Appendix Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

1. Subject must be able to understand and provide informed consent
2. Age 40-80
3. ≥10 pack-year smoking history
4. Post-bronchodilator FEV_1/FVC ratio ≥0.70
5. Baseline CAT≥10

Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol.
2. Subject is pregnant, breast-feeding, or plans to become pregnant.
3. Active pulmonary infection or prior pulmonary infection where treatment was completed ≤ 4 weeks prior to enrollment.
4. Post-BD FVC < 70% predicted.
5. A primary diagnosis of asthma established by each study investigator on the basis of the American Thoracic Society/European Respiratory Society guidelines as implemented in the MACRO study [13].

   In this implementation, physician investigators are asked apply the criteria above and if, after applying the these criteria, the clinicians are still unsure about the distinction in a specific patient, then bronchodilator testing with inhaled albuterol will be performed and patients with changes in FEV_1 > 400 mL will be excluded.

Clinical Features Differentiating COPD and Asthma

History	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptom onset < 35 yrs	Rare	Common
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Nighttime waking with breathlessness and wheeze	Uncommon	Common
Significant diurnal or day-to-day variation of symptoms	Uncommon	Common

6. Known concomitant lung disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), or clinically significant bronchiectasis.
7. History (or family history) of long QT syndrome.
8. History of paroxysmal (intermittent) atrial fibrillation will be considered an exclusion. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at

least 6 months and controlled with a rate control strategy (i.e., selective beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be considered for inclusion. In such patients, heart rate at enrollment must be < 100/min.

9. Patients with BMI < 15 or more than 40 kg/m2.
10. Patients with diabetes Type I or uncontrolled diabetes Type II.
11. Patients who, in the judgment of the investigator, have a clinically relevant laboratory abnormality or a clinically significant condition such as (but not limited to) significant renal disease, psychiatric disease, gastrointestinal disease, unstable ischemic heart disease, arrhythmia (excluding chronic stable atrial fibrillation), uncontrolled hypertension or any other condition which in the opinion of investigator might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.
12. Patients with any history of lung cancer.
13. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or severe renal impairment or urinary retention. Benign Prostatic Hyperplasia (BPH) patients who are stable on treatment can be considered.
14. Any other past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
15. Patients with a history of hypersensitivity to any of the study drugs or to drugs from similar chemical classification, including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof.
16. Patients unable to successfully use a dry powder inhaler device or perform spirometry measurements.
17. Use of other investigational drugs at the time of enrollment or within 30 days or 5 half-lives of enrollment, whichever is longer.
18. Patients receiving any prohibited medications in the classes or groups listed in Table 4.3-1.
19. Patients receiving any prohibited COPD related medications in the classes or groups in Table 4.3-2 must undergo the required washout period prior to Visit 1.

The class of medications listed in Table 4.3-1 are not permitted to be taken during the study and are considered exclusion criteria. Medications in Table 4.3-2 are also not permitted but subjects may be washed out per protocol, see Section 7. If a patient requires any of these medications and they cannot be safely washed out (with permission of the subject's primary physician) then they should not be included in the study. Short acting beta agonists are the only "rescue" medication allowed during the trial. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it allowed. If in doubt you should contact the Protocol Chairs before randomizing a patient or allowing a new medication to be started.

Appendix Table 2. Prohibited Medications

Class of medication
Cardiac anti-arrhythmics Class Ia
Cardiac anti-arrhythmics Class III
Tricyclic antidepressants
Monoamino-oxidase inhibitors
Other investigational drugs

Appendix Table 3. Prohibited COPD-related Medications Requiring Washout Period of 30 days

Class of medication	Minimum washout period prior to Visit 1
Long-acting anticholinergics	30 days
Short-acting anticholinergics	30 days
Fixed combinations of long-acting beta-agonists and inhaled corticosteroids	30 days
Fixed combinations of short acting beta agonists and short-acting anticholinergics	30 days
Long-acting beta agonists	30 days

Appendix Table 4. Schedule of Events for Participants Requiring Washout

	Pre-Screen Phone Call	On-Site Wash-out Visit 0	Phone Call	Screen/ Enroll-ment Visit 1	Phone Call	End of Study[3] Visit 2
Study Week	-8 to -4	≤ -4	≤ -1	0	4	12
Study Day	-60 to -31	-30	-7 to -1	0	28	84
Window (in days)					±7	±7
Informed consent		X				
Review of inclusion and exclusion criteria	X	X		X		
Demographics		X				
Baseline Medical history		X				
Smoking history/status	X	X		X	X	X
Physical exam including HR and BP		X		X		X
FEV_1 and FVC 15 mins after 4 puffs of albuterol		X				
FEV_1, FVC, SVC and IC before and 15 mins after 4 puffs of albuterol				X		
FEV_1, FVC, SVC and IC before administration of study drug and FEV_1 and FVC every hour after administration of study drug for a total of three hours (i.e. a trough and an AUC_{0-3} measurement).						X
Research Labs - Pregnancy test[1], Potassium Level Check[4]				X		
CAT	X	X		X		X
SGRQ				X		X
BDI/TD[2]				X		X
Review interim medical history			X	X	X	X
Review concomitant meds	X	X	X	X	X	X
Distribution of daily diary				X		
Collection of daily diary						X
Drug distribution				X		
Smoking cessation education		X[5]				
Capsule counts						X

1. Females of childbearing potential are required to have a negative pregnancy test prior to randomization.

2. BDI done at Screening/ Enrollment visit, TDI done at Visit 2.
3. Should a subject terminate early, the subject will be brought in to complete all assessments included at the Week 12 End of Study visit.
4. Serum potassium level check either at the enrollment visit or at a separate screening visit. The serum potassium level must be available and reviewed before randomization.
5. Current smokers only