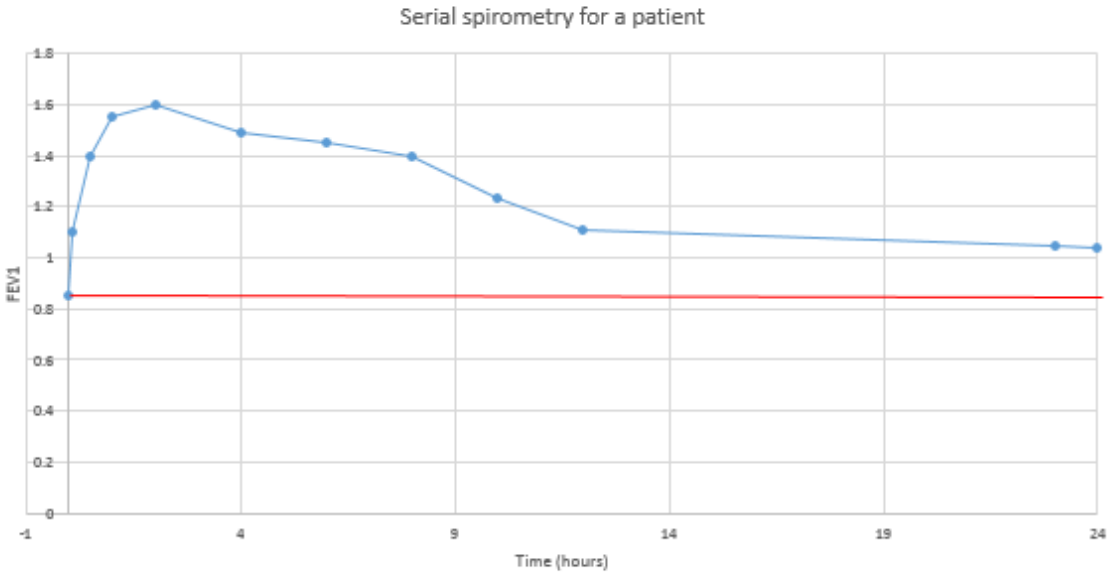
Baseline-adjusted FEV_1 will be calculated as postdose FEV_1 after subtracting the baseline FEV_1 value.

The general area under the concentration-time effect curve (AUC) formula by the trapezoidal rule is given below:

$$AUC_{(0-tn)} = \sum_{i=1}^{n} \frac{c_i + c_{i-1}}{2}(t_i - t_{i-1})$$

where t_n is the maximum time, n is the number of time points, and c_i is the change in FEV_1 from baseline at time t_i. For AUC calculations t_0 will be the start time of dose administration (t_0=0), and c_0 will be 0. AUC calculations will utilize the actual time of spirometry measurements.

Note- the area under the curve that is the primary variable is the area between the baseline value (straight red line and the curve). It is NOT measured from the x-axis.



9.3 Treatment, Washout and Follow-up

For summary purposes, treatment will be defined as days of dosing and days immediately after dosing, eg, day 0, 1, 21(+3), 22, 42(+3) and 43; washout will be days between treatments; follow-up is defined as 7 ±3days after visit 4 for Part 1, for patients who did not enter into the open-label Part 2 extension.

For Part 2, treatment is defined as first dosing date in Part 2 until the end of study or early termination (ET) for Part 2; follow-up is defined as 7 ±3days after visit 10.

9.4 Double-blind Period vs. Open-label Period

The double-blind period is defined as Part 1 of the study, from randomization to visit 4 or early termination before visit 4. For those who do not participate in Part 2 of the study (open-label), it also includes the follow-up period, which is 7 ±3days after visit 4.
Open-label period is defined as Part 2 of the study, from enrollment in Part 2 (open-label) to the end of Part 2 study or ET from Part 2. It also includes the follow-up period, which is 7 ±3days after visit 10.

9.5 Treatment Emergent Adverse Event (TEAE)

AEs will be summarized separately for TEAEs and Non-TEAEs.

Non-TEAEs are AEs observed after signing ICF until the initiation of the dose of the first experimental treatment.

A TEAE is defined as an event with an onset date/time on or after the initiation of the dose of the first experimental treatment after randomization or an event that is present at the initiation of the study medication and that subsequently increases in severity or frequency. AEs with a missing onset date and a stop date on or after 1st Dose Date or with a missing stop date, will be summarized as TEAEs.

9.6 Serious Adverse Event (SAE)

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

9.7 Spirometry (Part 1 Only)

FEV_1

The spirometry endpoint data will be captured using standardized equipment supplied by a central spirometry vendor - ERT.

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.

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.

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.

9.8 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.

9.9 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.

COPD exacerbations will be documented separately from AEs on a COPD exacerbation log in the electronic case report form (eCRF), unless the exacerbation meets the definition of an SAE. 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.

9.10 COPD Symptom Scores (Part 1 and Part 2)

During Part 1 (commencing at the time of consent) and Part 2 of the study, 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 the 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.

9.11 Methods for Handling Dropouts and Missing Data

Missing efficacy data will be handled in the following ways:

<u>For missing serial spirometry measurements:</u>
Missing data methods will be used provided that at least 9 of the 11 post-dose serial spirometry measurements are available. 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, expected to occur between 30 min to 2 hours post dose. 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.

<u>For missing measurements at the end of the time profile (i.e., no available FEV_1 value after a point in time):</u>

- 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.

- 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 pre-dose 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.

Two additional sensitivity analyses will be performed, where the missing data rules for the tail end of the profile will be based on the following: (a) the AUC calculation will be based on the time interval up to the last non-missing time point, and will then be standardized by dividing by the length of time for which FEV_1 measurements were included (ie. the AUC will be a weighted average), and (b) the baseline value will be substituted for the missing values.

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.

10.0 Analysis Population

10.1 Intention-to-Treat

The ITT analysis population 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 population will be the primary analysis population 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.

10.2 Per Protocol

The Per Protocol (PP) analysis population will be the primary analysis population used for the determination of BE between the Test and Reference products. The PP analysis population will exclude patients from the ITT population who have major protocol deviations in Part 1 of the study on either the Test treatment day or the Reference treatment day. Patients may have a major protocol deviation on the Placebo treatment day and still be

included in the Per Protocol population that will be used to asses BE although data from the Placebo day will be excluded from the analysis.

All patients with a major protocol deviation will be identified before the study blind is broken, and the removal of a patient from a treatment period will be documented within the clinical trial management system's protocol deviation file. In addition, individual FEV1 values from a patient may be removed from their 24-hour serial curve, including the 2 predose measurements, if they were the result of poor quality spirometry efforts. In those cases, the value will be set to missing and missing value rules applied as described in Section 9.11.

10.3 Safety

The safety analysis population will include all patients who receive at least one dose of any one of the randomized investigational products and for whom data have been collected after randomization.

10.4 Part 2 of the Study

All patients who begin treatment during the open-label portion of the study.

10.5 All Subjects

All patients who sign consent form for the study.

10.6 All Randomized Subjects

All patients who are randomized in the study.

11.0 Interim Analysis

11.1 Objective of the 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. The interim look is planned when 150 of the planned 240 randomized patients have completed Part 1 of the study. Issues impacting the choice of a final sample size will include the estimate of intra-patient variability and the estimate of the ratio of the means demonstrated in the pivotal PK study. The interim analysis will be conducted by PRA Health Sciences.

11.2 Endpoint for the Interim Analysis

The endpoint for the interim analysis is the baseline-adjusted FEV1 $AUC_{0\text{-}24h}$ on the single-dose treatment days.

11.3 Interim Analysis Population

The PP population will be used for the interim analysis. Patients who have major protocol deviations will be excluded from the interim analysis population.

11.4 Sample Size Re-calculation for the Interim Analysis

The original sample size estimate is based on an assumed intra-patient variability to which sample size estimates are very sensitive. From a review of studies on clinicaltrials.gov, there were a number of estimates available of between-patient variability for baseline-adjusted FEV1 AUC_{0-24}. From the 12 studies reviewed, the mean 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%. A blinded interim review of the data is planned to assess if this reduction is obtained. The missing data methods outlined in section 9.11 will be applied for the interim analysis, with the following exceptions: (1) no imputation would be performed during peak times, and (2) missing data at the tail-end of the spirometry profile would use Last Observation Carried Forward (LOCF) methods.

11.4.1 Intra-patient CV Estimation

In order to perform the interim sample size re-estimation (by nQuery7), the between-subject CV and the intra-subject CV need to be estimated using the interim data:

- Between-subject CV (CV_B)= σ_B / μ_R
- Intra-subject CV (CV_I)= σ_I / μ_R

Where σ_B is between-subject variance, σ_I is intra-subject variance and μ_R is the Least Square Mean (LSMean) of the reference (SPIRIVA) treatment.

To get estimates for σ_B, σ_I and μ_R, a mixed model can be used with a fixed effect for period and a random effect for patient using the PP population. The typical crossover model fixed effects for treatment and sequence are not included because the treatment codes are to remain blinded.

The SAS procedure to be used is:

```
proc mixed data=interim;
   class usubjid period;
   model Baseline-adjusted FEV1 AUC0-24h = period/ solution;
   random usubjid;
run;
```

where

- usubjid = patient
- period = treatment period

In the SAS output, the covariance (COV) estimate of σ_B will be called "Usubjid" and σ_I will be called "Residual". Normally we estimate μ_R as the LSMean for the reference (SPIRIVA) treatment, however, since this is a blinded estimation, we could instead use the estimate of CV_B from the Protocol as: $\mu_R = \sigma_B / 1.21$. Then, we use that estimate of μ_R to estimate $CV_I = \sigma_I / \mu_R$.

One downside of this approach is that it includes placebo which will almost surely inflate the intra-subject variance (and hence CV_I). The effect could be dramatic if the two active treatments are efficacious (i.e., much different from placebo). It should not affect between-subject variance.

To address this concern, 2 methods will be used to estimate the intra-subject variability and CV:

- Use the subject's AUC values from all 3 treatments to estimate the intra-subject CV. This method will provide a liberal (i.e., likely too large) sample size estimate since the placebo data will increase the intra-subject CV.
- Only use the data from the two "closest" AUC values from each subject's data to estimate the intra-subject CV. This approach mimics the inclusion of only the two active treatments in the sample size re-estimation (i.e., akin to excluding placebo). This method will produce a conservative (ie, likely too small) sample size estimate.

A decision on the sample size re-estimation will be made based on the results from the above 2 methods.

11.4.2 Sample Size Re-calculation

Once intra-patient CV is identified, sample size re-calculation will be performed using nQuery 7.0 with the following parameters:

- Power = 90%
- Expected ratio = 0.88 to 1.12
- Lower equivalence limit = 0.8
- Upper equivalence limit = 1.25
- Test significance level alpha (one-sided) = 0.05
- CV between subjects = 1.21 (assumption from the protocol)
- CV within subjects = new number calculated from the above mentioned model based on the actual interim data

The results of the 2 new sample size estimates (one based on data from all treatments and the other based on the 2 "closest" data values) will be available after using the above parameters. The estimate of the ratio of the means demonstrated in the pivotal PK study will help inform which expected ratio will be used in the final sample size chosen.

11.5 Results of the Interim Analysis

The final interim analysis report was dated 01Sep2017, and is attached in Appendix 3.

A total of 122 (of the 150) patients had 3 treatment periods with evaluable AUC data, and these data were included in the "closest" AUC analysis. Based on the results, the intra-patient CV was 0.3642 and the between-patient CV was 1.210. The table below summarizes the crossover design of two one-sided tests (TOST) for difference or ratio of means:

		Closest AUC (N=122)		
	Protocol	Low ratio	Ratio=1	High ratio
Test significance levels, α (one-sided)	0.050	0.050	0.050	0.050
Lower equivalence limit for μ_T / μ_R, D_L	0.800	0.800	0.800	0.800
Upper equivalence limit for μ_T / μ_R, D_U	1.250	1.250	1.250	1.250
Expected ratio, μ_T / μ_R	1.000	0.880	1.000	1.120
Coefficient of variation between subjects, CV_B	1.210	1.210	1.210	1.210
Coefficient of variation, intrasubject, CV_i	0.600	0.3642	0.3642	0.3642
Power (%)	90	90	90	90
n total	178	372	78	220

Results obtained from nQuery Advisor® 7.0

Based on the results, sample size estimates range from:

- a total of 372 across the six treatment sequences if the expected ratio of test to reference is 0.88
- a total of 220 patients across the six treatment sequences if the expected ratio of test to reference is 1.12

Assuming an expected ratio of means of 0.90 based on results from the pivotal PK study, an estimated 238 per-protocol patients would be needed to demonstrate equivalence between the test and reference products. Therefore, the Sponsor plans to randomize a total of approximately 378 patients (instead of 240 patients specified in the protocol with Amendment 1, dated 11May2017), to allow for a potential 30% withdrawal rate or loss from the per-protocol population due to protocol deviations.

12.0 Data Review

Final data for analysis should always be cleaned prior to receipt by Clinical Programming. The purpose of this section is to indicate the history of the data and the process used to ensure that the data are acceptable for statistical analysis prior to database lock.

12.1 Data Handling and Transfer

PRA prepares and delivers electronic media to each site of their respective subjects' eCRFs and a complete set of subject eCRFs are delivered to each site and Lupin Inc.

The data in the following table will be provided by third-party vendors:

Data Type	**Vendor**
Central Lab	Eurofins

Central Spirometry	ERT
ECG	ERT
eDiary	ERT
Randomization	YPrime

All of the study data will be provided in SAS® dataset format (SAS version 9.4 or later) and converted to Study Data Tabulation Model (SDTM) version 1.4 using the Study Data Tabulation Model Implementation Guide (SDTMIG) Version 3.1.4.

12.2 Data Screening

Review of 2 pre-freeze TFL dry runs allow for further data screening prior to lock. The pre-freeze TFL will be discussed with the sponsor in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA biostatistician and the sponsor must approve database lock.

13.0 Statistical Methods

The statistical analyses will be reported using summary tables, figures, and data listings. The summary tables will be presented separately for Part 1 and Part 2 of the study. All analyses will use SAS version 9.4 or higher.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (std), median, minimum, and maximum values.

Unless otherwise noted, categorical variables will be summarized by counts and percentages of patients in corresponding categories. Percentages will be rounded to one decimal place except for 100%, which will be displayed without any decimal places, and zero counts, for which the percentage will be displayed as zero percent.

Raw data obtained from eCRFs and transferred from third-part vendors and derived data will be included in data listings.

13.1 Subject Disposition

The number and percentage of patients with informed consent, screened, screen failure, randomization failure, randomized/enrolled, and analysis population will be presented, together with the number and percentage of patients who withdraw from the study prematurely and are excluded from a particular analysis population, and a breakdown of the corresponding reasons.

A tabulation of the number and percentage of patients randomized/enrolled at each center will also be presented.

13.2 Protocol Deviations

The study team and the sponsor will conduct on-going reviews of the deviation data throughout the study. The PP population must be identified prior to database lock.

Protocol deviation data will be categorized into one of the following categories:

- 01-Inclusion/Exclusion/Randomization Criteria
- 02-Continuation Criteria
- 03-Spirometry Evaluation
- 04-Study Procedures
- 05-Study Drug
- 06-Out of Window Visits
- 07-Informed Consent
- 08-Prohibited / Restricted Medications
- 09-Other
- 10-Diary
- 11-ICH/GCP

Each deviation will be further classified as major/minor as defined in the protocol deviation guidelines. A summary of the number of patients with major deviations will be presented by category and treatment for Part 1 and Part 2 of the study separately. All protocol deviation data will be listed.

13.3 Treatments

13.3.1 Extent of Study Drug Exposure

Summary statistics for study drug exposure for Part 1 include:

- Patients exposed to one or more treatments (1, 2 or 3)
- Patients exposed to a specific treatment (Lupin Tiotropium, SPIRIVA HANDIHALER or Placebo)

Summary statistics for study drug exposure for Part 2 include:

- Days of exposure

13.3.2 Prior and Concomitant Medications

A prior medication is defined as any medication started and stopped prior to the first randomized dose.

A concomitant medication is defined as any medication taken on or after the first randomized dose regardless of start day.

All medications will be coded using the WHO Drug Dictionary (version of September 2016), and Anatomical Therapeutic Chemical (ATC) classification system.

Prior and concomitant medications will be summarized by ATC classification for Part 1 and only concomitant medications will be summarized for Part 2. All prior and concomitant medications will be listed.

13.4 Demographic and Baseline Characteristics

Patient demographic and baseline characteristics will be summarized by treatment for the safety population, ITT population, PP population, and Part 2 of the study respectively and will include summary statistics for sex, age, age group (40 to <65, 65 to <75, ≥ 75), race, ethnicity, baseline height (cm), baseline weight (kg) and tobacco usage.

13.5 Medical History

Medical history will be summarized for Part 1 only. All medical history will be listed.

13.6 Efficacy Analyses

13.6.1 Primary Variable

The primary variable is the baseline-adjusted FEV_1 AUC_{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 1).

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

The SAS code for the model is as follows:

```
proc mixed data= final;

  class usubjid period treatment sequence;

  model Baseline-adjusted FEV1 AUC0-24h  = treatment period sequence /
solution ddfm=SAT;

  repeated period /type = un subject = usubjid;

  lsmeans treatment / alpha=0.05 cl diff;

run;
```

where

- usubjid = patient
- period = treatment period
- sequence = treatment sequence

13.6.2 Statistical Analysis for the Primary Variable

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

The hypotheses planned to be tested for the Superiority analysis are:

H_{01}: $\mu_T = \mu_P$ vs. H_{11}: $\mu_T \neq \mu_P$ and

H_{02}: $\mu_R = \mu_P$ vs. H_{12}: $\mu_R \neq \mu_P$

where μ_T = mean of baseline adjust FEV_1 AUC_{0-24} for the Test Group and

μ_R= mean of baseline adjust FEV_1 AUC_{0-24} for the Reference Group and

μ_P= mean of baseline adjust FEV_1 AUC_{0-24} for the Placebo Group

Study sensitivity will be demonstrated if the Reference (R) product is shown to be statistically superior to Placebo (P) ($p < 0.05$ [two-tailed]). Efficacy of the Test product will be demonstrated if the Test (T) product is shown to be statistically superior to Placebo (P) ($p < 0.05$ [two-tailed]). For these comparisons, the repeated measures model described in Section 13.6.1 will be applied to the ITT population.

13.6.2.2 Establishing Bioequivalence between Test (T) and Reference (R) products

The hypotheses planned to be tested for the BE analysis are:

H_0: $\mu_T / \mu_R \leq 0.8$ or $\mu_T / \mu_R \geq 1.25$

H_1: $0.8 < \mu_T / \mu_R < 1.25$

where μ_T = mean of the baseline adjusted FEV_1 AUC_{0-24} for Test Group, and

μ_R= mean of the baseline adjusted FEV_1 AUC_{0-24} for Reference Group

The analysis of the primary endpoint for BE will be the repeated measures analysis (described in the section 13.6.1) performed on the PP Analysis Set which will include all patients in the ITT population except those who had major protocol deviations.

The extension of Fieller's theorem to a 3-way crossover will be used as the primary method to assess the bioequivalence of the Test (T) and Reference (R) products. An analysis that applies Fieller's theorem only to the data of the Test (T) and Reference (R) products (i.e. ignoring data from the placebo treatment) will also be performed as a secondary method of analysis.

We use Fieller's theorem to create a $100(1-2\alpha)\%$ CI for $\theta = \mu_T / \mu_R$. The CI (θ_1, θ_2) will include all values of θ for which the above null hypotheses are rejected.

Fieller's theorem considers the quantity $G = Y_T - \theta * Y_R$, in which Y_T and Y_R are unbiased estimates of μ_T and μ_R. Note that $E(G)=0$. We want to find all values of the parameter θ that do not reject H_0: $G=0$ versus H_1: $G \neq 0$.

To do this computationally, we fit the crossover model to obtain the estimated means Y_T and Y_R (i.e., the estimated LSMeans). For this study, there are 6 treatment sequences with 3 periods, which gives the following LSMeans for μ_T and μ_R, respectively:

$$\text{LSmean (Test)} = \mu + \tau_T + 1/3(\pi_1 + \pi_2 + \pi_3) + 1/6*(\delta_1+\delta_2+\delta_3+\delta_4+\delta_5+\delta_6) \quad (1)$$

$$\text{LSmean (Reference)} = \mu + \tau_R + 1/3(\pi_1 + \pi_2 + \pi_3) + 1/6*(\delta_1+\delta_2+\delta_3+\delta_4+\delta_5+\delta_6), \quad (2)$$

where μ is the intercept, the τ's are the treatment effects, the π's are the period effects, and the δ's are the sequence effects from the mixed model. The placebo data are included in the analysis but the placebo treatment effect, τ_P, is not needed in the bioequivalence assessment.

Writing G with equations (1) and (2):

$$G = (\tau_T - \theta^* \tau_R) + (1 - \theta)\,[\mu + 1/3(\pi_1 + \pi_2 + \pi_3) + 1/6(\delta_1 + ... + \delta_6)], \quad (3)$$

We use various values of θ to test H_0: G=0, and the 100(1-2α)% C.I. (θ_1, θ_2) is defined as largest/smallest values which do not reject the two α-level tests for H_0 above (Note: This is equivalent to a two one-sided tests procedure). The construction of the estimate statements in PROC MIXED will be based on equation (3), and will include data for all sequences, treatments and periods (i.e., placebo data will not be deleted). A sample SAS code for this mixed model is shown below, where the estimate statements are used to obtain the 90% confidence limits:

```
proc mixed data=<<dataset>>;
      class usubjid treatment period sequence;
      model auc0_24 = treatment period sequence / DDFM=SAT solution;
      repeated period /type = un subject = usubjid;

*** Sample estimate statements ***;
      estimate ' 0.720' intercept  0.280 treatment  0  -0.72  1
                  period 0.0933 0.0933 0.0933
                  sequence 0.0467 0.0467 0.0467 0.0467 0.0467 0.0467 /alpha=0.05 upper;
      estimate ' 0.721' intercept  0.279 treatment  0 -0.721  1
                  period  0.093  0.093  0.093
                  sequence 0.0465 0.0465 0.0465 0.0465 0.0465 0.0465 /alpha=0.05 upper;
      estimate ' 0.722' intercept  0.278 treatment  0 -0.722  1
                  period 0.0927 0.0927 0.0927
                  sequence 0.0463 0.0463 0.0463 0.0463 0.0463 0.0463/alpha=0.05 upper;
      ...
      estimate ' 1.369' intercept -0.369 treatment  0 -1.369  1
                  period -0.123 -0.123 -0.123
                  sequence -0.061 -0.061 -0.061 -0.061 -0.061 -0.061/alpha=0.05 lower;
      estimate ' 1.370' intercept -0.370 treatment  0  -1.37  1
                  period -0.123 -0.123 -0.123
                  sequence -0.062 -0.062 -0.062 -0.062 -0.062 -0.062/alpha=0.05 lower;
*** end of sample estimate statements ***;
      lsmeans treatment / alpha=0.05 cl diff cov;
run;
```

The Satterthwaite (DDFM=SAT) option provides the usual within-subject error degrees of freedom (DF) in the case of no missing data, and provides an adjustment to the error DF in the case of missing data. In either case, the error degrees of freedom will be quite large given the sample size of this trial so that the test statistic will have a near normal distribution.

Bioequivalence (BE) will be declared if the estimated 90% CI, (θ_1, θ_2) is entirely contained within the required BE limits of 0.80 to 1.25.

In addition to the 3-treatment effect model above, a separate analysis will be done using a 2-treatment approach, where Placebo (P) will be removed from the data. The construction of

the 90% C.I. (θ_1, θ_2) will use the same approach as defined above, with only the 2 active treatments needed in the estimate statement.

The above approach is equivalent to a closed form solution created by Fieller's theorem which only requires the Test (T) and Reference (R) LSMean estimates and their variances/covariances, and the critical value of the test statistic (T-test or Z-test).

13.6.2.3 Time to Maximum Bronchodilator Response

The time to maximum bronchodilator response (t_{max}) is defined as the time post-dosing of the maximum FEV1 value for a patient. This will be summarized using descriptive statistics by treatment and sequence.

13.6.3 Subgroup Analyses

No subgroup analyses are planned for this study.

13.6.4 Multiplicity

In this clinical trial, 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.

13.6.5 Pooling of Sites

Pooling of sites is not planned for this study.

13.7 Safety Analyses

Safety analyses will be summarized by treatment for the safety population as defined in Section 10.3 for Part 1 and Part 2 separately. Summary statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) will be included for continuous variables. Summarizations of categorical variables will be presented in tabular form (number of subjects and percentages). Safety of drug regimen will be assessed for adverse events, serious adverse events (SAEs), COPD exacerbations, vital signs, physical examinations, HEENT and chest examinations, ECG recordings, SABA (albuterol/salbutamol MDI) and concomitant medication use.

Listings of all safety measurements will be provided.

13.7.1 Adverse Events

The adverse event (AE) data will be summarized separately for Part 1 and Part 2 of the study by treatment and total.

Summaries of treatment-emergent adverse events (TEAEs), including the number and percentage of events reported, the number and percentage of patients reporting at least one AE, at least one severe AE, at least one treatment-related AE, at least one SAE, at least one treatment-related SAE, at least one non-SAE, at least one AE leading to withdrawal, and at least one AE resulting in death will be presented by treatment. Treatment-emergent adverse events are those which first occur or increase in severity or relationship to study drug after the first dose of study drug after randomization.

A breakdown of the number and percentage of patients reporting each adverse event, categorized by System Organ Class (SOC) and Preferred Term (PT) according to MedDRA 20.0, will be presented by treatment. Note that counting will be by patient not event and patients are only counted once within each SOC or PT.

A further tabulation of these data, categorized by relationship to study drug, will be presented. Relationship to study drug is categorized as Related/Not Related as recorded on the CRF.

A summary of events reported, categorized by severity (Mild, Moderate and Severe), will also be provided. Patients with multiple events within a particular body system or preferred term will be counted under the category of their most severe event within that SOC or PT.

A summary of SAEs, AEs leading to discontinuation and AEs leading to death will be provided by treatment, study part and total, grouped by SOC and PT.

Adverse events (AEs) that occur before randomization will be summarized separately and will be listed. Those patients will not be part of the safety population.

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed.

13.7.1.1 AE Summary for Part 1 of the Study

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

- The double-blinded study treatment period (Lupin Tiotropium Inhalation Powder, SPIRIVA HANDIHALER and Placebo)
- during washout
- during follow-up

Adverse events (AEs) occurring after a study treatment during a treatment day and the day immediately after the treatment will be assigned to the relevant study treatment group. AEs occurring between the treatment days will be assigned to the washout period.

13.7.1.2 AE Summary for Part 2 of the Study

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

- The open-label study treatment period, which starts after the first dose of Part 2
- During follow-up

13.7.2 Laboratory Data

Standard clinical laboratory tests including hematology, chemistry, urinalysis and immunochemistry (serum pregnancy) will be performed as indicated in Table 2 Schedule of Eventsusing a central laboratory as indicated in the study procedures manual.

All laboratory data (including re-tests) provided by the central laboratory will be listed.

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

13.7.4 Physical Examinations

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) to 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 PEs 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) to the end of the open-label extension using the 3 by 3 shift tables described above.

13.7.5 HEENT, Chest Examination, and Electrocardiograms (ECG)

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

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 four 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 four 3 by 3 shift tables where the shift is from screening (visit 1) to each of the 4 visits during treatment, 2 visits in Part 1 and 2 visits in Part 2.

13.7.6 COPD Exacerbations

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

13.7.7 Safety Spirometry

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

For Part 1, FEV_1 will be measured once daily: prior to dosing in the morning at approximately the same time each day.

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.

Values for each patient will be listed.

13.7.8 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.

13.7.9 Albuterol/Salbutamol Usage

Albuterol/Salbutamol usage will be summarized and/or listed by treatment and study period.

13.7.10 Urine/Serum Pregnancy Test

Urine/Serum pregnancy test results will be listed.

13.7.11 Urine Drug Screen

Urine drug screen results will be listed.

In addition, drug accountability, smoking restriction, DPI training and In-Check training will also be listed.

13.7.12 Inhaler Robustness (Part 1 and Part 2)

13.7.12.1 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 separately for Part 1 and Part 2.

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

- Misuse (impact, moisture, other) and
- Issues identified (hard to open cover/mouthpiece, hard to insert capsule, hard to pierce capsule, capsule not rattling with inhalation, hard to remove capsule, hard to close mouthpiece/cover, COPD worsening/seems ineffective, other)

13.7.12.2 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.

14.0 Validation

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

15.0 References

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Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomic Therapeutic Classification
AUC_{0-24}	Area Under The Curve From Time Zero To 24 Hours Post-dose
BE	Bioequivalence
BMI	Body Mass Index
CI	Confidence Interval
CV	Coefficient Of Variation
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
ER-S	Evaluating Respiratory Symptoms
ET	End Of Treatment
EXACT	Exacerbations Of Chronic Pulmonary Disease Tool
FEV1	Forced Expiratory Volume In The First Second
GCP	Good Clinical Practice
HEENT	Head, Ears, Eyes, Nose, And Throat
ICH	International Conference On Harmonization
ICS	Inhaled Corticosteroid
ID	Identification
IRT	Interactive Response Technology
ITT	Intention-To-Treat
LABA	Long-Acting Beta Agonist
LAMA	Long-Acting Anti-Muscarinic Agent
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary For Regulatory Activities
P	Placebo
PDV	Protocol Deviation
PK	Pharmacokinetic
PP	Per Protocol

PRO	Patient Reported Outcome
PT	Preferred Term
R	Reference
SABA	Short-Acting Bronchodilator
SAMA	Short-Acting Anti-Muscarinic Agent
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SI	International System
SOC	System Organ Class
T	Test
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization

Appendix 2: 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
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