CLINICAL STUDY PROTOCOL

Study Title: A Phase 3, 52-week, Randomized, Active-Controlled Parallel Group Study to Evaluate the Safety and Tolerability of Nebulized TD-4208 in Subjects with Chronic Obstructive Pulmonary Disease

Study Short Title: A 52-Week Parallel Group Safety Study of TD-4208 in COPD

Sponsor Study No.: 0128

Date: 21 January 2016, [redacted]

Test Product: TD-4208

US IND: [redacted]

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

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: Study TD-4208-0128: A Phase 3, 52-week, Randomized, Active-Controlled Parallel-Group Study to Evaluate the Safety and Tolerability of Nebulized TD-4208 in Subjects with Chronic Obstructive Pulmonary Disease

Study Short Title: A 52-Week Parallel Group Safety Study of TD-4208 in COPD

Estimated Number of Study Centers and Countries or Regions: Approximately [redacted] in the United States

Background and Rationale: [redacted]

PROTOCOL SYNOPSIS (CONTINUED)

Objectives: The primary objective of the study is as follows:

- To characterize the safety and tolerability of TD-4208 administered once daily for 52 weeks in a population of patients with moderate to very severe COPD

The exploratory objectives of the study are:

[redacted]

Study Design: This is a randomized, active-controlled, parallel-group study.

Each subject will receive treatment once daily for a total of 52 weeks. There will be three treatment groups (TD-4208 88 µg, TD-4208 175 µg and tiotropium 18 µg). TD-4208 will be administered as a 3 mL solution by inhalation using the [redacted] jet nebulizer and tiotropium will be administered as a dry powder capsule with the [redacted] device. The study will be double-blind with respect to the TD-4208 dose arms, and open-label with respect to the tiotropium control arm.

Subjects who are currently using LABA-containing products (LABA monotherapy or LABA/ICS fixed dose combination) will be permitted to continue the use of these concomitant medications throughout the course of the study. [redacted] Subjects that are not on a LABA-containing therapy when they enter the study and require a LABA-containing therapy to treat a COPD exacerbation (either temporarily or from that point onwards) during the treatment phase of the study will be allowed to remain in the study.

Screening will involve either one or two visits, depending on whether a washout period is required. The first visit will be an Initial Screening Visit (Visit 1A) when informed consent will be obtained and the subject's existing COPD medication will be assessed to decide whether any adjustments are required to comply with the requirements of the protocol. The subject will start a washout period only after signing the informed consent form.

After completing the washout (if required) the subject will return for further screening assessments, including an Ipratropium Reversibility Visit (Visit 1B) and baseline blood tests, ECG and vitals. It is only necessary to conduct the Initial Screening Visit (Visit 1A) and Ipratropium Reversibility Visit (Visit 1B) as separate visits if a washout period or a stable ICS/LABA run-in period (at least 30 days) is required. If a washout period is not required, these two visits may be performed as one visit.

If a washout period is required, the time from the Initial Screening Visit (Visit 1A) to Visit 1B will be no longer than 45 days.

At the Ipratropium Reversibility Visit (Visit 1B), the FEV_1 response to a nebulized dose of ipratropium (500 µg) will be tested to confirm the subject's COPD status and GOLD Stage {1}.

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

[redacted] A paper diary will be used for the recording of concomitant medications and adverse events.

All remaining inclusion and exclusion criteria will be reviewed at this Visit 1B

[redacted]

On Visit 2 (Day 1 of dosing), eligible subjects will be randomized to one of three treatment groups in the study. [redacted]

The treatment period will involve 6 visits:

- Visit 2 (Day 1)
- Visit 3 (Day 29)
- Visit 4 (Day 92)
- Visit 5 (Day 183)
- Visit 6 (Day 274)
- Visit 7 (Day 365)

All visits will have a visit window of ±5 days with the exception of Day 1. On these visit days, subjects will attend the clinic for assessment of pre-dose vital signs and ECG, trough (pre-dose) FEV_1, review of diary card for AEs and concomitant medications. Subjects will administer study medication under supervision at all clinic visits (with the exception of Visit 7) to assess nebulizer technique and to correct and retrain as required. PIFR (Peak Inspiratory Flow Rate) will be measured using the In-check Dial device for all subjects on Visit 2 prior to any assessments. ECG and vitals will be measured 60 minutes pre-dose and 10 minutes post-dose at these visits. On all visits with the exception of Visit 3, subjects will return the used vials of study medication and the study-specific rescue medication they have been issued. On all visits with the exception of Visit 7 (12 month visit), subjects will be issued sufficient study medication and rescue medication albuterol MDI to use for at least 3 months until the time of their next clinic visit.

Subjects with a concomitant LABA will dose the LABA or LABA/ICS immediately prior to nebulization with TD-4208 (or administration of tiotropium for those subjects in the tiotropium control arm) on all treatment visit days (Visit 2-7).

A diary will be used for recording study medication dosing times, study-specific rescue medication use, concomitant medications, and adverse events throughout the 52-week dosing period and the 1-week follow-up period [redacted]

A follow-up visit (Visit 8) by telephone will be performed 7 days after the final dose of study drug.

PROTOCOL SYNOPSIS (CONTINUED)

[redacted]

In a subset of subjects at specific sites (n=150 in total), subjects will undergo 24-hour Holter (Ambulatory ECG monitor) monitoring at Visit 1B, Visit 3 (1 month) and Visit 5 (6 months).

Subjects who experience 1 or 2 moderate or severe acute exacerbations of COPD (AECOPD) will be allowed to continue study drug throughout the exacerbation and will not be withdrawn from the study. All patients will be offered appropriate therapy for their AECOPD, including oral steroids, and/or antibiotics for a period of up to 14 days. Subjects will also be allowed to initiate LABA with or without inhaled corticosteroids (ICS) at the investigator's discretion in accordance with current COPD guidelines or to have their existing dose of ICS increased in response to the AECOPD. Subjects who experience >2 AECOPD episodes (each separated by more than 1 month to confirm that they are separate events) will be withdrawn from the study and treated appropriately.

An independent external Clinical Events Committee (CEC) will perform ongoing blinded review and adjudication of pre-specified cardiovascular (CV) events of interest collected in the electronic case report forms and other pre-specified subject-level source documents during the conduct of the study.

Duration of Study Participation: The screening period will be variable in length, depending on whether a washout period is required. The minimum duration from Visit 1A to Visit 2 is 1 week (7 days) and the maximum duration is 7 weeks (57 days). Randomization at Visit 2 will be followed by 12 months of dosing. A follow-up visit by telephone will be performed 7 days after the final treatment visit. The total number of days of participation for each completed subject therefore may range from a minimum of 54 weeks to a maximum of 60 weeks.

Number of Subjects per Group: Approximately 350 subjects will be enrolled in each of 3 treatment groups in a blinded 1:1:1 fashion (total of 1050 subjects).

Subjects who experience 1 or 2 moderate or severe acute exacerbations during the study will be treated as appropriate but will be permitted to continue in the study.

PROTOCOL SYNOPSIS (CONTINUED)

Study Population:

Patients with moderate to very severe COPD who meet the criteria for study enrollment.

Inclusion Criteria

1. Subject is a male or female subject 40 years of age or older (age at Visit 1A).
2. Subject is willing and able to provide signed and dated written informed consent to participate at Visit 1A prior to initiation of any study related procedures.
3. Subject is capable of performing reproducible spirometry maneuvers as described by current American Thoracic Society (ATS) Guidelines and has a post-ipratropium FEV_1/FVC ratio <0.7 at Visit 1B.
4. Subject has moderate-to-very severe stable COPD with a post-ipratropium FEV_1 less than 80% of predicted normal at Visit 1B and a post-ipratropium FEV_1 >700 mL at Visit 1B.
5. Subject has a current or past cigarette smoking history (or equivalent for cigar or pipe smoking history) of at least 10 pack-years.
6. Subject must be willing and able to attend study visits according to the visit schedule.
7. Women of either child bearing potential or non-child bearing potential as follows:
   - Women of childbearing potential must have documentation of a negative urine pregnancy test at Visit 1B and Visit 2 (prior to randomization). If a urine pregnancy test is positive, it must be confirmed via a second urine pregnancy test. All female subjects of childbearing potential must agree to use a highly effective method of birth control during the study and for at least 1 month after completion of study drug dosing.
     - A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as condom + diaphragm, condom + spermicide, diaphragm + spermicide, or intrauterine device [IUD] with documented failure rate of <1% per year, or oral/injectable/implanted hormonal contraceptives used in combination with an additional barrier method.
     - Women are considered to be not of childbearing potential if they have had a total hysterectomy and/or bilateral tubal ligation (documentation for either must be provided before enrollment) or are at least 2 years postmenopausal.
8. Subject (or care giver) based on the investigator's assessment is able to properly prepare and administer study medication administered either by nebulizer or [redacted]

PROTOCOL SYNOPSIS (CONTINUED)

Exclusion Criteria:

1. Females who are pregnant, lactating, breastfeeding or planning to become pregnant during the study.
2. Subject has a significant respiratory disease or disorder other than COPD that, in the opinion of the investigator, would affect the interpretation of data from this study, including but not limited to restrictive lung disorders, benign or malignant tumors of the lung, chronic pulmonary infections such as tuberculosis, occupational lung disease such as silicosis or asbestosis, inflammatory disorders of the lung, alpha-1-antitrypsin deficiency, and/or abnormalities of the chest wall or musculature (e.g., scoliosis, myasthenia gravis, phrenic nerve palsy).
3. Subject has a history of cancer of any organ, treated or untreated in the 5 years prior to Visit 1A (excludes localized basal cell or squamous cell carcinoma of the skin; localized prostate cancer in situ of grade 1; localized cervical cancer in situ of grade 0).
4. Subject has a concurrent disease or condition that, in the opinion of the investigator, would interfere with study participation or confound the evaluation of safety, tolerability, or pharmacokinetics of the study drug.
5. Subject has a history of reactions or hypersensitivity to inhaled or nebulized anticholinergics or short-acting beta-agonists.
6. Subject suffers from any medical condition that would preclude the use of inhaled anticholinergics, including narrow-angle glaucoma, symptomatic benign prostatic hyperplasia, bladder neck obstruction, or urinary retention.
7. Subject has a significantly increased risk of cardiovascular events, as indicated by a history at Visit 1A of myocardial infarction or unstable angina within the last 6 months, unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months, or New York Heart Association (NYHA) Class IV heart failure.
8. Subjects with clinically significant and uncontrolled hypertension, hypercholesterolemia or Type II diabetes mellitus.
9. Subject has been hospitalized for COPD or pneumonia within 8 weeks prior to Visit 1B.
10. Subject has used systemic corticosteroids within 6 weeks of Visit 1B.
11. Subject has used antibiotics for respiratory tract infections within 6 weeks of Visit 1B.
12. Subject has undergone lung volume reduction surgery or lobectomy within 12 months prior to Visit 1B
13. Subject has an abnormal and clinically significant 12-lead ECG findings at Visit 1B according to the following criteria:
    - atrial fibrillation (AF) with rapid ventricular rate >120 beats per minute
    - sustained or nonsustained ventricular tachycardia (VT)
    - second degree heart block Mobitz type II
    - third degree heart block (unless pacemaker or defibrillator had been inserted)
    - QT interval corrected for heart rate (QTcF) ≥500 milliseconds (msec)

PROTOCOL SYNOPSIS (CONTINUED)

14. Subject is unwilling or unable to stop the use of prohibited medications during the washout (if required) and treatment period and follow-up period of the study.
15. Subject has participated in a previous TD-4208 study.
16. Subject has used any other investigational medication within 30 days or five drug half-lives (whichever is longer) of screening.
17. Subject has a history of known or suspected alcohol or drug abuse within 2 years prior to screening, at the discretion of the investigator.
18. Subject is affiliated with the investigator site (e.g., investigator, study coordinator, site employee, etc.).
19. Subject requires long-term oxygen therapy (>15 hours a day) on a daily basis for chronic hypoxemia.
20. Subjects who are participating in the initiation phase of a supervised pulmonary rehabilitation program (subjects in the maintenance phase will be eligible).

Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment:

- TD-4208 solution for inhalation by jet nebulizer. Daily (QD) administration every morning for 52 weeks (dose 88 µg or 175 µg).

Reference Therapy, Dose, and Route of Administration; Regimen; Duration of Treatment:

- Tiotropium dry powder administered using capsules with the [redacted] device. Daily (QD) administration every morning for 52 weeks (dose 18 µg).

Statistical Methods

Sample Size:
Sample size (n=350 per group) is based on meeting ICH regulatory requirements for long-term safety for chronic use in this indication. [redacted]

Study Endpoints:
The primary endpoint(s) of this study assess the long-term safety and tolerability of TD-4208 in the treatment of COPD:

- Frequency and severity of adverse events, including exacerbations
- Vital signs
- Clinical laboratory evaluations
- 12-lead ECG changes from baseline

PROTOCOL SYNOPSIS (CONTINUED)

In addition, the following exploratory endpoints will be characterized:

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

Analysis:

All safety data will be presented in listings. Descriptive summary tables will be provided for treatment-emergent adverse events, laboratory evaluations, vital signs, 12-lead ECG parameters, and concomitant medications.

[redacted]

SCHEDULE OF STUDY PROCEDURES

Table 1: Schedule of Study Procedures

Procedure	Screening		Treatment Period						Early termination/ Withdrawal*	Telephone Follow-up
	Visit 1A[a]	Visit 1B[a]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7		Visit 8
			Day 1	Day 29 (±5)	Day 92 (±5)	Day 183 (±5)	Day 274 (±5)	Day 365 (±5)		7±2 days after Visit 7 or early termination
Informed Consent	■									
Medication and Medical History	■									
Washout of COPD Medications (as required)	■									
Physical examination		■				■		■	■	
Height and Weight		■						■	■	
PIFR			■							
Vital Signs[b]		■	■	■	■	■	■	■	■	
ECG (12-lead)[b]		■	■	■	■	■	■	■	■	
24 hour Holter monitor (substudy subjects only)[c]		■		■		■				
Ipratropium Reversibility[d]		■								
Hematology, Serum Chemistry, Urinalysis		■	■	■	■	■	■	■	■	
Urine Pregnancy Test[e]		■	■[e]	■	■	■	■	■	■	
[redacted]	[redacted]									
Review Inclusion/Exclusion Criteria	■	■	■							
Randomization			■							
Baseline [redacted] Spirometry			[redacted]							
LABA Dosing (as appropriate)			■	■	■	■	■	■		
Study Drug Dosing[h]			■	■	■	■	■			
[redacted]	[redacted]									
Concomitant Medications	■	■	■	■	■	■	■	■	■	■

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

Procedure	Screening		Treatment Period						Early termination/ Withdrawal*	Telephone Follow-up
	Visit 1A[a]	Visit 1B[a]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7		Visit 8
			Day 1	Day 29 (±5)	Day 92 (±5)	Day 183 (±5)	Day 274 (±5)	Day 365 (±5)		7±2 days after Visit 7 or early termination
Adverse Events		■	■	■	■	■	■	■	■	■
Dispensing of study drug for home use			■	■	■	■	■			
Collect and reconcile returned study drug				■	■	■	■	■	■	
Dispense Rescue Medication as needed	■		■	■	■	■	■			
Collect and reconcile returned rescue medication (as appropriate)			■	■	■	■	■	■	■	
Training on use of Diaries		■								
Dispense Diaries[k]		■								
Review/Collect Diaries			■	■	■	■	■	■	■	
Assess compliance				■	■	■	■	■	■	
Demonstrate proper use of nebulizer or [redacted] and retrain as necessary			■	■	■	■	■			

a The duration of each of the screening visits is approximately 1 hour for Visit 1A and 4 hours for Visit 1B. Visit 1A and 1B may be conducted on the same day if a washout period is not required.

b Vital signs and ECG performed at approximately 60 min pre-dose and at 10 minutes post dose. Subjects need to be resting in a semi-recumbent position approximately 5 minutes prior to assessment of vital signs and ECG. The sequence of performing these procedures at each visit is vital signs, then ECG followed by spirometry. ECG and Vitals done at the screening visit (1B) will be done once, prior to the ipratropium reversibility testing, and once at Visit 7.

c The 24 hour Holter will be performed at selected sites as a substudy.

d Spirometry will be performed pre-dose and 45 min post-dose for ipratropium reversibility.

e Urine pregnancy test performed prior to randomization (as applicable).

f A Treatment Satisfaction Questionnaire will be performed by the subject to determine baseline characteristics related to preferences for drug administration and, at the end of the study to determine [redacted] with study drug.

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

g Spirometry measurements will be performed 45 and 15 minutes pre-dose. At Visit 7 spirometry will be performed as a trough measurement, however study drug will not be administered.

h Study drug dosing will be in-clinic on study visit days. The last dose of study drug will be at home the day before on Day 364.

i [redacted]

k Diaries will be used to collect timing of study drug dosing, [redacted], concomitant medications, and adverse events.

* All Subjects who terminate early, regardless of reason, will have a 12 month follow-up telephone call to determine vital status.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
ACh	Acetylcholine
AE	adverse event
AECOPD	acute exacerbations of chronic obstructive pulmonary disease
ALT	alanine aminotransferase
ASM	airway smooth muscle
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under concentration curve
AUC_{0-t}	area under the concentration-versus-time curve calculated from time zero to the last detectable time point
BDI/TDI	Baseline Dyspnea Index / Transitional Dyspnea Index
BP	blood pressure
CL_r	renal clearance calculated as Ae/AUC_{0-t}
C_{max}	observed maximum concentration
CEC	Clinical Events Committee
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
COA	Clinical outcome assessment
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRU	clinical research unit
DPI	dry powder inhaler
ECG	Electrocardiogram
EDC	electronic data capture
EXACT	Exacerbations in COPD Tool
FEV_1	forced expiratory volume in 1 second
FPM	fine particle mass
FTIH	first time in human
FVC	forced vital capacity
GCP	Good Clinical Practice
hERG	human ether-à-go-go-related gene
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization (Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IH	Inhalation

Abbreviation	Description
IRB	Institutional Review Board
LABA	long-acting $beta_2$ agonist
LAMA	long-acting muscarinic antagonist
LTOT	Long Term Oxygen Therapy
mAChR	muscarinic acetylcholine receptor
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
MDI	Metered-dose inhaler
mMRC	Modified Medical Research Council Dyspnea Index
M_1	muscarinic receptor 1 (subtype)
M_2	muscarinic receptor 2 (subtype)
M_3	muscarinic receptor 3 (subtype)
M_4	muscarinic receptor 4 (subtype)
M_5	muscarinic receptor 5 (subtype)
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PE	physical examination
PIFR	Peak Inspiratory Flow Rate
PFM	peak flow meter
PI	principal investigator
PK	pharmacokinetic(s)
PRO	Patient Reported Outcome
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	respiratory rate
SABA	short-acting $beta_2$ agonist
SAE	serious adverse event
SGRQ	St. George’s Respiratory Questionnaire
SOP	standard operating procedure
$t_{1/2}$	terminal half-life, estimated as ln 2/λz where λz is the terminal elimination rate constant determined by the slope of the terminal phase of the plasma concentration-versus-time curve
T_{max}	time to maximum concentration

1 INTRODUCTION

Pharmacologic treatment of chronic obstructive pulmonary disease (COPD) with bronchodilators is central to the management of both the symptoms and the long term risks of the condition. Long-acting inhaled bronchodilators are convenient and may be more effective for long-term symptom relief than short-acting bronchodilators; accordingly, widely-accepted treatment guidelines such as those produced by the Global Initiative for the Treatment of Obstructive Lung Disease (GOLD) recommend the use of long-acting muscarinic antagonist (LAMA) bronchodilators as first-line therapies for subjects with persistent COPD symptoms {1}. For some patients, bronchodilator therapy is most effectively provided using a nebulizer device. TD-4208 is designed as a once-daily agent to be administered using a standard jet nebulizer.

1.1 Background and Rationale

1.2 Nonclinical Profile

A review of the nonclinical profile of TD-4208 can be found in the current version of the TD-4208 Investigator's Brochure (IB). The following is a brief summary of the pertinent findings.

1.2.1 Pharmacology

[redacted] Overall, the pharmacology of TD-4208, when administered into the lungs, is consistent with that of a long-acting muscarinic antagonist and demonstrates good selectivity for lung versus systemic effects.

Safety pharmacology studies for TD-4208 included assessments of potential effects on cardiovascular and respiratory function and for potential neurobehavioral effects. These studies are summarized in the Investigator's Brochure

1.2.2 Toxicology

The toxicology assessment of TD-4208 included single-dose, repeated-dose and genetic toxicity studies. The results of these studies are summarized in the Investigator's Brochure.

1.2.3 Pharmacokinetics

The nonclinical pharmacokinetic assessment of TD-4208 included single and repeat-dose pharmacokinetic studies in animals and an evaluation of the metabolic fate and drug-drug interaction potential of TD-4208. TD-4208 PK is characterized by high selectivity for lung tissue and low systemic plasma concentrations after inhaled administration. There is a low potential for drug-drug interactions. The results of these studies are summarized in the Investigator's Brochure.

1.3 Clinical Experience

[redacted]

[redacted]

[redacted]

[redacted]

1.4 Risks and Benefits

Subjects participating in this study may be at risk of experiencing adverse events related to muscarinic antagonism, including headache, mouth dryness, constipation, blurred vision, dizziness and urinary retention.

Subjects participating in this study may experience discomfort due to repeated blood sampling.

During the single dose study in which TD-4208 was administered as a dry powder, the most common adverse events were dysgeusia and headache.

In Study [redacted] a single nebulized dose (350 or 700 µg) of TD-4208 was administered to COPD subjects according to a crossover design. The study also involved ipratropium and placebo. Adverse events were generally mild and occurred with similar frequencies in all periods of the study – including the placebo period. The most common adverse events were headache and dyspnea. In Study [redacted] subjects with COPD received doses ranging between 22 and 700 µg (or placebo) once daily for 7 days. Each subject was assigned to 5 different treatment periods with a 2-week washout between each period. A range of adverse events occurred in this population most of which were consistent with the

underlying disease state (COPD) and not unanticipated in a study of this duration. There were no deaths. There were three SAEs (pneumonia, transient ischemic attack and chest pain (non-ischemic); none of which were attributed to study drug. Other adverse events were generally mild and occurred with similar frequencies in all treatment periods including the placebo period. The most common adverse events reported in this study were headache, cough and dyspnea.

In Study [redacted], the most common adverse event was dyspnea. There was one serious adverse event, a death, in the study. This event occurred in a 57 year old female subject during the washout period following completion of the 7-day 175 µg dosing period. Prior to the subject being discharged from the unit after the routine 24-hour in-patient stay on Day 7, the investigator had obtained a history, performed a physical examination and obtained an ECG on the subject. There were no abnormalities observed at the time of these evaluations. An autopsy was performed and reported 95% and 70% occlusion of the left and right coronary artery respectively. The coroner reported the cause of death as coronary artery insufficiency due to atherosclerosis. The investigator assessed the event as unrelated to study medication.

Administration of placebo in study [redacted] resulted in asymptomatic declines in FEV_1 of >15% in 42.2% of patients, and this result was also observed following the evening dose of placebo in the 175 µg QD dosing arm. No administration-related bronchospasm was reported in the study. The phenomenon appeared to be short-lived following administration, resolved within one hour of dosing and was blunted or ablated by the presence of TD-4208. The immediate postdose transient decline in FEV_1 that was observed with TD-4208 appears to be similar to what has been observed with other nebulized products that use nebulized citrate-buffered 0.9% saline as a vehicle. This effect is consistent with evidence in patients with COPD of a transient decrease in FEV_1 following inhalation of normal (0.9%) saline despite the pre-administration of a short-acting bronchodilator, such as albuterol.

In Study [redacted], the most common adverse events were dyspnea, cough, chronic obstructive pulmonary disease, back pain, and oropharyngeal pain. There were 4 SAEs reported in the study. These included (worsening) hypertension (175 µg), intestinal obstruction (350 µg), and unstable angina (175 µg); all were considered unrelated to study drug by the blinded Investigator on the basis of previous medical history and timing of the event. The fourth event, supraventricular tachycardia (44 µg), was considered possibly related by the blinded

Investigator; subsequent, review of all the available cardiovascular data including the pre-randomization Holter record by an independent cardiologist concluded that the supraventricular tachycardia (SVTs) were not likely to represent a study drug-induced change and represented only a slight worsening of pre-existing SVTs.

Clinically significant bronchodilation has been observed in each of the study populations of COPD subjects thus far in the development program, however TD-4208 is an investigational drug and its benefits and risks continue to be evaluated in phase 3.

2 OBJECTIVES

The primary objective of the study is:

- To characterize the safety and tolerability of TD-4208 administered once daily for 52 weeks in a population of patients with moderate to very severe COPD

The exploratory objectives of the study are:

[redacted]

3 STUDY DESIGN

3.1 Overview

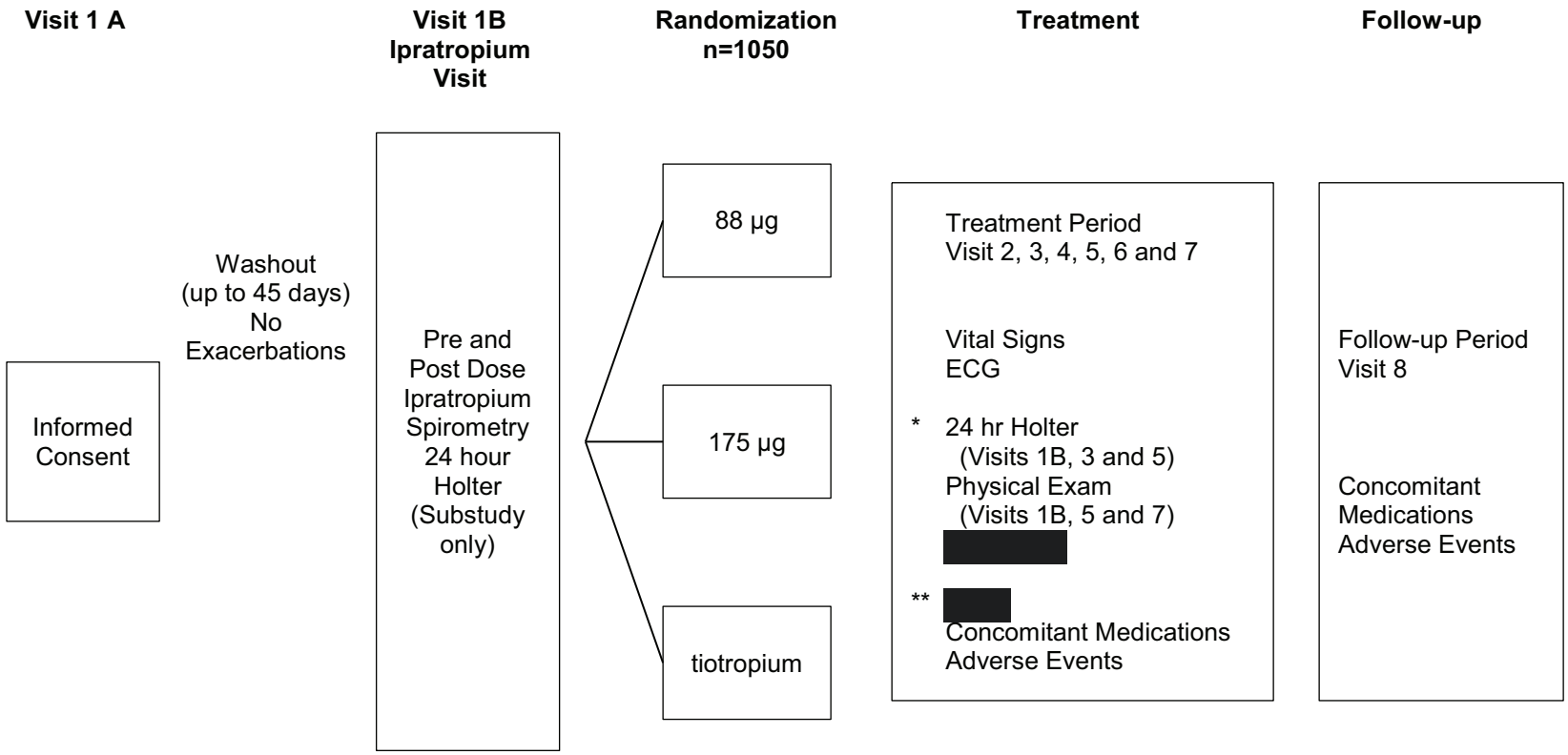
This is a randomized, active-controlled, parallel-group study. Each subject will receive treatment once daily in the morning for a total of 52 weeks. There will be three treatment groups (TD-4208 88 µg, TD-4208 175 µg, and tiotropium 18 µg). TD-4208 will be administered as a 3 mL solution by inhalation using the [redacted] jet nebulizer and tiotropium as a dry powder capsules with the [redacted] device. The study will be double-blind with respect to the TD-4208 dose arms, and open-label with respect to the tiotropium control arm.

There will be 1050 subjects randomized [redacted] Screening will ensure that subjects are eligible for inclusion in the study. Subjects will undergo washout from prohibited medications as appropriate, including all products containing long-acting antimuscarinics [LAMA] (either in combination or alone). Patients who are currently on long-acting beta-agonists [LABA] (with or without inhaled corticosteroids) will be permitted to be enrolled in the study. Subjects that are not on a LABA or LABA / ICS when they enter the study and require a LABA or LABA/ICS to treat a COPD exacerbation at the discretion of the investigator in accordance with COPD guidelines will be allowed to remain in the study.

[redacted]

The study will consist of 1 or 2 screening visits, depending on whether a washout period is required and 6 treatment period visits and a telephone follow-up visit as shown in the study design schematic (Figure 1).

Figure 1: Study Design Schematic



* 24 Hour Holter for sub-study subjects only

** [redacted]

The procedures for each study visit are specified in the Schedule of Study Procedures and described in Section 6 Study Procedures.

3.2 Rationale for Study Design

This is a Phase 3 study to assess long term safety and tolerability of two doses (88 and 175 µg) of TD-4208 administered once-daily for 52 weeks. The active control group will be treated with tiotropium to allow comparisons to a LAMA that is commercially available. [redacted] The two doses were selected from the Phase 2 studies as appropriate doses with an optimal benefit:risk ratio to further characterize the safety and efficacy of TD-4208 in phase 3.

The study is designed as an active-controlled parallel-group study, with 350 subjects randomized to each treatment group [redacted]. This study increases the experience of TD-4208 dosing with a longer term treatment period compared to the Phase 2 studies. A parallel group design is suitable and practical to meet the objectives of the study. Study medication will be identical in appearance for each of the two doses of TD-4208, and both the study subjects and investigative site staff will remain blinded to the dose of TD-4208, however the tiotropium will be administered as an open-label treatment. Randomization allows for an unbiased assessment of treatment effects across the doses of TD-4208 tested, and provides for comparisons with open-label tiotropium. The duration of treatment is limited, and all subjects will have study-specific rescue medication (albuterol via MDI) provided for the full duration of the study, including during the screening and follow-up periods. Subjects who experience 1 or 2 moderate or severe acute exacerbations of COPD (AECOPD) will be allowed to continue study drug throughout the exacerbation and will not be withdrawn from the study. Any subjects who experience more than 2 exacerbations will be withdrawn and placed on appropriate therapy.

Subjects will be required to meet the standard spirometry definitions for moderate to very severe COPD (post-bronchodilator FEV_1/FVC ratio of <0.7 and a post-bronchodilator FEV_1<80% of predicted normal and a post-bronchodilator FEV_1 >700 mL, [NHANES III]) {5}. Subjects will be eligible for enrollment regardless of the improvement in their FEV_1 following ipratropium administration at screening. The inclusion of both highly responsive and poorly

responsive subjects from a broad range of disease severities in Phase 3 is intended to reflect the same population that was used in Phase 2 as well as the intended population if TD-4208 is approved. Patients who are already on a background of LABA-containing therapy (LABA alone or LABA/ICS) will be included and allowed to continue their concomitant LABA-containing therapy, to represent the concomitant therapies that subjects may be using if TD-4208 is approved.

Assessments of subject status and safety laboratory evaluations are designed to ensure subject safety and compliance with medication during the course of the 52 week period of dosing.

3.3 Selection of Doses and Duration of Treatment

The doses selected for this study have been chosen on the basis of experience with TD-4208 in 4 previously conducted studies where study drug was administered via nebulizer – studies 0059, 0091, 0116, and 0117.

Study 0059 examined single doses of 350 and 700 µg and Study 0091 examined doses of 22, 44, 88, 175, 350 and 700 µg once daily in a 7 day placebo controlled crossover design. Twenty four hours after the last (Day 7) dose in each period, the FEV_1 for each of the doses of TD-4208 was statistically greater than that following placebo, although 22 and 44 µg produced sub-therapeutic effects. At doses from 88-350 µg there was a greater increase in lung function (both trough and weighted mean). There appeared to be no additional benefit of dosing with 700 µg compared with 350 µg.

All doses were well tolerated in Study 0091, adverse events were infrequent throughout the study and there was no evidence of a dose response relationship for TD-4208 or even an excess of AEs in any of treatment arms in relation to the observed adverse event rates in the placebo arm.

Study 0117 was a definitive dose-ranging study and evaluated the doses of 44, 88, 175 and 350 µg once daily over 28 days in a randomized, placebo-controlled parallel group design. The lowest and highest doses in this range represented the upper and lower parts of the dose response curve on which to assess the 88 and 175 µg treatment effects. TD-4208 was generally well tolerated and 88 µg was confirmed as the minimally effective dose. The 44 µg dose was subeffective and was not statistically significant compared to placebo. The fourth study was a mechanistic study to assess dose interval and tested doses of 175 µg QD and

44 µg BID in a randomized, placebo-controlled crossover study. The study confirmed QD dosing as the appropriate dose frequency for TD-4208, with no advantage observed with dosing a lower total daily dose given in divided intervals (44 µg BID).

The study will evaluateTD-4208 QD at the two doses 88 µg and 175 µg in COPD. These doses were selected from the Phase 2B dose-ranging study (Study 0117) as the two doses having the optimal benefit:risk ratio in terms of efficacy and safety to move forward and further investigate in the Phase 3 program.

3.4 Study Endpoints

The primary endpoint(s) of this study assess the long-term safety and tolerability of TD-4208 in the treatment of COPD:

- Frequency and severity of adverse events, including exacerbations
- Vital signs
- Clinical laboratory evaluations
- 12-lead ECG changes from baseline

In addition, the following exploratory endpoints will be characterized:

- [redacted]

3.5 Minimization of Bias

Bias will be minimized through the use of randomization and blinding (with regard to TD-4208 dose).

3.5.1 Blinding

All study subjects, study investigators and their staff, and the Sponsor's staff involved in the conduct of the study will be blinded to treatment assignment with regard to dose of TD-4208. The tiotropium comparator arm will be open-label, and subjects will be assigned in random order to tiotropium or TD-4208 according to the randomization schedule. The only personnel who will have access to the randomization schedule before database lock are:

- The nominated statistician at the Contract Research Organization responsible for generation of the randomization schedule.

In the event of an untoward safety observation, the investigator may unblind a subject's treatment assignment using the IWRS. If possible, the investigator should first contact the Theravance Clinical Study Director before unblinding. The blind should be broken only if knowledge of the subject's study medication would affect subsequent treatment and such knowledge is required for the clinical management of the subject. Any investigator unblinding will be documented within the appropriate section of the subject's case report from (CRF) and will be captured in the IWRS.

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

3.5.2 Treatment Assignment

After a subject is screened and the investigator determines that the subject is eligible for enrollment, the subject will be randomized to one of the three treatment groups using IWRS (Day 1 visit). [redacted]

4 STUDY POPULATION

The following inclusion and exclusion criteria must be satisfied before subjects are entered into the study:

4.1 Inclusion Criteria

1. Subject is a male or female subject 40 years of age or older (age at Visit 1A).
2. Subject is willing and able to provide signed and dated written informed consent to participate at Visit 1A prior to initiation of any study related procedures.
3. Subject is capable of performing reproducible spirometry maneuvers as described by current American Thoracic Society (ATS) Guidelines and has a post-ipratropium FEV_1/FVC ratio <0.7 at Visit 1B.
4. Subject has moderate to very severe stable COPD with a post-ipratropium FEV_1 less than 80% of predicted normal at Visit 1B and a post-ipratropium FEV_1 >700 mL at Visit 1B.
5. Subject has a current or past cigarette smoking history (or equivalent for cigar or pipe smoking history) of at least 10 pack-years.
6. Subject must be willing and able to attend study visits according to the visit schedule.
7. Women of either child bearing potential or non-child bearing potential as follows:
    - Women of childbearing potential must have documentation of a negative urine pregnancy test at Visit 1B and Visit 2 (prior to randomization). If a urine pregnancy test is positive, it must be confirmed via a second urine pregnancy test. All female subjects of childbearing potential must agree to use a highly effective method of birth control during the study and for at least 1 month after completion of study drug dosing.
        - A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as condom + diaphragm, condom + spermicide, diaphragm + spermicide, or intrauterine device [IUD] with documented failure rate of <1% per year, or oral/injectable/implanted hormonal contraceptives used in combination with an additional barrier method.
    - Women are considered to be not of childbearing potential if they have had a total hysterectomy and/or bilateral tubal ligation (documentation for either must be provided before enrollment) or are at least 2 years postmenopausal.
8. Subject (or care giver) based on the investigator's assessment is able to properly prepare and administer study medication administered either by nebulizer or [redacted].

4.2 Exclusion Criteria

1. Females who are pregnant, lactating, breastfeeding or planning to become pregnant during the study.
2. Subject has a significant respiratory disease or disorder other than COPD that, in the opinion of the investigator, would affect the interpretation of data from this study, including but not limited to restrictive lung disorders, benign or malignant tumors of the lung, chronic pulmonary infections such as tuberculosis, occupational lung disease such as silicosis or asbestosis, inflammatory disorders of the lung, alpha-1-antitrypsin deficiency, and/or abnormalities of the chest wall or musculature (e.g., scoliosis, myasthenia gravis, phrenic nerve palsy).
3. Subject has a history of cancer of any organ, treated or untreated in the 5 years prior to Visit 1A (excludes localized basal cell or squamous cell carcinoma of the skin; localized prostate cancer in situ of grade 1; localized cervical cancer in situ of grade 0).
4. Subject has a concurrent disease or condition that, in the opinion of the investigator, would interfere with study participation or confound the evaluation of safety, tolerability, or pharmacokinetics of the study drug.
5. Subject has a history of reactions or hypersensitivity to inhaled or nebulized anticholinergics or short-acting beta-agonists.
6. Subject suffers from any medical condition that would preclude the use of inhaled anticholinergics, including narrow-angle glaucoma, symptomatic benign prostatic hyperplasia, bladder neck obstruction, or urinary retention.
7. Subject has a significantly increased risk of cardiovascular events, as indicated by a history at Visit 1A of myocardial infarction or unstable angina within the last 6 months, unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months, or New York Heart Association (NYHA) Class IV heart failure.
8. Subjects with clinically significant and uncontrolled hypertension, hypercholesterolemia or Type II diabetes mellitus.
9. Subject has been hospitalized for COPD or pneumonia within 8 weeks prior to Visit 1B.
10. Subject has used systemic corticosteroids within 6 weeks of Visit 1B.
11. Subject has used antibiotics for respiratory tract infections within 6 weeks of Visit 1B.
12. Subject has undergone lung volume reduction surgery or lobectomy within 12 months prior to Visit 1B.
13. Subject has an abnormal and clinically significant 12-lead ECG findings at Visit 1B according to the following criteria:
    - atrial fibrillation (AF) with rapid ventricular rate >120 beats per minute
    - sustained or nonsustained ventricular tachycardia (VT)
    - second degree heart block Mobitz type II
    - third degree heart block (unless pacemaker or defibrillator had been inserted)
    - QT interval corrected for heart rate (QTcF) ≥500 milliseconds (msec).
14. Subject is unwilling or unable to stop the use of prohibited medications during the washout (if required) and treatment period and follow-up period of the study.
15. Subject has participated in a previous TD-4208 study.

16. Subject has used any other investigational medication within 30 days or five drug half-lives (whichever is longer) of screening.
17. Subject has a history of known or suspected alcohol or drug abuse within 2 years prior to screening, at the discretion of the investigator.
18. Subject is affiliated with the investigator site (e.g., investigator, study coordinator, site employee, etc.).
19. Subject requires long-term oxygen therapy (>15 hours a day) on a daily basis for chronic hypoxemia.
20. Subjects who are participating in the initiation phase of a supervised pulmonary rehabilitation program (subjects in the maintenance phase will be eligible).

5 STUDY DRUGS

All study drug supplied by the Sponsor must be stored in a secure refrigerated location accessible only to designated study personnel. The assignment of subjects to one of the treatment groups will be accomplished by randomizing the subject through the IWRS. Each drug kit will contain a unique kit number which will be provided by the IWRS on Day 1 and at each of the study visits thereafter to identify the study drug kits to dispense to a particular subject.

Study drug will be administered to the subjects under supervision at the clinic during study visits on the morning of Day 1, Day 29, Day 92, Day 183, and Day 274. Study drug will not be administered at the last study visit on Day 365 as the last dose of study drug will be at home the day before on Day 364. Subjects will be dispensed study drug to take home with them on Day 1 for home administration each morning on Day 2 through 28, and similarly at each study visit thereafter to provide a sufficient supply for home administration in between study visits. The time window for study drug administration will be between 6 am and 11 am. All subjects must return all used and unused study drug on each of the study visits where this applies.

More information regarding study drug dispensing, administration, handling and storage are provided in a separate Pharmacy Manual.

5.1 Description of Study Drugs

5.1.1 TD-4208

TD-4208 free base has a molecular weight of [redacted] It is a [redacted]

[redacted]

TD-4208 and its placebo must be stored [redacted] accessible only to designated study personnel. On days in which the study medication is administered in the clinic on the day it is dispensed, [redacted]

[redacted]

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

5.1.2 Tiotropium

Tiotropium will be provided in the commercially available presentation which consists of [redacted] dry powder capsules administered using the [redacted] device. The drug should be stored at 25°C (77°F) with excursions permitted to 15°C to 30°C (59°C to 86°F).

Detailed instructions for administration will be provided in the Package Insert.

5.1.3 Agents for Reversibility Testing

5.1.3.1 Ipratropium

Ipratropium will be provided as a solution for administration via jet nebulizer for reversibility testing during screening, at a dose of 500 µg. Refer to the package insert for further information.

5.1.4 Agents for Rescue Therapy

5.1.4.1 Albuterol

Subjects who are randomized to the study will return the study-specific rescue medication they used during screening at Visit 2 and will be issued with a new study-specific rescue medication albuterol MDI.

Subjects will be dispensed rescue medication as needed on each of the remaining study visits to ensure they have adequate access to rescue medication throughout the study. It is important to dispense a sufficient quantity of albuterol MDI so that the subject does not run out of albuterol in between study visits based on the subject's normal usage. Subjects will bring all rescue medication they have been dispensed as they return for each study visit for reconciliation.

Refer to the package insert for further information.

5.2 Dose Administration

5.2.1 TD-4208

TD-4208 will be administered on the morning of Day 1 in the clinic. The subject will take the jet nebulizer, compressor and study drug home where dosing will occur every morning at approximately the same time. This time will be chosen based on convenience for the study subject and will be within the window of 6 am and 11 am. At each of the remaining study visits subjects will be required to bring their nebulizer and compressor back to the clinic for in-clinic dosing on visit days. If a subject has taken their dose of study drug in the morning prior to their in-clinic visit, this visit will be rescheduled. At each study visit subjects will be dispensed sufficient study drug for home dosing until the time the subject returns for their next study visit.

Training on the home use of the nebulizer will take place after the subject is randomized on Visit 2 prior to discharge from the clinic. Subjects will be trained to administer the study drug until nebulization of the study drug solution is complete, which takes approximately 10 minutes and is evidenced by “spluttering” of the nebulizer. Administration will be once daily in the morning at approximately the same time each day and the time of administration will be recorded by the subject in their eDiary. This time will be chosen based on convenience for the subject and will remain the same for the duration of the study. The subject may receive additional instruction at the site based on the judgment of the investigator. Additional information on the training of the subject on home nebulization is contained in the Pharmacy Manual.

5.2.2 Tiotropium

Tiotropium will be administered on the morning of Day 1 (Visit 2) in the clinic.

The subject will take the [redacted] device and the tiotropium dry powder capsules home where dosing will occur every morning at approximately the same time. This time will be chosen based on convenience for the study subject and will be within the window of 6 am and 11 am. The time of administration will be recorded by the subject in their eDiary. At each of the remaining study visits subjects will be required to bring their [redacted] device and unused tiotropium capsules back to the clinic for in-clinic dosing on visit days. At each study visit subjects will be dispensed sufficient tiotropium capsules for home dosing until the time the subject returns for their next study visit.

Training on the home use of the [redacted] device will take place at Visit 2 after the subject is randomized. The subject may receive additional instruction at the site based on the judgment of the investigator. Additional information on the training of the subject on the use of the [redacted] device is contained in the Package Insert.

5.2.3 Agents Used for Reversibility Testing

5.2.3.1 Ipratropium

Ipratropium will be provided as 2.5 mL vials containing a solution of 500 µg to be administered via nebulizer. See package insert for further information.

5.2.4 Agents Used for Rescue Medication

5.2.4.1 Albuterol

Albuterol will be provided as a MDI for rescue medication on an as-needed basis and administered at a dosage of 90 µg per puff. See package insert for further information.

5.3 Treatment Compliance

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

The eDiaries will be used to record the timing of dosing by the subject (or caregiver).

5.4 Drug Accountability and Reconciliation

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

Study drug accountability will be performed at every study visit following Day 1 to document compliance with the dosing regimen. Subjects will be instructed to bring back all remaining study drug and all study drug packaging at each study visit for drug accountability.

Treatment compliance will be assessed by counting the empty foil pouches from the used study drug and the unused vials (for TD-4208) and used and unused blister cards (for tiotropium). If a subject does not return the foil pouches, the unused vials or blister cards it will be assumed that the subject did not administer the study drug. If a subject misses recording any dose of study drug based on the subject's eDiary the site should discuss the missing entries to determine if the missing entries are due to not recording the administration in the eDiary and remind the subject of the importance of recording this in their diary. Discrepancies between the subject's eDiary and the count of returned study drug should be documented in the source documents.

Subjects will record their use of study-specific rescue medication (albuterol) in their diaries, recording any use (or not) in each 24 hour period in the study including the screening and follow-up period.

6 STUDY PROCEDURES

6.1 Schedule of Study Procedures

The schedule of study procedures is summarized in Table 1.

Throughout the study investigators should conduct the order of the assessments for each study visit as indicated in the study procedures and strive to maintain consistency in this order. With the exception of Screening Visit 1, all study procedures for a visit must be completed on the same day. Any missed visits, test not done, or procedures that are not conducted must be reported as such on the electronic case report forms (eCRFs).

The scheduling of Visits 3, 4, 5, 6, and 7, are based on the date of occurrence of Visit 2 (Day 1 of the treatment period when the subject is randomized). If a visit does not occur on schedule, the following visits should still occur relative to when the Day 1 visit occurred. The Day 29 Visit will be allowed to have a visit window of 5 days on either side of the assigned date if scheduling does not allow for the subject to be seen on the assigned day. The visits thereafter (Visits 4, 5, 6, and 7) will also have a visit window of 5 days on either side of the assigned date. The follow-up visit should be scheduled 7 days after Visit 7, with a 2 day visit window on either side of the assigned date.

6.2 Total Blood Volume

The total volume of blood to be drawn from each subject for safety laboratory assessments for the entire period of the study is approximately 105 mL. Additional samples may be drawn for safety laboratory testing as considered necessary by the investigator.

6.3 Procedures by Visit

6.3.1 Screening

Screening assessments and study procedures outlined in this section can only be performed after obtaining informed consent. Importantly, this includes any washout of a subject's current medication for the purpose of participation in the study or changing a subject's combination medication containing an inhaled steroid to inhaled steroid monotherapy (see Table 2 for specific washout periods required).

Participants in this study who, at the time of screening are taking COPD medications requiring a washout will have two screening visits (1A and 1B). Long acting bronchodilators requiring a washout include LAMAs (tiotropium ([redacted]), glycopyrronium bromide, aclidinium ([redacted], umeclidinium ([redacted] or any other approved LAMA); combination LAMA/LABA products including [redacted], olodaterol/tiotropium or any other approved combination LAMA/LABA; and roflumilast (Table 2). The effects of the long acting agent will be washed out between Visits 1A and 1B and this washout period will be no longer than 45 days. Subjects not taking these long acting bronchodilators, or other COPD medications requiring a washout, at screening will need only one screening visit (1A/B).

Subjects on LABAs (e.g., salmeterol, indacaterol, vilanterol, formoterol, arformoterol, olodaterol) either alone or in combination with an ICS (e.g., fluticasone propionate, fluticasone fuorate, budesonide, ciclesonide, beclomethasone will not need to be washed out before enrolling in the study and will be allowed to be randomized on this background therapy.

The first visit will be Visit 1A (Initial Screening Visit) when informed consent will be obtained and the subject's existing COPD medication will be assessed to decide whether any adjustments are required to comply with the requirements of the protocol. The subject will start a washout period only after signing the informed consent form. After completing the washout (if required) the subject will return for Visit 1B (Ipratropium Reversibility Visit). It is only necessary to conduct Visit 1A and 1B as separate visits if a washout period is required. If a washout period is not required these two visits may be performed as one visit.

If a washout period or a stable ICS/LABA run-in period (at least 30 days) is required the time from the Initial Screening Visit to Visit 1B will be no longer than 45 days. If a washout period or a stable ICS/LABA run-in period (at least 30 days) is not required then the two screening visits (Visit 1A and Visit 1B) may be conducted as one visit. The time period from Visit 1B (i.e., the Ipratropium Reversibility Visit, whether this is combined with Visit 1A or not) until Day 1 of dosing (Visit 2), will be 7 to 12 days.

If a subject does not meet the eligibility criteria for reasons of a failed screening test due to a properly administered procedure, this test or procedure will not be allowed to be repeated and the subject should be screen failed. This includes spirometry, i.e., if a subject fails to

meet any spirometry related criteria after the first attempt the subject should similarly be screen failed.

6.3.1.1 Visit 1A (Initial Screening Visit) – (performed up to 45 days before Visit 1B)

The following procedures will be performed at this visit:

- Written informed consent after the nature of the study has been explained and before any study procedure is performed
- Complete Treatment Satisfaction Questionnaire
- Medication and medical history including an assessment of the subject's COPD medication
- Review of inclusion and exclusion criteria
- If required, based on the washout periods specified in Table 2, subject will begin their washout. If subject is receiving a combination COPD medication containing an inhaled steroid this may include changing this medication to an inhaled steroid monotherapy.
- Subject will be dispensed 1 inhaler of albuterol as rescue medication.

6.3.1.2 Visit 1B (Ipratropium Reversibility Visit) – (if a washout or a stable ICS/LABA run-in period (at least 30 days) is not required Visit 1A and 1B may be conducted as one visit)

The following procedures will be performed at this visit:

- Pre-dose of ipratropium
    - Vital signs. Subjects need to be resting in a semi-recumbent position approximately 5 minutes prior to assessment of vital signs and ECG.
    - ECG (12 lead)
    - Complete physical examination
    - Height and weight
- Spirometry reversibility testing pre- and post-dose ipratropium after withholding bronchodilators as specified in Table 2. Spirometry will be performed pre-dose and 45 minutes post-dose.
- Blood collection
    - Hematology
    - Serum chemistry
- Urine collection
    - Urinalysis (microscopy not required)
    - Urine pregnancy test in women of child bearing potential
- Review of inclusion and exclusion criteria
- Subject will be trained on and dispensed the diaries

- Concomitant medications
- Adverse events
- [redacted]
- Dispense diaries
- 24-hour Holter monitor applied (substudy subjects only)

  NOTE: Substudy subjects will be asked to return to the clinic the following day to have the Holter Monitor removed

6.3.2 Treatment and Follow-up Period

6.3.2.1 Visit 2

The following procedures will be performed at Visit 2. The timing of procedures pre-dose study drug administration is relative to the start of nebulization. The timing of procedures post-dose study drug administration is relative to the completion of nebulization.

Prior to any assessments on Visit 2, randomized subjects will measure their Peak Inspiratory Flow Rate (PIFR) using the In-check Dial device. This procedure will be performed by trained site staff. Subjects will perform three attempts with resistance dialed to [redacted] and three attempts without any resistance. The highest value of the three attempts for each setting will be recorded.

Procedures performed at the same timepoints will be performed in the following sequence - vital signs, then ECG, followed by spirometry. All attempts should be made to perform the spirometry at the required timepoints (i.e., the spirometry procedure will take priority over other procedures and if necessary the timing of the other procedures are approximate and may be adjusted to accomplish this requirement). Such adjustments will not be considered protocol deviations as long as the appropriate reason is documented in the source documents.

The sequence of events for the subject to follow at home will be as follows: recording in the eDiary whether albuterol was used or not in the last 24 hours and the start time of study drug nebulization, then administering study drug. It is important at study visits that the trough FEV_1 be done before receiving study drug (or LABA if applicable). If the subject is taking a LABA this must be taken immediately before the study drug. Subject should not have taken their LABA for approximately 12 hours (if on BID therapy) or approximately 24 hours (if on QD therapy) prior to taking it in the clinic.

- [redacted]
- Vital signs (approximately 60 min pre-dose and 10 minutes post dose).
- 12-lead ECG (approximately 60 minutes pre-dose and 10 minutes post dose)
- Blood collection
    - Hematology
    - Serum chemistry
- Urine collection
    - Urinalysis (microscopy not required)
    - Urine pregnancy test in women of child bearing potential
- Review of inclusion and exclusion criteria
- Randomization (subject eligibility must be confirmed by investigator before randomizing subject)
- [redacted]
- Administer LABA containing product (as appropriate for those on existing LABA-containing therapy)
- Study drug dosing via nebulizer (if randomized to TD-4208) or the [redacted] (if randomized to tiotropium). Training on the specific device will be performed as part of the first dose administered.
- Concomitant medications
- Adverse events
- Dispense study drug (IWRS will assign 1 kit)
- Collect and reconcile rescue medication as appropriate
- Dispense new rescue medication as needed (IWRS can assign 1 to 4 inhalers); the rescue medication used in screening will be collected

6.3.2.2 Visits 3, 4, 5, 6, and 7

The following procedures will be performed at these visits:

- [redacted]
- Vital signs (approximately 60 minutes pre-dose and 10 minutes post dose)
- 12-lead ECG (approximately 60 minutes pre-dose and 10 minutes post dose)
- Physical exam (at Visits 5 and 7 only)
- Weight (at Visit 7 only)
- Blood collection
    - Hematology

- Serum chemistry

- Urine collection
  - Urinalysis (microscopy not required)
  - Urine pregnancy test in women of child bearing potential
- Review of diary
- [redacted]
- Administer LABA containing product (as appropriate for those on existing LABA-containing therapy)
- Study drug dosing via nebulizer or [redacted] (as applicable) and retraining as necessary (at Visit 3, 4, 5, and 6 only)
- 24-hour Holter monitor applied (substudy subjects only) (Visits 3 & 5 only)

  NOTE: Substudy subjects will be asked to return to the clinic the following day to have the Holter Monitor removed
- Concomitant medications
- Adverse events
- Dispense study drug for home use (IWRS will assign kits at each visit as needed) (at Visit 3, 4, 5, and 6 only)
- Dispense rescue medication as needed
- Collect and reconcile returned study drug
- Collect and reconcile rescue medication as appropriate
- [redacted]
- Assess Compliance

6.3.3 Visit 8 (Telephone Follow-up)

The following reviews with the subject will take place via telephone.

- Concomitant medications
- Adverse events

6.3.4 Early Termination/Withdrawal Visit

- [redacted]
- [redacted]
- Vital signs
- Weight
- ECG
- Physical Exam
- Blood collection

  - Hematology
  - Serum chemistry
- Urine collection
  - Urinalysis (microscopy not required)
  - Urine pregnancy test in women of child bearing potential
- Review of diary
- [redacted]
- Concomitant medications
- Adverse events
- Collect and reconcile returned study drug
- Collect and reconcile rescue medication as appropriate
- [redacted]
- Assess Compliance

(In the instance of a subject terminating early due to an adverse event a telephone follow-up visit will be conducted 30 days afterwards to review concomitant medications and adverse events.)

All subjects who terminate early, regardless of the reason, will have a follow-up telephone call at 12 months from Day 1 (randomization) to determine their vital status.

6.3.5 Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the subject's request, or as deemed necessary by the investigator. The date and reason for the unscheduled visit should be recorded in the source documentation. The following activities may be completed at unscheduled visits as medically indicated:

- Medical history update
- Vital signs
- 12-lead ECG
- Laboratory assessment (hematology and chemistry to be performed by a central lab)
- Physical examination
- Record concomitant medications
- Record adverse events

6.4 Description of Study Assessments

6.4.1 Demographic and Baseline Assessments

After obtaining informed consent, each subject will be asked to provide a relevant medical history including medication history, concomitant medications, and demographic information including date of birth, sex, race, and ethnicity. The subject will also undergo a physical examination including vital signs, height, and weight, ECG, laboratory evaluations including hematology, serum chemistry, urinalysis, FEV_1 measurements (pre- and post-ipratropium inhalation and on a separate screening visit pre- and post-albuterol inhalation), and a urine pregnancy test for females of child-bearing potential.

[redacted]

6.4.3 Safety Assessments

6.4.3.1 Adverse Events

Adverse events will be reviewed and recorded from the signing of the informed consent form through the last day of the follow-up visit. Adverse events may be observed by the site study

personnel or spontaneously reported by the subject. Subjects will be reminded to call the site to report AEs that occur between visits.

6.4.3.2 Medical History

Complete medical history at screening will include evaluation for past and present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary, substance abuse, surgical history, or any other diseases or disorders.

Any changes that occur following the subject signing the informed consent form will be captured as adverse events.

6.4.3.3 Physical Examination

Physical examinations will include examination of the following: general appearance; head, ears, eyes, nose, and throat; neck, skin, cardiovascular system, respiratory system, abdominal system, lymphatic system, dermatologic system, musculoskeletal system, and nervous system.

6.4.3.4 Vital Signs

Blood pressure (BP), and heart rate (HR), will be recorded only once in the eCRF for each protocol specified time point; at screening only, a second measurement may be obtained to rule out sustained elevation/decrease of either systolic or diastolic blood pressure. BP will be measured manually using a mercury sphygmomanometer or calibrated automatic blood pressure device. HR will be measured by palpation of the radial pulse over a 60-second period or by the automated blood pressure device.

Vital signs (HR and BP) will be monitored at 60 minutes pre-dose and at 10 minutes post dose.

6.4.3.5 Laboratory Tests

A central lab will be used for all laboratory assessments. Specimen collections times are specified in the Schedule of Study Procedures and all assessments will be performed non-fasting.

6.4.3.5.1 Hematology

Hematocrit and hemoglobin, red blood cell count, white blood cell count, including differential count of total neutrophils, eosinophils, basophils, monocytes, lymphocytes; mean corpuscular volume; mean corpuscular hemoglobin; and mean corpuscular hemoglobin concentration, and platelet count.

6.4.3.5.2 Serum Chemistry

Sodium, potassium, chloride, bicarbonate (if available), BUN, creatinine, magnesium, calcium, phosphate, total bilirubin, direct and indirect bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase, and GFR (derived from serum creatinine).

6.4.3.5.3 Urinalysis

Urinalysis includes determination of pH; specific gravity; presence of blood, glucose, protein, ketones, bilirubin, urobilinogen, nitrite, and leukocytes.

6.4.3.5.4 Pregnancy

Urine pregnancy tests will be performed in women of child bearing potential. A positive urine pregnancy test will be confirmed with a second urine test. If the subject is an early termination or withdrawal, a urine pregnancy test will also be performed at the early termination visit.

6.4.3.6 ECG – 12-lead

ECGs will be done singly following a 5-minute semi-recumbent rest at Screening Visit 1B and 60 minutes pre-dose and 10 minutes post dose at Visits 2 – 6.

6.4.3.7 24-hour Holter Substudy

A substudy will be conducted at selected sites where subjects will perform a 24-hour Holter monitor recording at Visit 1B, Visit 3 (1 month), and Visit 5 (6 months). Subjects will return to the site from 1 to 4 days after the visit so that the Holter monitor may be retrieved by the site. If the recording is incomplete (either missing or < 6 hours duration) then another 24-hour Holter should be performed.

All subjects will be asked to participate in the substudy at these sites until enrollment in the substudy is complete at approximately 150 subjects. Once enrollment is complete in the substudy, these sites can continue to enroll subjects into the main study.

6.5 Concomitant Medications

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

Inhaled maintenance steroid therapy will be continued at the allowed maintenance dose throughout the treatment and washout periods. Albuterol will be allowed as required (or “PRN”) during the study. Albuterol should be withheld for 6 hours before the first spirometry performed at each study visit until all spirometry is completed.

If subjects have used albuterol within 6 hours of the spirometry measurement on Visit 1B or Visit 2 the visit must be rescheduled. If subjects have used albuterol within 6 hours of the spirometry measurement at Visits 3, 4, 5, 6 or 7 then the visit should still be performed as scheduled. Use of albuterol as a rescue inhaler will be documented in a medication eDiary and recorded in the eCRF.

Subjects who are receiving a LABA or LABA/ICS (either QD or BID) may be enrolled into the study provided that the dose has been stable for at least 30 days prior to Visit 1B and the steroid component is ≤1000 µg/day equivalent to fluticasone propionate. For reversibility testing at screening, subjects who are on a QD regimen should not have had their last dose within approximately the last 24 hours and for BID subjects not within approximately the last 12 hours, prior to the reversibility test. Once enrolled it is important to standardize administration of the subject’s LABA or LABA/ICS together with the study drug, as the spirometry will be measuring the combined effect of receiving the LABA and the study drug. These subjects should administer their LABA or LABA/ICS in the morning immediately prior to the nebulization of study drug. This administration should be documented in the source documents on study visit days and subjects should be instructed to follow the same procedure while at home between study visits. If subjects have used their LABA or LABA/ICS on the morning prior to their in-clinic visit instead of taking it immediately prior to study drug nebulization at Visit 2, this visit will be rescheduled. During any of the other treatment period visits, if subjects have used their LABA or LABA/ICS in the morning prior to

their in-clinic visit instead of taking it immediately prior to study drug nebulization the visit should still be performed as scheduled.

LABA and LABA/ICS drugs include the following examples:

- fluticasone propionate/salmeterol combination product
- budesonide/formoterol fumarate dihydrate combination product
- fluticasone furoate/vilanterol combination product
- mometasone/formoterol

LABA (with or without ICS) may be started for the treatment of an exacerbation for those subjects who were not previously on LABA-containing therapy and may be continued after the exacerbation is resolved for the remainder of the study at the investigator's discretion in accordance with COPD guidelines. During treatment for the exacerbation, study drug may be discontinued for no longer than 14 days. When an exacerbation occurs the symptoms must be resolved completely before their in-clinic visit. If prescribed for treatment of exacerbation, subjects should also complete their steroids and antibiotics regimen before they schedule their in-clinic visit.

Albuterol use (whether there has been any use in the last 24 hours) will be recorded in the subject's eDiary every day.

Table 2 lists the medications that require washout prior to Visit 1B. These medications are also prohibited throughout the study from Visit 1B to Visit 8 (24 hours after the last dose of study drug) inclusive. Subjects will be permitted to restart their routine medications after the completion of Visit 8.

[redacted]

[redacted]

6.6 Restrictions

Subjects are to observe the following restrictions from Screening through to Day 365:

- Use of recreational drugs
- Medicinal marijuana
- Excessive alcohol during the study period
- Participation in another investigational drug study
- Donation of ≥500 mL blood (or equivalent)

During study visits (i.e., when the subject is in clinic), excessive smoking, exercise, or caffeine intake or large meals should be restricted (further details provided in the Study 0128 Spirometry Manual).

6.7 Discontinuation

6.7.1 Subject Discontinuation

Any subject (or his or her legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the investigator and in accordance with his or her clinical judgment. When possible, the tests and evaluations listed for the termination visit should be carried out. If a subject withdraws before completing the study, the reason for withdrawal is to be documented on the CRF. All efforts should be made however to minimize discontinuations from the study.

Exacerbations of COPD will be classified as mild, moderate, or severe according to the below criteria. Subjects who experience 1 or 2 moderate or severe acute exacerbations of COPD (AECOPD) will be allowed to continue study drug throughout the exacerbation and will not be withdrawn from the study. Any subjects who experience more than 2 exacerbations (each separated by more than 1 month to confirm that they are separate events) will be withdrawn and placed on appropriate therapy. Subjects that are not on a LABA-containing therapy when they enter the study and require a LABA-containing therapy (either LABA alone or LABA/ICS) to treat a COPD exacerbation (either temporarily or from that point onwards at the discretion of the investigator in accordance with COPD guidelines) during the treatment phase of the study will be allowed to remain in the study. During treatment for the exacerbation, study drug may be discontinued for no longer than 14 days.

Table 3: Severity Criteria for COPD Exacerbations

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

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

The Sponsor will be notified of all subject withdrawals.

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

- Adverse event
- Subject choice
- Major deviation of the protocol
- Termination of the study by the Sponsor
- Other

Subjects who discontinue study drug early because of an adverse reaction should be encouraged to continue their participation in the follow-up safety assessments. A telephone follow-up visit will be conducted 30 days after discontinuation to review concomitant medications and adverse events if the discontinuation was due to an AE. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. This will consist of at least 3 telephone calls followed by a registered letter to the subject.

All subjects who terminate early, regardless of the reason, will have a follow-up telephone call at 12 months from Day 1 (randomization) to determine their vital status.

6.7.2 Subject Replacement

[redacted]

6.7.3 Study Discontinuation

The Sponsor reserves the right to discontinue this study at any time for any reason.

Certain circumstances may require the premature termination of the study, if the principal investigator and the Sponsor feel that the type, number and/or severity of AEs justify discontinuation of the trial, as for example, when several cases of similar SAEs (SUSARs) considered related by both the investigator and the Sponsor occurs. The Sponsor reserves the right to discontinue this study at any time for any reason.

6.8 Pregnancy

If a female subject becomes pregnant during the study, the clinical study director (or designee) must be notified immediately and the subject discontinued from the study. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7 ADVERSE EVENTS

7.1 Regulatory Definition of an Adverse Event

In the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice, Section 1.2 defines an adverse event (AE) as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

7.2 Adverse Event Definition for the Purposes of This Study

For the purposes of this clinical study, adverse events will be defined as follows:

An adverse event (AE) is any untoward medical occurrence in a subject who has signed an informed consent form and is participating in a clinical investigation. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not considered related to the study drug (investigational product).

Preexisting events that increase in frequency or severity or change in nature during or as a consequence of participation in clinical studies will also be considered as adverse events. An AE may also include pre- or post-treatment complications that occur as a result of a protocol-mandated procedure (such as a biopsy).

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

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

An AE does not include the following:

- Medical or surgical procedures (such as surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an adverse event
- Preexisting diseases or conditions present or detected before signing an informed consent form that do not worsen

- Situations where an untoward medical occurrence has not occurred (such as hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of either study drug or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation

7.3 Assessment of Adverse Events

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

Clinical severity should be recorded and graded using mild, moderate or severe as described below.

Mild	= Awareness of signs or symptoms, but easily tolerated
Moderate	= Discomfort sufficient to cause interference with usual activities
Severe	= Incapacitation with inability to work or perform usual activities

The relationship to study drug therapy should be assessed using the following definitions:

- **Not Related:** Evidence exists that the adverse event has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Possibly/Probably Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

These criteria in addition to good clinical judgment should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

7.4 Serious Adverse Events

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

- Death
- Life-threatening situation (subject is at immediate risk of death)

- In-subject-hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events)
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are as follows:

  Intensive treatment in an emergency room or at home for allergic bronchospasm

  Blood dyscrasias or convulsions that do not result in hospitalization

  Development of drug dependency or drug abuse

Additional Considerations for Serious Adverse Events

- Death is an outcome of an adverse event and not an adverse event in itself. In reports of death due to disease progression, where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study drug(s).
- All deaths, regardless of cause, must be reported for subjects if the death occurs while the subject is participating in the study.
- “Occurring at any dose” does not imply that the subject is receiving study drug at the time of the event; dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- “Life-threatening” means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- “In-subject-hospitalization” means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

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

Abnormal laboratory findings (such as clinical chemistry, hematology, or urinalysis) or other abnormal assessments (such as electrocardiograms [ECGs], X-rays, or vital signs) that are associated with signs and/or symptoms or are considered clinically significant in the judgment of the investigator must be recorded as AEs or SAEs if they meet the definition of

an adverse event (or serious adverse event), as described in Sections 7.2 (Adverse Event Definition for the Purposes of This Study) and 7.4 (Serious Adverse Events).

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

7.6 Serious Adverse Event Reporting

Any SAE that occurs after a subject signs an informed consent form through the follow-up visit (or at the time a subject is determined to be ineligible for the study or who does not enroll in the study), regardless of causal relationship, must be reported to the Sponsor within 24 hours of the investigator's knowledge of the event. To report an SAE, complete and fax the Serious Adverse Event Report Form to the following:

Theravance Clinical Drug Safety
Fax: [redacted]

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

Sponsor Medical Monitor Contact Information:
[redacted]
Telephone: [redacted]
Email: [redacted]

As an alternate, contact:
[redacted]
Telephone: [redacted]
Email: [redacted]

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

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the study drug and is unexpected/unlisted based on the current TD-4208 Investigator's Brochure. In this case, all investigators will receive notification of the event. The investigator is responsible for notifying the Institutional Review Board or Ethics Committee and

documenting the notification, as required by local regulatory authorities and in accordance with the local institutional policy.

7.7 Adverse Event Follow-up

A subject experiencing an AE or SAE will be followed by the investigator or his/her trained delegate(s) through the follow-up visit or until the investigator and/or the Sponsor has determined that the AE or SAE has resolved or a stable clinical endpoint is reached, whichever is longer. The Sponsor may request follow-up of certain adverse events until resolution and documentation of assessments made during this period.

The investigator must take all therapeutic measures necessary for resolution of an SAE. Any medications necessary for treatment of the SAE must be recorded in the concomitant medication section of the case report form.

8 STATISTICAL CONSIDERATIONS

8.1 General Considerations

All individual data will be listed as measured. All statistical summaries and analyses will be performed using SAS software (SAS Institute, Cary, North Carolina, USA).

Continuous data will be summarized using [redacted]

Categorical data will be summarized using the [redacted]

Any changes to the protocol-specified analyses will be pre-specified in the Statistical Analysis Plan prior to data lock.

8.2 Sample Size and Power

Sample size (n=350 per group) is based on meeting ICH regulatory requirements for long-term safety for chronic use in this indication. [redacted]

8.3 Analysis Sets

8.3.1 Analysis Sets

The Safety (Safety) analysis set will include all subjects receiving at least one dose of study drug summarized by actual drug received. The Safety analysis set will be the primary analysis for General and Safety analyses.

The Intent-to-Treat (ITT) analysis set will include all randomized subjects receiving at least one dose of study drug and at least one post-baseline FEV_1 assessment. The ITT analysis set will be the primary analysis set for the summarization of efficacy analyses.

The modified Intent-to-Treat (mITT) analysis set will include all ITT subjects with no switch in maintenance bronchodilator therapy (e.g. addition of a LABA therapy) during the study.

The Per-protocol (PP) analysis set will include all subjects in the ITT analysis set with no major protocol deviations

8.3.2 Examination of Subgroups

The following subgroups are pre-defined at baseline:

- Baseline smoking status [redacted]
- Age [redacted]
- Current ICS use [redacted]
- Reversibility to ipratropium,
- Baseline post bronchodilator % predicted FEV_1 [redacted]
- Baseline use of a LABA-containing therapy

Selected efficacy analyses, as defined in the statistical analysis plan (SAP), will be conducted using the subgroup examination sets. Additional subgroups may be defined in the SAP.

8.3.3 Major Protocol Deviations

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

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

Additional criteria may be specified in the SAP.

8.4 General Analyses

8.4.1 Demographics and Other Baseline Characteristics

Demographics (including age, sex, race, ethnicity, height, weight, and BMI) and baseline characteristics (concomitant LABA and ICS use) will be summarized for the Safety analysis set.

8.4.2 Screening and Baseline Spirometry

A summary of pulmonary function at screening, including reversibility, and at baseline using the Safety analysis set will be provided.

Reversibility to ipratropium is defined as a post-bronchodilator increase of 12% and at least a 200 mL increase in FEV_1 relative to the pre-bronchodilator response at the relative screening visit.

8.4.3 COPD Clinical History and Smoking History

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

8.4.4 Select Medical History

A summary of select medical history/characteristics using the Safety analysis set will be provided characterizing co-morbidities and disease severity.

8.5 Safety Analyses

For all safety analyses, the safety analysis set will be used.

Safety variables to be summarized include vital signs, adverse events, clinical laboratory results (hematology, chemistry, and urinalysis), corrected QT interval (QTc, from standard safety digital ECGs) and exacerbation data. Vital signs will be summarized in terms of observed values and changes from baseline.

8.5.1 Extent of Exposure

A subject's data for the extent of exposure to study drug will be generated from the study drug administration page of the CRF. Dosing information for individual subjects will be listed. Using drug administration data, estimates of exposure to TD-4208 will be summarized. Dose discontinuations and reasons for study drug discontinuation will be listed and summarized.

8.5.2 Adverse Event Data

8.5.2.1 Adverse Events

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

A treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus the number of days in the follow-up period. AEs observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from TEAEs.

All AEs and all TEAEs will be listed by subject. The frequency of subjects who experience TEAEs will be summarized overall and by treatment group. AEs will also be summarized by relationship to treatment (study drug) and severity.

A listing will be provided for all subjects who experience an SAE. Data listings will also be provided for subjects who discontinued the study due to any AE, as well as for a SAE.

8.5.2.2 [redacted]

[redacted]

8.5.2.3 Exacerbations

Exacerbations will be summarized descriptively using both exacerbations reported as adverse events and [redacted] in separate summaries. Exacerbation data will be summarized for the following categories: a) All exacerbations, b) Moderate and severe exacerbations, and c) Severe exacerbations.

The rate of exacerbations per subject per year over the treatment period will be analyzed using a [redacted]

The time to first exacerbation will be analyzed using [redacted].

Additional exacerbation analyses may be specified in the SAP.

8.5.2.4 Cardiovascular Events of Interest

Adjudicated CV events will be presented by CV events categories, showing number (%) of patients with at least 1 adjudicated treatment emergent CV events, sorted by alphabetical order. Listings will be provided for all adjudicated treatment emergent CV events by treatment group and patient.

8.5.3 Concomitant Medications

Medications will be summarized both prior and during the 12-month treatment period. Medications will be summarized as COPD bronchodilator, ICS and non-COPD medications.

8.5.4 Laboratory Data

Laboratory data will be summarized in terms of observed values, changes from baseline, values relative to normal ranges, and changes from baseline relative to normal ranges. Listings will flag laboratory values that are outside of normal range.

Clinical laboratory test results will be listed by subject. Reference ranges provided by the laboratory for each parameter will be used to evaluate the clinical significance of laboratory test results. Values falling outside of the relevant reference range will be flagged, as appropriate, in the data listings. Abnormalities in clinical laboratory test results will be listed in a separate listing.

8.5.5 Vital Signs Data

Vital Signs data will be summarized in terms of observed values (by time point), changes from baseline (by time point), and counts and percentages within appropriately defined categories (Table 4).

Table 4: Outlier Threshold for Vital Signs

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

8.5.6 ECG Data

The QTcF, PR interval, QRS duration, and HR from standard digital ECGs will be summarized in terms of observed values, changes from baseline, and counts and percentages within appropriately defined categories (Table 5).

Table 5: ECG Test Outlier Thresholds

Heart Rate (bpm)	Heart Rate Change From Baseline (bpm)	PR Interval (msec)	PR % Change From Baseline (%)	QRS Interval (msec)	QT_cF (msec)	QT_cF Change From Baseline (msec)
>120 >130	≥20 ≥30	≥200 ≥220	≥15 ≥25	≥120	≤450 >450, ≤480 >480, ≤500 >500	≤30 >30, ≤60 >60

Treatment emergent ECG abnormalities are defined as those not present at baseline, or those that worsened after treatment, e.g., borderline at baseline, but were prolonged after treatment. QTcF will also be summarized by the following categories, Normal (males <430, females <450), Borderline (males (≥430, <450); females (≥450, <470)) and Prolonged (males ≥450, females ≥470).

When multiple values exist for the same nominal time point (e.g., triplicate reading), the average of the readings taken for ECG parameters will be used in the data analysis, including the outlier analysis stated below.

[redacted]

All recorded values for the ECG parameters will be presented in a by-subject listing. A separate listing of subjects with values of QTcF >500 msec or an increase >60 msec will be provided, as necessary.

Cumulative distribution plots will be provided for maximum change in QTcF by visit.

8.5.7 Holter ECGs

Results of Holter interpretation will provide the following heart rate (HR) variables in units of bpm: maximum (max) HR, minimum (min) HR, and mean HR for the entire recording, and count of supraventricular premature beats (PACs) singles and, separately, couplets, and ventricular premature beats (VPCs) singles and, separately, couplets normalized for 24 hours.

Holter interpretation will provide numbers of episodes of arrhythmia including pauses, supraventricular couplets, supraventricular runs, supraventricular tachycardia, atrial fibrillation or flutter, ventricular couplets, ventricular runs and ventricular tachycardia; and episodes of other diagnostic findings including, e.g., abnormal ST segments, junctional rhythm and atrioventricular block.

8.6 Efficacy Analyses

[redacted]

8.6.1 Efficacy Endpoints

The exploratory efficacy endpoints are:

- [redacted]

Endpoints will be reported as nominal p-value without control for multiplicity.

8.6.2 [redacted]

[redacted]

8.6.3 [redacted]

[redacted]

[redacted]

[redacted] **Treatment Satisfaction Questionnaires**

[redacted].

8.8 Missing Data Handling

[redacted]

[redacted].

8.9 Clinical Events Committee

An independent external Clinical Events Committee (CEC) will perform ongoing blinded review and adjudication of pre-specified CV events of interest collected in the electronic case report forms and other pre-specified subject-level source documents during the conduct of the study. Further information on the composition and processes followed by the CEC can be found in the CEC Charter.

8.10 Data Monitoring Committee

No data monitoring committee is planned for this study.

9 STUDY ADMINISTRATION

This study will be conducted in compliance with all applicable regulations.

9.1 Principal Investigator Responsibilities

Before beginning the study, the principal investigator (PI) at each site must provide to the Sponsor or its designee a fully executed and signed Form FDA 1572 and, if applicable, a financial disclosure form. For applicable studies, financial disclosure forms must also be completed for all subinvestigators who will be directly involved in the treatment or evaluation of research subjects in this study. (A subinvestigator is defined in ICH E6 as any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions [e.g., associates, residents, research fellows].)

The PI will ensure the following:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- He or she will report to the Sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- He or she has read and understands the information in the TD-4208 Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC complies with the requirements of 21 CFR Part 56, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC. Additionally, he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

9.2 Institutional Review Board/Independent Ethics Committee

Before beginning study-specific research, the investigator will obtain written confirmation that the IRB, IEC, or Research Ethics Board (REB) is properly constituted and compliant with ICH and GCP requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to the Sponsor or its designee. The protocol, informed consent form (ICF), IB, and any other appropriate written information provided to the subjects that the IRB/IEC/REB may require to fulfill its responsibilities will be submitted to the IRB/IEC/REB in advance of the study. The Sponsor or its designee must approve the ICF and all subject recruitment materials before they are submitted to the IRB/IEC/REB. The study will not proceed until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol and the ICF are obtained by the investigator and copies are received by the Sponsor or its designee. If possible, the approval document should refer to the study by study protocol title and the Sponsor study number, identify the documents reviewed, and include the date of the review and approval. The written approval of the IRB/IEC/REB will be retained as part of the study file. The study may proceed before approval of consent forms and other study documents translated to a language other than the native language of the clinical site, provided that written IRB/IEC/REB approval of the translated documents is obtained before they are used. Any amendments to the protocol should be reviewed promptly.

The investigator must provide the appropriate periodic reports on the progress of the study to the IRB/IEC/REB and the Sponsor in accordance with local IRB/IEC/REB requirements and applicable governmental regulations, whichever is strictest.

9.3 Informed Consent

A properly written and executed ICF, in compliance with ICH E6 (GCP Guideline, Section 4.8), 21 CFR §50, and other applicable local regulations, will be obtained for each subject before enrollment of the subject into the study. The investigator will prepare the ICF or revise the template ICF and provide the documents to the Sponsor (or designee) for approval before submission to the IRB/IEC/REB. The Sponsor and the IRB/IEC/REB must approve the documents before they are implemented.

The investigator will provide copies of the signed ICF to each subject (or the subject's legally authorized representative) and will maintain the original in the subject's record file.

9.4 Data Recording and Quality Assurance

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used.

Electronic data capture (EDC) technology will be used for this study. All clinical information requested in this protocol will be recorded on the electronic case report forms approved by the Sponsor, or via other data collection methods, e.g., electronic laboratory data transfer. Study site personnel will enter (in English) study data into the CRFs for each randomized subject. Training on the EDC application will be completed and documented before access to the EDC system is given.

In the event of a CRF data change (e.g., correction of an error or addition of new information), corrections will be made to the CRF. Corrections to the CRFs, including the reason for change, will be automatically documented through the EDC system's audit trail.

The investigator is responsible for reviewing all CRFs, verifying them for accuracy, and approving them via an electronic signature. The investigator is designated as the signatory coordinating investigator.

An electronic copy of the CRF casebooks will be sent to the site for retention with other study documents after full completion of the study, i.e., after database lock.

The investigator is responsible for maintaining accurate, authentic, complete, and up-to-date records for each subject. The investigator is also responsible for ensuring the availability of any original source documentation related to the study (including any films, tracings, computer discs, tapes, and worksheets). In most cases the source is the subject's medical record. Data collected on the CRFs must match the source documents.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded in the CRF and for which the CRF will stand as the source document.

9.5 Document Retention

Until otherwise notified by the Sponsor, an investigative site must retain in a controlled manner all study documents required by the Sponsor and by the applicable regulations. The investigative site must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) and any original source documents that are electronic, as required by applicable regulations.

The investigator must consult the Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location or disposition of the study files. If an investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study documents, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian and must approve this transfer of responsibility.

9.6 Confidentiality

The investigator or designee must explain to each subject, before enrollment into the study, that, for evaluation of study results, the subject's confidential medical information obtained during the study may be shared with the study sponsor, the study sponsor's designated service providers, regulatory agencies, and the institutional review board (IRB) or independent ethics committee (IEC). Suppliers used in the study will also have access to some of the subjects' medical information as part of providing their services in the study (e.g., central lab and central spirometry). The investigator (or designee) is responsible for obtaining written permission to use confidential medical information in accordance with country-specific regulations (such as the Health Insurance Portability and Accountability Act in the United States) from each subject or, if appropriate, the subject's legally authorized representative. If permission to use confidential medical information is withdrawn, the investigator is responsible for documenting that no further data from the subject will be collected.

Subject medical information obtained during this study is confidential, and disclosure to unauthorized third parties is prohibited. The pertinent sections of data protection laws will be complied with in full. Study records containing subject information will only be identified by

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

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

Before and during the conduct of the study, no study-related details may be disclosed, i.e., placed on the internet, published, or otherwise publicized, or provided to a third party without prior written permission from the Sponsor. The policy for publication of data after completion of the study is described in Section 9.9 (Publication).

9.7 Access to Data and Documents

Upon receipt of the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Study data recorded on the CRFs must be verifiable to the source data. All original recordings, laboratory reports, and subject records generated by this study must be available to the Sponsor, representatives of the Sponsor, the IRB/IEC/REB, and applicable regulatory authorities, and they may be used for submission to regulatory authorities. In addition, all source data should be attributable (signed and dated), consistent with local medical practice. The investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representatives) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent.

9.8 Quality Control: Study Monitoring and Auditing

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP and standard operating procedures (SOPs) for compliance with applicable government regulations. The investigator agrees to allow these monitors direct access to the clinical data and supplies, dispensing, and storage areas and, if requested, agrees to assist the monitors. The investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Members of the Sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA or other Regulatory Agencies, including IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the investigator should notify the Sponsor immediately. The investigator will ensure that the auditors have access to the clinical supplies, study site facilities, laboratory and all data (including original source documentation) and all study files are available, if requested.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an investigator, institution, institution staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued noncompliance may result in termination of the investigator's involvement in the study. The IRB/IEC/REB and relevant regulatory authority will be informed.

9.9 Publication

The Sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and presentation at seminars or conferences. The Sponsor will retain the ownership of the data collected in this study. The investigator will provide any proposed manuscript or abstract to the Sponsor before submission for publication or presentation of any results or data obtained in this study.

Additional details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Study Agreement between the Sponsor and the investigator.

10 REFERENCES

The following references are available upon request.

1. Global initiative for chronic obstructive lung disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Updated 2011. Available at: http://goldcopd.com.
2. Beckett WS, McDonnell WF, Horstman DH, House DE. Role of the parasympathetic nervous system in acute lung response to ozone. J Appl Physiol. 1985 Dec;59(6):1879-85.
3. Belmonte KE. Cholinergic pathways in the lungs and anticholinergic therapy for chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005;2(4):297-304; discussion 311-2.
4. Fryer AD, Adamko DJ, Yost BL, Jacoby DB. Effects of inflammatory cells on neuronal M2 muscarinic receptor function in the lung. Life Sci. 1999; 64(6-7):449-55.
5. Miller, MR, Hankinson, J, Brusasco, V, Burgos, F, Casaburi, R, Coates, A, & Wanger. Standardisation of spirometry. *Eur Respir J*, 2005:*26*(2), 319-38.

Appendix 1: Signature Page

Protocol Signature Form

Title: **Study TD-4208-0128: A Phase 3, 52-week, Randomized, Active−Controlled Parallel Group Study to Evaluate the Safety and Tolerability of Nebulized TD−4208 in Subjects with Chronic Obstructive Pulmonary Disease**

Study No.: 0128

Date: 21 January 2016

I have read the forgoing protocol and agree to conduct this study in accordance with the current protocol. I also agree to conduct the study in compliance with all applicable regulations.

_____
Investigator's Name (print)

_____ _____
Investigator's Signature Date