

Protocol: D6560C00002

- **Protocol number: D6560C00002**
- **Document title: Double-blind, Randomized, Placebo-controlled, Parallel-group, Phase IV Study to Evaluate the Effect of Acridinium Bromide on Long-term Cardiovascular Safety and COPD Exacerbations in Patients with Moderate to Very Severe COPD (ASCENT COPD)**
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1. TITLE PAGE



Sponsor: AstraZeneca AB, S-151 85 Södertälje, Sweden

Double-blind, Randomized, Placebo-controlled, Parallel-group, Phase IV Study to Evaluate the Effect of Aclidinium Bromide on Long-term Cardiovascular Safety and COPD Exacerbations in Patients with Moderate to Very Severe COPD (ASCENT COPD)

LAS-MD-45 (D6560C00002)

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Confidentiality Statement

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object. This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

2. SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study LAS-MD-45 (D6560C00002)	
Study Number	LAS-MD-45 (D6560C00002)
Title of Study	Double-blind, Randomized, Placebo-controlled, Parallel-group, Phase IV Study to Evaluate the Effect of <u>A</u> clidinium Bromide on Long-Term Cardiovascular <u>S</u> afety and <u>C</u> OPD <u>E</u> xacerbations in <u>P</u> atients with Moderate to Very Severe <u>C</u> OPD (ASCENT COPD)
Study Centers (Region)	~500 (North America)
Development Phase	4
Objective	<ol style="list-style-type: none"> 1. To assess the safety of acclidinium bromide on major adverse cardiovascular events (MACE) 2. To assess the overall safety of acclidinium bromide 3. To assess whether acclidinium bromide reduces moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations
Methodology	Double-blind, randomized, placebo-controlled, parallel-group
Number of Patients	4000 planned
Diagnosis and Main Criteria for Inclusion	Male and female outpatients ≥ 40 years of age with moderate to very severe COPD (% predicted forced expiratory volume in 1 second (FEV ₁) < 80%) and a history of cardiovascular or cerebrovascular disease and/or significant cardiovascular risk factors.
Test Product, Dosage, and Mode of Administration	Acclidinium bromide 400 µg administered BID, once in the morning and once in the evening, via a multi-dose dry-powder inhaler (DPI)
Study Duration	Two-week washout/run-in period [for patients on a long-acting muscarinic antagonist (LAMA)] followed by a maximum of 36-month double-blind treatment period
Reference Therapy, Dosage, and Mode of Administration	Placebo, inhalation administered BID, once in the morning and once in the evening, via a multi-dose DPI
Criteria for Evaluation	
Pharmacokinetic Analysis	Not applicable
Primary Outcome Measure(s)	<ul style="list-style-type: none"> • Time to first MACE • The rate of moderate or severe COPD exacerbations per patient per year during the first year of treatment
Secondary Outcome Measure(s)	<ul style="list-style-type: none"> • Rate of hospitalizations due to COPD exacerbations per patient per year during the first year of treatment • Time to first MACE or other serious cardiovascular events of interest (i.e. standardized MedDRA query (SMQ) of cardiac disorders and SMQ of cerebrovascular disorders)

<p>Safety Measures</p>	<p>Physical examination, vital signs, adverse event (AE) monitoring, serious adverse event (SAE) reporting, electrocardiograms (ECGs), and vital status</p>
<p>Statistical Methods</p>	<p>The Full Analysis Set (FAS) is defined as any patient who was randomized in the trial and took at least one dose of treatment. Patients will be analyzed according to their randomized treatment.</p> <p>This study will be completed after 122 patients have an adjudicated MACE. The primary safety endpoint of time to first MACE will be presented for the FAS Population and will be based on on-study analysis. The on-study analysis is defined as all events that occurred while the patients was in the study, irrespective of treatment exposure (i.e., this includes all events that occurred while a subject was on treatment or off treatment, including post treatment follow-up). The time to first MACE will be analyzed by means of Cox proportional hazards regression model including baseline cardiovascular (CV) severity, smoking status, and treatment group as factors. The CV severity at baseline will be defined as 2 categories: 1) patients who had 2 CV risk factors, and 2) patients who had more than 2 CV risk factors or at least one non-fatal stroke or non-fatal myocardial infarction. The upper bound of the 95% confidence interval (based on Cox regression) for the hazard ratio (aclidinium relative to placebo) of time to first MACE will be used to rule out the null hypothesis. If the upper bound of the 95% confidence interval is less than the 1.8 margin of the hazard ratio, then the hazard ratio of 1.8 or higher will be ruled out.</p> <p>The primary efficacy endpoint of rate of moderate or severe COPD exacerbation per patient per year during the first year of treatment will be analyzed using Negative Binomial regression model. The model will include treatment group, baseline ICS use, baseline COPD severity, history of at least one exacerbation in the past year and smoking status as factors and the log exposure in years will be included as an offset variable. The rate ratio of moderate or severe COPD exacerbation per patient per year due to the effect of aclidinium bromide 400 µg BID relative to placebo will be estimated along with its confidence interval and the corresponding p-value. The two-sided p-value for aclidinium bromide 400 µg BID relative to placebo in reducing the rate of exacerbation will be compared to the 0.05 significance level.</p> <p>For this study, a total of 122 MACE will be needed to have 90% power, at 5% significance level, to rule out a hazard ratio of 1.8 in time to first MACE in aclidinium bromide treated patients relative to placebo.</p> <p>The sample size of 4,000 patients after 1 year of treatment will have ~89% power to detect a reduction in the rate of moderate or severe COPD exacerbations per patient per year of 14% (rate ratio of 0.86 in aclidinium bromide relative to placebo) at 0.05 alpha level. The 89% power was calculated assuming a discontinuation rate of 30% during the first year, a placebo rate of 0.8 exacerbation per patient per year (reduced from 1 to 0.8 as not all patients will have a history of exacerbation prior to randomization), and an over-dispersion factor of 0.67.</p>

SCHEDULE OF EVALUATIONS: Study LAS-MD-45 (D6560C00002)																	
	Double-blind Treatment Period																
	Washout/ Run-in	Visit 0 ^a	Visit 1A (Screening)	Visit 1B (Baseline)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 ^b	Visit 8	Visit 9 ^b	Visit 10	Visit 11 ^b	Visit 12	EOT	TC ^x
Study Month	-0.5			0	1		6		12		18		24		36		
Study Week	-3		-1	0	4	16	28	40	52	65	78	91	104	130	156	N/A	N/A
Visit window ^b (days)	N/A		+7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	N/A	N/A
Informed consent ^c	X	X	X														
Access IWRS	X	X	X	X		X	X	X	X		X		X		X	X	
Inclusion/ Exclusion criteria	X	X	X	X													
Patient demographics	X ^d		X ^d														
Medical and surgical history	X ^e		X ^e														
Medication history	X ^f		X ^f														
Smoking status assessment		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
AEs ^g		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory assessments ^h		X	X						X				X		X	X	
Vital signs ⁱ		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG ^j		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination ^k		X	X				X		X				X		X	X	
Pregnancy test ^l		X	X						X				X		X	X	

SCHEDULE OF EVALUATIONS: Study LAS-MD-45 (D6560C00002)																									
	<i>Washout/ Run-in</i>	<i>Double-blind Treatment Period</i>													<i>TC^x</i>										
		<i>Visit 0^a</i>	<i>Visit 1A (Screening)</i>	<i>Visit 1B (Baseline)</i>	<i>Visit 2</i>	<i>Visit 3</i>	<i>Visit 4</i>	<i>Visit 5</i>	<i>Visit 6</i>	<i>Visit 7^b</i>	<i>Visit 8</i>	<i>Visit 9^b</i>	<i>Visit 10</i>	<i>Visit 11^b</i>		<i>Visit 12</i>	<i>EOT</i>								
Study Month	-0.5			0	1				12				18				24			36					
Study Week	-3		-1	0	4				52				78				104			156				N/A	N/A
Visit window^b (days)	N/A		+7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	N/A	N/A
Pulmonary function testing ⁿ	X ^w	X ⁿ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization ^o			X																						
COPD Exacerbation Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CAT assessment			X						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rescue medication dispensing	X																								
Diary dispensing/training ^u	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary collection/review ^p																									
IP training ^q /IP dispensing ^r			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP dosing			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP collection ^s /compliance ^t																									

- a For patients who require a washout, PFTs should be performed to assess patients COPD severity. Patients will then come back in 2 weeks to perform Visit 1A. Patients who do not require a washout will sign the ICF and begin the study at Visit 1A.
- b Visit 7, Visit 9, and Visit 11 will occur by telephone. Information regarding AEs, concomitant medications, smoking status, and COPD exacerbations will be collected. The CAT will also be completed and mailed back to the study site.
- c ICF must be signed at the first visit for all patients prior to performing any study procedure. For patients requiring a washout, ICF must be signed at Visit 0, and then patients will return in 2 weeks to perform Visit 1A. ICF must be signed within the 30 days prior to Visit 1A. Rescue medication will only be dispensed after signing the ICF.
- d At Visit 0 for patients who require a washout or at Visit 1A for patients who do not require a washout, patient demographics will be collected to assess eligibility.
- e At Visit 0 for patients who require a washout or at Visit 1A for patients who do not require a washout, medical history will be collected to assess eligibility.
- f At Visit 0 for patients who require a washout or at Visit 1A for patients who do not require a washout, medication history will be collected to assess eligibility.
- g Any adverse event occurring from the time the ICF is signed until 15 days after the last dose of study drug must be recorded. AEs will be collected at Visit 1A for patients who completed a Visit 0. For patients who prematurely discontinue IP, only SAEs (including MACE) will be collected until the last visit/end of study.
- h Although fasting is not required, the patient should be encouraged to fast prior to each visit. The patient's fasting condition should be consistent at all visits. For patients taking Theophylline, blood serum levels will be measured.
- i Vital signs will consist of pulse rate, systolic and diastolic BP. Pulse and BP will be taken after the patient has been sitting for 10 minutes. Height will only be measured at Visit 1A and weight will be measured at Visit 1A and Visit 12 or EOT.
- j One ECG will be performed at Visit 1A, and a 2 hour post-dose ECG will be performed at Visit 1B. A 1 hour pre-dose and 2 hour post-dose ECG will be performed at Visits 2, 3, 4, 5, 6, 8, 10 and 12. Patients should be supine for at least 10 minutes before the test is performed. At EOT, only one ECG will be performed.
- k Genitourinary examinations are not required unless medically indicated.
- l For women of childbearing potential, a serum pregnancy test must be performed at Visit 1A and Visit 12 or EOT. A urine pregnancy test will be performed at Visits 6 and 10.
- m Two pre-dose measurements (30-45 mins apart) will be taken at Visits 1B prior to the first dose of IP. At all subsequent visits and EOT, only one measurement will be taken at Visit 1A. pre- and post-bronchodilator measurements will be performed to assess eligibility. The test will be performed using the rescue inhaler dispensed to the patient upon signature of the ICF. Perform pre-bronchodilator test followed by administration of 4 puffs of bronchodilator (albuterol/salbutamol) with a spacer. Administration of bronchodilator can begin as soon as 10 minutes after the completion of the last pre-bronchodilator spirometric effort if the patient is rested and comfortable. Post-bronchodilator maneuvers will be completed within 10-15 minutes after administration of bronchodilator.
- o Randomization must occur in IWRS at Visit 1B within the 3-5 day visit window. All tests/procedures including pre-dose PFTs must be performed, inclusion/exclusion verified, and laboratory results reviewed by the PI or medically qualified designee prior to randomization.
- p A paper diary will be used to record IP usage. The paper diary will be reviewed and used to primarily assess compliance at all indicated visits.
- q Placebo inhaler devices are available for training and practice.
- r IP dispensing will be issued through IWRS.
- s IP will be collected at Visits 3, 4, 5, 6, 8, 10, and 12 or EOT.
- t IP compliance will also be measured by dose indicator assessment at Visits 2, 3, 4, 5, 6, 8, 10 and 12 or EOT.
- u Dispense rescue medication diary at Visit 0 for patients who require a washout or at Visit 1A for patients who do not require a washout. Dispense IP diary at Visit 1B (randomization).
- v Visit 1B will be conducted within 3-5 days of Visit A upon receipt of clinical laboratory results. Patient Visit dates for the study will be based on the date of randomization.
- w At Visit 0 PFTs will be performed to assess COPD severity.
- x A telephone contact will be performed 15 days after the last known dose of IP is taken to assess any AEs that may have occurred since the last dose taken at the final visit and any changes to or new concomitant medications taken.

EOT = End of Treatment; TC = telephone contact

3. TABLE OF CONTENTS

1.	TITLE PAGE.....	1
2.	SYNOPSIS AND SCHEDULE OF EVALUATIONS.....	3
3.	TABLE OF CONTENTS.....	8
3.1	List of In-Text Tables.....	11
4.	LIST OF ABBREVIATIONS.....	12
5.	ETHICAL CONSIDERATIONS.....	14
5.1	Institutional Review Board and Independent Ethics Committee.....	14
5.2	Ethical Conduct of the Study.....	14
5.3	Patient Information and Informed Consent.....	14
6.	INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE.....	15
7.	INTRODUCTION.....	16
8.	STUDY OBJECTIVES.....	17
9.	INVESTIGATIONAL PLAN.....	18
9.1	Overall Study Design and Plan: Description.....	18
9.2	Discussion of Study Design, Including the Choice of Control Groups.....	18
9.3	Selection of Study Population.....	20
9.3.1	Inclusion Criteria.....	20
9.3.2	Exclusion Criteria.....	21
9.3.3	Removal of Patients from Treatment and Study Conduct.....	22
9.3.3.1	Removal of Patients from Investigational Product.....	22
9.3.3.2	Removal of Patients from the Study.....	24
9.3.4	Patient Replacement Procedures.....	24
9.4	Treatments.....	24
9.4.1	Treatments Administered.....	24
9.4.2	Identity of Investigational Product(s).....	26
9.4.3	Method of Assigning Patients to Treatment Groups.....	27
9.4.4	Selection of Dosages in the Study.....	27
9.4.5	Selection and Timing of Dose for Each Patient.....	27
9.4.6	Blinding.....	28
9.4.7	Unblinding.....	28
9.4.8	Prior and Concomitant Therapy.....	28
9.4.9	Monitoring Treatment Compliance.....	28
9.4.10	Medication, Dietary, and Activity Restrictions Before Study Visits.....	28
9.5	Efficacy and Safety Variables.....	29
9.5.1	Efficacy Assessment(s).....	29
9.5.1.1	Primary and Secondary Efficacy Assessment(s).....	29
9.5.1.2	Additional Efficacy Assessment(s).....	30

9.5.2	Safety Assessments	30
9.5.2.1	Adverse Events	31
9.5.2.2	Causality Assessment	31
9.5.2.3	Severity Assessment	32
9.5.2.4	Serious Adverse Events	32
9.5.2.5	Reporting Adverse Events and Serious Adverse Events	33
9.5.2.6	Immediate Reporting of Serious Adverse Events	34
9.5.2.7	Overdose	35
9.5.2.8	Exposure to Investigational Product During Pregnancy	35
9.5.2.9	Potential Hy's Law Cases	35
9.5.2.10	Major Adverse Cardiovascular Events	36
9.5.2.11	Clinical Laboratory Determinations	37
9.5.2.12	Vital Signs	38
9.5.2.13	Electrocardiograms	38
9.5.2.14	Other Safety Assessments	38
9.5.2.15	Data Safety Monitoring Board	38
9.5.2.16	Joint Advisory Committee	38
9.5.3	Investigational Product Concentration Measurements	39
9.5.4	Health Economic and Outcomes Research Assessments	39
9.5.5	Schedule of Assessments	39
9.5.5.1	Informed Consent	39
9.5.5.2	Washout/Run-in (Visit 0)	39
9.5.5.3	Screening (Visit 1A)	40
9.5.5.4	Baseline (Visit 1B)	41
9.5.5.5	Visit 2	42
9.5.5.6	Visits 3, 4, 5, 6, 8, and 10	43
9.5.5.7	Visits 7, 9, and 11	44
9.5.5.8	Visit 12	44
9.5.5.9	End of Treatment (EOT) Visit	45
9.5.5.10	Contacts between treatment visits	46
9.5.5.11	Vital Status Follow-up	46
9.5.5.12	Completion of Study	47
9.6	Data Quality Assurance	47
9.6.1	Data Monitoring	47
9.6.2	Data Recording and Documentation	47
9.7	Statistical Methods and Determination of Sample Size	48
9.7.1	Patient Populations	48
9.7.1.1	Screened Population	48
9.7.1.2	Randomized Population	48
9.7.1.3	Full Analysis Set Population	48
9.7.2	Patient Disposition	48
9.7.3	Demographics and Other Baseline Characteristics	49
9.7.4	Extent of Exposure and Treatment Compliance	50
9.7.4.1	Extent of Exposure	50
9.7.4.2	Measurement of Treatment Compliance	50
9.7.5	Efficacy Analyses	51

9.7.5.1	Primary Efficacy Parameter.....	51
9.7.5.2	Secondary Efficacy Parameter.....	52
9.7.5.3	Additional Efficacy Parameters.....	52
9.7.6	Safety Analyses.....	54
9.7.6.1	Primary Safety Parameter.....	54
9.7.6.2	Secondary Safety Parameter.....	55
9.7.6.3	Additional Safety Parameters.....	56
9.7.7	Health Economics and Outcomes Research Analyses.....	58
9.7.8	Interim Analysis.....	58
9.7.9	Determination of Sample Size.....	58
9.7.9.1	Power for the Primary Safety Endpoint: Time to First MACE Event.....	58
9.7.9.2	Power for the Primary Efficacy Endpoint: Rate of Moderate or Severe Exacerbations Per Patient Per Year During First Year of Treatment.....	59
9.7.10	Computer Methods.....	60
9.8	Changes in the Conduct of the Study or Planned Analyses.....	60
9.9	Protocol Deviations and Violations.....	60
10.	STUDY SPONSORSHIP.....	61
10.1	Study Termination.....	61
10.2	Reporting and Publication.....	61
11.	INVESTIGATOR OBLIGATIONS.....	62
11.1	Documentation.....	62
11.2	Performance.....	62
11.3	Use of Investigational Materials.....	62
11.4	Case Report Forms.....	63
11.5	Retention and Review of Records.....	63
11.6	Patient Confidentiality.....	63
12.	INVESTIGATOR'S STATEMENT.....	64
13.	APPENDICES.....	65
	APPENDIX I. ELEMENTS OF INFORMED CONSENT.....	65
	APPENDIX II. CONCOMITANT MEDICATIONS.....	67
	APPENDIX III. PULMONARY FUNCTION TESTS.....	69
	APPENDIX IV. POWER COMPUTATION DETAILS.....	71
	Appendix V. COPD ASSESSMENT TEST - CAT.....	76
	Appendix VI. WAIST CIRCUMFERENCE MEASUREMENT INSTRUCTIONS.....	77
14.	LITERATURE CITED.....	78

3.1 List of In-Text Tables

Table 9.3.3–1. Schedule of Visits and Telephone Contacts for Patients in Post-treatment Follow Up	23
Table 9.4.1–1. Dispensing Schedule	25
Table 9.7.9–1. Summary of Statistical Power to Detect a Specific Rate Ratio (Aclidinium Over Placebo) as Statistically Significant for a Range of Rate Ratio: One Study with 4,000 Patients in Total to be Tested at 0.05 Level	59
Table 13–1. Summary of Moderate or Severe COPD Exacerbations and of Patients with Exacerbations Leading to Hospitalizations per Patient per Year in the Phase III Placebo Controlled Studies of Aclidinium (Studies LAS-MD-33, LAS-MD-38A, and M/34273/34 Pooled) Intent-to-treat Population.....	71
Table 13–2. Rate of Moderate or Severe COPD Exacerbations per Patient per Year based on the Pooled Phase III Placebo Controlled Studies of acclidinium (Studies LAS-MD-33, LAS-MD-38A, and M/34273/34 Pooled) Intent-to-treat Population.....	72
Table 13–3. Exacerbation Outcomes (Benefit from Tiotropium Treatment in Handihaler®) from the UPLIFT trial	72
Table 13–4. Justification of the Selected Margin for Hazard Ratio for this Study Based on Benefit-Risk Approach: Risk Quantified using NNT for 1 year to Harm with 1 MACE and Benefit Quantified Using NNT for 1 Year to Reduce 1 Exacerbation.....	75

4. LIST OF ABBREVIATIONS

AE	adverse event
AZ	AstraZeneca
BID	twice a day (<i>bis in die</i>)
BP	blood pressure
BPH	benign prostatic hyperplasia
CAT	COPD Assessment Test
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
COPD	chronic obstructive pulmonary disease
CV	cardiovascular
DSMB	Data Safety Monitoring Board
DHHS	Department of Health and Human Services
DPI	dry powder inhaler
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
FEV ₁	forced expiratory volume after one second
FR	Federal Register
FVC	forced vital capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	inhaled corticosteroid
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
ITT	intent to treat

IWRS	interactive web response system
JAC	Joint Advisory Committee
LABA	long-acting β_2 -adrenergic agonists
LAMA	long-acting muscarinic antagonist
LAR	Legally Authorized Representative
MACE	major adverse cardiovascular event(s)
MDRD	modification of diet in renal disease
MI	myocardial infarction
MMRM	Mixed Model for Repeated Measures
NNH	Number Needed to Harm
NNT	number needed to treat
PADAC	Pulmonary-Allergy Drug Advisory Committee
PCS	potentially clinically significant
PFT	pulmonary function test
PI	principal investigator
PID	patient identification
PRN	as needed (<i>Pro Re Nata</i>)
PT	preferred term
RSM	Regional Site Manager
SABA	short-acting β_2 -adrenergic agonists
SAE	serious adverse event
SAMA	short-acting inhaled anticholinergic
SAP	statistical analysis plan
SD	standard deviation
SMQ	standardized MedDRA query
Sponsor	AstraZeneca
TEAE	treatment-emergent adverse event

5. ETHICAL CONSIDERATIONS

5.1 Institutional Review Board and Independent Ethics Committee

Within the United States

Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Principal Investigator (PI). A copy of the approval letter will be supplied to AstraZeneca (AZ), along with a roster of IRB members or the DHHS (US Department of Health and Human Services) general assurance number. During the course of the study, the PI will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRBs at the study centers in conformance with Code of Federal Regulations (CFR), Title 21, Part 56.

Outside of the United States

This study will be carried out in full compliance with the guidelines of the independent ethics committee (IEC) and government agencies of each respective country, where applicable. Before the study begins, the study centers will require approval from an IEC and government agency. During the course of the study, the Sponsor or authorized representative will provide timely and accurate reports to the IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate) and will notify the IEC of SAEs or other significant safety findings. The study protocol, ICF, information sheet advertisements, and amendments (if any) will be approved by the IEC at the study centers in conformance with CFR, Title 21, Part 56, and local regulations.

5.2 Ethical Conduct of the Study

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

This clinical study will comply with the International Conference on Harmonisation (ICH) Guidances on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, December 17, 1997) and Good Clinical Practice (ICH-E6; 62 FR 25692, May 9, 1997), as well as Part 312 of the Code of Federal Regulations (CFR).

5.3 Patient Information and Informed Consent

Patients, after being given an explanation of the study, will give voluntary and written informed consent and HIPAA (Health Insurance Portability and Accountability Act of 1996) authorization (in compliance with 21 CFR, Parts 50 and 312) or other appropriate form(s) before participating in any study-related procedures.

The informed consent statement contains all the elements of informed consent listed in Appendix I of this protocol. Signed copies of the ICF and the HIPAA or other locally applicable form will be given to the patient, and both documents will be placed in the PI's study files.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at approximately 500 study centers in North America

The PI is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, GCP guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the investigator's care; and for the control of investigational products under investigation. An investigator shall, obtain the informed consent of each human patient prior to the patient enrolling in the study and/or submitted to any study related activity.

The PI at each study center must meet their obligations to the patients, ethics committee, sponsor and regulatory authorities by maintaining oversight and control of the study's conduct and the study staff. It is the responsibility of the PI to ensure that any and all delegated duties be assigned to qualified staff; by education, experience and licensure (in accordance with local regulations) and that the PI oversight has to be documented and assessment of their capabilities and performance consistent with the study investigational plan. The PI at each study center will be responsible for the management of the study, which will consist of maintaining the study file and the patient records, corresponding with the IRB, and completing the electronic case report forms (eCRFs).

7. INTRODUCTION

Acclidinium bromide is a long-acting muscarinic antagonist delivered by the Pressair[®] dry powder inhalation device (DPI) for the treatment of bronchospasm in patients with chronic obstructive pulmonary disease (COPD).

COPD is a major cause of morbidity and mortality with a high and increasing prevalence, a natural history of progressive deterioration, and a loss of pulmonary function characterized by incompletely reversible expiratory airflow limitation (Mannino, 2008; Rennard, 1998). The characteristic symptoms of COPD include cough, sputum production, and chronic and progressive dyspnea. Furthermore, although COPD is primarily a lung disease, it has also significant systemic manifestations, which include significant comorbidities such as diabetes, cardiovascular (CV) disease, muscle wasting, and bone loss (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2015; Huiart et al, 2005; Soriano et al, 2005; Wouters, 2002).

Bronchodilators are central to the management of COPD and may be used on an as needed basis for acute symptomatic relief or as a maintenance treatment for prevention or reduction of symptoms. GOLD recommends regular use of one or more long-acting bronchodilators in patients with COPD of at least moderate severity. Currently used bronchodilators include β_2 -agonists (short and long acting), anticholinergics (short and long acting), theophylline, or a combination of these drugs. The choice of bronchodilator therapy depends on availability and individual response in terms of symptom relief and tolerability. Inhaled corticosteroids (ICS) are typically used in patients with more severe disease and/or frequent exacerbations.

8. STUDY OBJECTIVES

The objective(s) of this study are:

- To assess the safety of aclidinium bromide on major adverse cardiovascular events (MACE)
- To assess the overall safety of aclidinium bromide
- To assess whether aclidinium bromide reduces moderate or severe COPD exacerbations

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan: Description

This study will be a double-blind, randomized, placebo-controlled, parallel-group study to evaluate the effect of acclidinium bromide on cardiovascular safety and COPD exacerbations in patients with moderate to very severe COPD, as defined by the GOLD criteria (GOLD, 2015).

A total of 4000 patients will be enrolled across approximately 500 study centers. Patients meeting entry criteria will be randomized (1:1) to acclidinium bromide 400 µg twice a day (BID) or placebo BID with a background of standard of care treatment. Rescue medication (albuterol/salbutamol) will be provided for all patients.

The study will consist of a 2 week washout/run-in period followed by a maximum of 36-month double-blind treatment period.

Patients on a long-acting muscarinic antagonist (LAMA) (i.e. inhaled anticholinergics) must washout 2 weeks prior to randomization. During this time, the patient should be started on alternate therapy (e.g., long-acting β₂-adrenergic agonist (LABA or LABA/inhaled corticosteroid (ICS)) and should be contacted by the PI during the washout period to assess COPD stability. AstraZeneca will allow for the reimbursement of background controller medication for patients switching their current treatment from a LAMA to an alternate controller medication for patients without any healthcare coverage or are not covered by their insurance plan, (e.g., long-acting β₂-adrenergic agonist (LABA or LABA/inhaled corticosteroid (ICS)) when entering the washout period and for the duration of the study.

Patients on a combination of both LAMA and LABA/ICS therapies at washout or screening will not be eligible to participate (Section 9.3.2).

Patients will be assessed according to the Schedule of Evaluations (Section 2).

Patients who prematurely discontinue investigational product (IP) will participate in a post-treatment follow-up period. The follow-up period will include on-site visits and telephone visits to collect MACE, COPD exacerbations, concomitant medications, and SAEs for the remainder of the study duration.

This study will conclude when 122 patients have experienced an adjudicated MACE (Section 9.5.2.10).

9.2 Discussion of Study Design, Including the Choice of Control Groups

Acclidinium bromide 400 µg in the Pressair[®] DPI is approved by the FDA for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

During the Pulmonary-Allergy Drug Advisory Committee (PADAC) meeting held on February 23, 2012, the expert panel noted that there is a large population of COPD patients with cardiovascular conditions and due to the small number of adverse events (AEs), the impact on cardiovascular safety could not be established. Subsequently, Forest Research Institute (IND holder when Tudorza® was approved) and the Food and Drug Administration (FDA) agreed that a separate study would be needed to conclusively answer the question of cardiovascular safety. This study will therefore evaluate MACE and other cardiovascular events of interest for up to 3 years in patients with moderate to very severe COPD.

Results from the placebo-controlled studies of acclidinium bromide showed significant decreases in COPD exacerbations after three and six months of treatment. These data support the possibility that moderate to severe COPD exacerbations and associated hospitalizations may be reduced in COPD patients who receive longer term treatment with acclidinium bromide in the Pressair® DPI. This study is also designed to assess the effect of acclidinium bromide on the reduction of COPD exacerbations.

Moreover, this study will also include a health-related quality of life assessment, the COPD Assessment Test (CAT) (Jones, 2009).

To qualify for this study, patients must have a clinical diagnosis of moderate to very severe COPD, a history of cardiovascular or cerebrovascular disease or cardiovascular risk factors and may be treated per current standard of care, including treatment with β -blockers.

Patients with COPD have a higher risk of acute myocardial infarction (MI), congestive heart failure, arrhythmia, and mortality secondary to hospitalization for cardiovascular disease when compared to an age- and sex-matched non-COPD population. Results of a longitudinal population based study indicate that COPD patients with poor lung function have the highest risk of cardiovascular mortality independent of smoking status (Sin et al, 2006). Moreover, it has been reported that even modest reductions in lung function increase the risk of ischemic heart disease, stroke, and sudden cardiac death 2 to 3 fold independent of other risk factors (Sin et al, 2003). The patients selected for this study will have lung function < 80% predicted with no protocol-required lower limit. In addition, exacerbations have also been associated with increased cardiovascular events. Specifically, 1 to 5 days after an exacerbation the risk of MI increases 2.7-fold and the risk of stroke increases 1.26-fold 1 to 49 days after a COPD exacerbation (Donaldson et al, 2010). Therefore, inclusion of patients with severe to very severe lung disease will enrich the population for cardiovascular disease.

COPD is a complex disease involving more than airflow obstruction. The increased circulation inflammatory mediators in response to inflammation and/or alterations in repair mechanisms may result in systemic manifestations or worsening of co-morbid diseases such as ischemic heart disease and heart failure (Barnes et al, 2009). Therefore, it is anticipated that the occurrence of MACE will be achieved in the proposed COPD patient population given the Inclusion/Exclusion Criteria (Section 9.3), specifically those patients with a history of cardiac disease/risk factors.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet the following criteria:

1. Male or female outpatients ≥ 40 years of age
2. Current or former cigarette smokers with a smoking history of at least 10 pack-years
3. A diagnosis of stable, moderate to very severe COPD (GOLD, 2015) with a post-bronchodilator $FEV_1 < 80\%$ predicted and $FEV_1/\text{forced vital capacity (FVC)}$ ratio $< 70\%$ at Visit 1A
4. Must have at least one of the following 4 criteria:
 - a. Documented cerebrovascular disease (stroke or transient ischemic attack, carotid stenosis)
 - b. Documented coronary artery disease (angina, MI, angioplasty/stent/bypass)
 - c. Documented peripheral vascular disease or history of claudication
 - d. At least 2 of the following atherothrombotic risk factors as determined by the PI:
 - Male ≥ 65 years or female ≥ 70 years
 - Diabetes
 - Dyslipidemia
 - Hypertension
 - Waist circumference inches males ≥ 40 in or in females ≥ 38 inches
 - Evidence of renal dysfunction ($eGFR < 60$) and microalbuminuria ($eGFR$ is based on modification of diet in renal disease [MDRD] equation, microalbuminuria is defined as ≥ 30 - 300 mcg/mg creatinine on a spot urine or ≥ 30 mg creatinine on a 24hr urine test)
5. Maintained stable respiratory medications for 2 weeks prior to randomization (Appendix II)
6. Able to perform pulmonary function test (PFT) maneuvers and follow study procedures
7. Women of childbearing potential must have a negative serum β -human chorionic gonadotropin (HCG) pregnancy test at Visit 1A and be practicing medically acceptable method of contraception. Otherwise, female patients should be at least 1 year postmenopausal, surgically sterile (defined as having a hysterectomy or tubal ligation).

8. Should understand study procedures and be willing to participate in the study as indicated by signing the ICF

9.3.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Significant diseases other than COPD or cardiovascular disease (e.g., metastatic cancer) which, in the opinion of the PI, may either put the patient at risk because of participation in the study or a disease which may influence the results of the study or the patient's ability to participate in the study
2. Unstable or life threatening cardiovascular disease or COPD as determined by the PI
3. Patients with comorbid lung disease such as asthma, cystic fibrosis, bronchiectasis, interstitial lung disease, or pulmonary thromboembolic disease
4. Planned lung transplant or lung volume reduction surgery
5. Currently treated with a combination of LAMA and LABA/ICS therapy.
6. Malignancy for which patient has undergone resection, radiation therapy or chemotherapy within 5 years prior to screening. Patients with treated basal cell and squamous cell (skin) carcinoma are allowed
7. Respiratory infection or COPD exacerbation at Screening and/or within 4 weeks prior to screening.

NOTE: In the event of a Respiratory infection or COPD exacerbation four weeks prior to Screening and/or during the Screening period between (Visit 0 and 1B) the screening visit may be extended once only after the last increased additional dose of steroid burst and/or antibiotics is given to ensure patient has recovered from the exacerbation.

8. Uncontrolled infection resulting from human immunodeficiency virus (HIV) and/or active hepatitis
9. Reported history of drug or alcohol abuse within the past 12 months
10. History of hypersensitivity reaction to inhaled anticholinergics, sympathomimetic amines, or inhaled medication or any component thereof (including report of paradoxical bronchospasm)
11. History of acute urinary retention, treatment refractory benign prostatic hyperplasia (BPH), bladder neck obstruction, or narrow-angle glaucoma (Note: Patients with controlled, stable BPH are not excluded)
12. Patients unable to use a multidose DPI or a pressurized metered-dose inhaler
13. Treatment with any other investigational drug within 30 days (or 6 half-lives, whichever is longer) before Visit 1A

14. Women who are pregnant or breastfeeding
15. Use of any prohibited medication listed in Appendix II
16. Employee or immediate relative of an employee of AstraZeneca, any of its affiliates or partners, or the study center

Only patients who meet all inclusion/exclusion criteria at Baseline (Visit 1B) as confirmed and documented by a medically qualified investigator will be randomized and allowed to continue to Visit 2. On a case-by-case basis and upon review by the AZ Study Physician and approval of the Sponsor, patients who do not meet all inclusion/exclusion criteria may repeat the full visit; however, whenever a patient is rescreened, a new patient identification (PID) number is to be assigned and the patient to be re-consented.

Patients cannot participate in another clinical trial during treatment period and post-treatment follow-up period.

9.3.3 Removal of Patients from Treatment and Study Conduct

9.3.3.1 Removal of Patients from Investigational Product

Discontinuation of IP does not necessarily mean discontinuation of follow-up or termination of study participation. Compliant subjects who are discontinued from the IP should be encouraged to continue to undergo all study related visits/procedures for the full 36-months study period in order to support the final efficacy and safety analysis for acclidinium bromide. The reason for premature discontinuation of IP will be documented in the source documentation. It is essential to collect as much data as possible for all subjects throughout the study and especially all potential endpoint events. Complete withdrawal from the study (i.e., withdrawal of consent) has a direct negative impact on the potential validity of all study data and should be avoided wherever possible.

The post-treatment follow up period will include assessments at on-site visits and telephone visits to collect MACE, COPD exacerbations, concomitant medications, and SAEs for the remainder of the study duration.

After this period, the subjects will perform the EOT visit as described above. As per Section 9.5.5.9, randomized patients who prematurely discontinue IP will enter into a post-treatment follow-up period alternating telephone contacts and on-site visits (Table 9.3.3-1).

Patients who experience a MACE must be discontinued from IP and enter into the post-treatment follow-up period.

Patients can also be prematurely discontinued from IP and enter into the post-treatment follow-up period for one of the following reasons:

- Adverse event
- COPD exacerbation

- Insufficient therapeutic response
- Other reasons, such as specified or pregnancy

If IP is temporarily suspended (for any reason) for more than 30 consecutive days or a total of 60 aggregate days within the previous 6 months, the patient must be permanently discontinued from study drug and enter into the post-treatment follow-up period.

If the EOT visit occurs within 2 weeks of the next scheduled visit (TC or on-site), then the next visit can be skipped.

For unforeseen circumstances (e.g., patients move), post-treatment follow up period phone calls may be conducted in lieu of on-site visits, however, this must be pre-approved by the Sponsor.

Table 9.3.3–1. Schedule of Visits and Telephone Contacts for Patients in Post-treatment Follow Up

<i>Patient Visit</i> <i>Discontinued</i>	<i>Visit</i>											
	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>	<i>10</i>	<i>11</i>	<i>12</i>
Study Month	0	1		6		12		18		24		36
Study Week	0	4	16	28	40	52	65	78	91	104	130	156
At Visit 2	—	EOT	TC ^a	X ^b	TC ^a	X ^b	TC ^a	X ^b	TC ^a	X ^b	X ^b	X ^b
At Visit 3	—	—	EOT	TC ^a	X ^b	TC ^a	X ^b	TC ^a	X ^b	TC ^a	X ^b	X ^b
At Visit 4	—	—	—	EOT	TC ^a	X ^b	TC ^a	X ^b	TC ^a	X ^b	X ^b	X ^b
At Visit 5	—	—	—	—	EOT	TC ^a	X ^b	TC ^a	X ^b	TC ^a	X ^b	X ^b
At Visit 6	—	—	—	—	—	EOT	TC ^a	X ^b	TC ^a	X ^b	X ^b	X ^b
At Visit 7	—	—	—	—	—	—	EOT	TC ^a	X ^b	TC ^a	X ^b	X ^b
At Visit 8	—	—	—	—	—	—	—	EOT	TC ^a	X ^b	X ^b	X ^b
At Visit 9	—	—	—	—	—	—	—	—	EOT	TC ^a	X ^b	X ^b
At Visit 10	—	—	—	—	—	—	—	—	—	EOT	X ^b	X ^b
At Visit 11	—	—	—	—	—	—	—	—	—	—	EOT	X ^b

a Telephone contact (TC) to occur at designated time points to collect the following: MACE, COPD exacerbations, concomitant medications, SAEs, and arrange for provision of rescue medication as needed.

b On-site patient visits to occur at designated time points to collect the following: MACE, COPD exacerbations, concomitant medications, SAEs, and arrange for provision of rescue medication as needed.

AEs that occur from signing of ICF until 15 days after the last dose of study drug must be recorded.

EOT = End of Treatment (discontinue IP); TC = telephone contact; X = on-site visit.

9.3.3.2 Removal of Patients from the Study

Patients may withdraw from study participation for one of the following reasons:

- Failure to meet inclusion/exclusion criteria (only for screen failures)
- Adverse event (ex: death, long-term disability/hospitalization, etc.)
- COPD exacerbation (ex: death, long-term disability/hospitalization, etc.)
- Withdrawal of consent (a clear reason must be documented); patients who withdraw consent will not enter the post-treatment follow-up period
- Lost to follow-up. Every effort must be made to contact the patient. A certified letter must be sent after 2 documented unsuccessful attempts are made to contact the patient to come in for an EOT visit and to return any unused IP. All efforts to regain contact with the patient must be documented. In the event that contact is reestablished, the subject should not be considered lost to follow-up and post-treatment follow-up should resume according to [Table 9.3.3–1](#).
- Study or site prematurely terminated by the Sponsor for any reason

9.3.4 Patient Replacement Procedures

Patients in this study who prematurely discontinue treatment will not be replaced.

9.4 Treatments

This clinical study will be a double-blind, randomized, placebo-controlled, parallel-group clinical trial of inhaled aclidinium bromide 400 µg and placebo via the *Pressair*[™] DPI.

9.4.1 Treatments Administered

Double-blind IP will be provided by AZ in the form of *Pressair*[™] DPIs containing 60 doses of aclidinium bromide 400 µg or placebo.

IP will be dispensed at Visits 1B, 3, 4, 5, 6, 8, and 10. Patients will be supplied enough IP until the next scheduled visit. Patients will also be instructed to bring the double-blind IP back to the study center at Visits 2, 3, 4, 5, 6, 8, 10, and 12 or *EOT*.

IP will be supplied individually as indicated below, with each IP inhaler enclosed in an aluminium pouch. Each study center will be provided with drug supplies corresponding to a sequence of randomization numbers.

[Table 9.4.1–1](#) specifies the IP inhalers to be dispensed and returned at each visit.

Table 9.4.1–1. Dispensing Schedule

<i>Visit</i>		
<i>0^a</i>	<i>Washout/Run-in No IP Drug Dispensed 1 Albuterol/Salbutamol Rescue Inhaler and 1 AeroChamber Plus</i>	
<i>1A</i>	<i>Screening (If patient did not require a washout) No IP Drug Dispensed 1 Albuterol/Salbutamol Rescue Inhaler and 1 AeroChamber Plus</i>	
	<i>Double-Blind Phase</i>	
	<u><i>Aclidinium Bromide 400µg</i></u>	<u><i>Placebo</i></u>
<i>1B</i>	<i>1 kit containing 5 Aclidinium Bromide 400µg 60 Doses Inhalation Powder Inhalers (5 inhalers) 3 Albuterol/Salbutamol Rescue Inhalers as needed</i>	<i>1 kit containing 5 Placebo 60 Doses Inhalation Powder Inhalers (5 inhalers) 3 Albuterol/Salbutamol Rescue Inhalers as needed</i>
<i>2</i>	<u><i>Continue dosing from Visit 1B Study Medication</i></u>	
<i>3</i>	<i>1 kit containing 5 Aclidinium Bromide 400µg 60 Doses Inhalation Powder Inhalers (5 inhalers) 3 Albuterol/Salbutamol Rescue Inhalers as needed</i>	<i>1 kit containing 5 Placebo 60 Doses Inhalation Powder Inhalers (5 inhalers) 3 Albuterol/Salbutamol Rescue Inhalers as needed</i>
<i>4</i>	<i>1 kit containing 5 Aclidinium Bromide 400µg 60 Doses Inhalation Powder Inhalers (5 inhalers) 3 Albuterol/Salbutamol Rescue Inhalers as needed</i>	<i>1 kit containing 5 Placebo 60 Doses Inhalation Powder Inhalers (5 inhalers) 3 Albuterol/Salbutamol Rescue Inhalers as needed</i>
<i>5</i>	<i>1 kit containing 5 Aclidinium Bromide 400µg 60 Doses Inhalation Powder Inhalers (5 inhalers) 3 Albuterol/Salbutamol Rescue Inhalers as needed</i>	<i>1 kit containing 5 Placebo 60 Doses Inhalation Powder Inhalers (5 inhalers) 3 Albuterol/Salbutamol Rescue Inhalers as needed</i>
<i>6</i>	<i>2 kits containing 5 Aclidinium Bromide 400µg 60 Doses Inhalation Powder Inhalers (5 inhalers) 6 Albuterol/Salbutamol Rescue Inhalers as needed</i>	<i>2 kits containing 5 Placebo 60 Doses Inhalation Powder Inhalers (5 inhalers) 6 Albuterol/Salbutamol Rescue Inhalers as needed</i>
<i>7^b</i>	<i>Telephone Visit No IP Drug Dispensed</i>	
<i>8</i>	<i>2 kits containing 5 Aclidinium Bromide 400µg 60 Doses Inhalation Powder Inhalers (5 inhalers) 6 Albuterol/Salbutamol Rescue Inhalers as needed</i>	<i>2 kits containing 5 Placebo 60 Doses Inhalation Powder Inhalers (5 inhalers) 6 Albuterol/Salbutamol Rescue Inhalers as needed</i>
<i>9^b</i>	<i>Telephone Visit No IP Drug Dispensed</i>	
<i>10</i>	<i>4 kits containing 5 Aclidinium Bromide 400µg 60 Doses Inhalation Powder Inhalers (5 inhalers)</i>	<i>4 kits containing 5 Placebo 60 Doses Inhalation Powder Inhalers (5 inhalers)</i>

Table 9.4.1–1. Dispensing Schedule

<i>Visit</i>		
	<i>12 Albuterol/Salbutamol Rescue Inhalers as needed</i>	<i>12 Albuterol/Salbutamol Rescue Inhalers as needed</i>
<i>11^b</i>	<i>Telephone Visit No IP Drug Dispensed</i>	
<i>12 ET</i>	<i>End of Treatment IP Collection</i>	

If IP dosing is interrupted (for any reason) for more than 30 consecutive days or a total of 60 aggregate days within the previous 6 months, the patient must be discontinued from study drug and enter into the post-treatment follow-up period.

Marketed albuterol (108 µg per puff) or salbutamol sulfate (100 µg/puff), supplied by AZ, will be the only rescue medication permitted during the IP treatment period of the study. The investigator or designee will provide the patient with this medication upon signing the ICF at Visit 0 or Visit 1B and at other visits as necessary according to use. Rescue medication will be provided by AZ during the study treatment period and the post-treatment follow-up period (Section 9.3.3.1). Rescue medication will be provided locally for all visits (except for visit 1A in the US where Albuterol for reversibility testing will be assigned to the patient via IWRS).

At Visit 1A (for patients who do not require a washout), 4 puffs of albuterol or salbutamol from the dispensed rescue inhaler should be given with a spacer device (AeroChamber Plus) to ensure proper inhalation. During the study, the use of spacers for albuterol/salbutamol administration is not required. If a spacer is used, it must be used consistently throughout the study at each visit.

Albuterol/salbutamol should be discontinued at least 6 hours before all visits (including Visit 0 and Visit 1A) and not used again until after the completion of the last study measurement of the visit. Rescue medication should only be used during a visit if absolutely necessary.

9.4.2 Identity of Investigational Product(s)

IP will be identified with the protocol number, kit number, and inhaler number and labelled with storage information, warning language (“Caution: New Drug - Limited by Federal Law to Investigational Use”), space for the coordinator to write in the visit number, and instructions for using the inhaler as directed. Immediately before dispensing IP, the study coordinator will write on the label of the kit and the pouches the PID number, the patient’s initials, the visit number, and the date dispensed. Labelling will be provided in the local language, and specific language related to local laws will be included.

Double-blind IP will be prepared according to the randomization list. Each manufacturing process will be performed and documented in conformity with good manufacturing practices.

Placebo Pressair™ devices for training purposes will also be supplied and identified accordingly.

The IP should be stored at 25°C (77°F); in accordance with instructions given on the IP label, the range of 15°C to 30°C (59°F-86°F) should not be exceeded. All IP must be stored in an appropriate, secure area (e.g., a locked cabinet in a locked room).

The PI is responsible for recording the receipt and use of all IP supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused IP must be returned; and, whenever IP is returned, unit counts must be performed. All IP must be accounted for. All unused IP and empty IP packages in US/Canada, following approval by AZ, should be destroyed unless otherwise instructed.

9.4.3 Method of Assigning Patients to Treatment Groups

After a patient signs the ICF at the first screening visit, study personnel will register the patient in the interactive web response system (IWRS), and the system will assign the patient a sequential PID number. The first patient to sign the ICF at each site will be assigned the first number in the sequence by the system. The PID number will consist of nine digits: the first four will represent the study center (0101, 0202, etc), followed by the two digit study number (45) and a three digit screening number (001, 002, etc). As an example, at site number 0101, performing protocol number 45, the sequence of numbers for that site will be [REDACTED] CCI [REDACTED], etc. This PID number will be used to identify the patient throughout the study (i.e., at all study phases).

The study center must contact the IWRS at screening and at all subsequent study visits in order to obtain the kit number to be dispensed to the patient at that visit.

Confirmation of the IP and number will be faxed or e-mailed (per the study center's preference) to the study center following each assignment. A detailed description of IWRS procedures is contained in the IWRS Manual in the Study Reference Binder.

9.4.4 Selection of Dosages in the Study

The acclidinium bromide dosage chosen for this study is based on the 400 µg BID dose currently approved by the FDA for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

9.4.5 Selection and Timing of Dose for Each Patient

The first dose of IP will be administered at Visit 1B after pre-dose PFT measurements under the supervision of study staff. IP will continue to be taken twice daily approximately 12 hours apart. The morning dose of IP will be taken prior to 11:00 AM throughout the study. On visits where trough FEV₁ is measured, the last dose of IP must be taken 12-14 hours prior to the study visit.

At Visit 1B, following randomization, the PI, or a qualified designee, should make sure the patient understands the instructions and the correct use of the study medication IP inhaler. Patients will be provided with verbal and written instructions.

At each visit, the PI will ensure that the patient is properly using the study medication IP inhaler; reinstruction will follow when needed (the training device may be used again if appropriate).

9.4.6 Blinding

A list of patient randomization codes will be generated by Statistical Programming at AZ and implemented by the IWRS vendor (an electronic version will be stored on a secure server). This list will identify each patient by randomization number and include the patient's corresponding treatment assignment.

9.4.7 Unblinding

Any unblinding at the study site level should be done only in an emergency that requires the IP to be identified for the medical management of the patient. The PI has to notify the study physician immediately and a full written explanation will be provided if the blind is broken. Before IP is unblinded, every attempt should be made to discuss the case with the Study Physician. Breaking the code at the study center will immediately disqualify the patient from further participation in the study; however, the patient should enter into the post-treatment follow-up period.

Treatment codes may be broken by Global Patient Safety at AZ for regulatory reporting purposes. In such cases, the study staff will be kept blinded and the patient will not need to be disqualified from the study.

In an emergency, the PI can obtain the treatment assignment of any patient at his or her study center through the IWRS. In an emergency, the PI will access the IWRS to break the blind.

9.4.8 Prior and Concomitant Therapy

A list of medication classes that are allowed and not allowed as concomitant medications for either episodic or chronic use is provided in Appendix II. Medications taken during the previous 15 days will be recorded at Screening (Visit 1A) and /Baseline (Visit 1B) in the eCRF. Thereafter, any changes in concomitant medications or new medications added will be recorded in the eCRF.

9.4.9 Monitoring Treatment Compliance

Compliance will be monitored primarily by paper diary review. Treatment compliance based on the diary will be recorded in the eCRF.

Dose counter indicator will act as a secondary measure of compliance.

Before new IP is dispensed at each visit, every effort will be made to collect all unused IP.

9.4.10 Medication, Dietary, and Activity Restrictions Before Study Visits

The following are prohibited within the times indicated before any study visit:

- Vigorous physical activity should be avoided for at least 20 minutes before each visit
- Alcohol consumption should be avoided at least 4 hours before each visit
- The intake of caffeinated products (e.g., coffee, tea, soda) will not be permitted for at least 6 hours before each visit until completion of all procedures on that day

- Smoking, prolonged exposure to cold air, dust or polluted air should be avoided for at least 1 hour before each visit until the completion of all study procedures. For patients who cannot avoid smoking, smoking will be permitted during the visits; however, it should be stopped at least 1 hour before any spirometric testing is performed.
- Large meals should be avoided for at least 2 hours before the visit. Patients should fast overnight before coming in for clinical laboratory assessments at Visits 1 (screening), Visit 6, Visit 10, and Visit 12 or EOT.
- Supplemental oxygen must be discontinued at least 2 hours before any study visit
- Albuterol must be discontinued at least 6 hours before the visit.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy Assessment(s)

COPD exacerbations will be assessed in this study.

9.5.1.1 Primary and Secondary Efficacy Assessment(s)

The primary efficacy endpoint is the rate of moderate to severe COPD exacerbations per patient per year during the first year of treatment.

COPD exacerbations will be evaluated by the PI throughout the study.

The onset and end of an exacerbation is defined by the investigator in their assessment of patient symptoms and initiation/finalization of treatment (as defined below for the severity of exacerbation).

The severity of a COPD exacerbation is to be assessed according to the following scale:

- Mild:** Increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, sputum purulence) during at least 2 consecutive days, managed by the patient at home by increasing short-acting bronchodilator and/or ICS use
- Moderate:** Increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, sputum purulence) during at least 2 consecutive days that does not lead to hospitalization but is treated with antibiotics and/or systemic corticosteroids
- Severe:** Increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, sputum purulence) during at least 2 consecutive days that leads to hospitalization (overnight stay at hospital or emergency room) or death

The interval between 2 consecutive COPD exacerbations must be at least 7 days. Therefore, if 2 COPD exacerbations occur within 7 days of each other, it will be considered as 1 event.

Patients who experience a moderate COPD exacerbation may be treated with the addition of an allowed concomitant medication and remain on IP at the discretion of the PI.

Patients who experience a severe or recurrent COPD exacerbation may be treated with the addition of an allowed concomitant medication and remain on IP at the discretion of the PI.

Patients who experience a severe or recurrent COPD exacerbation and require treatment with a LAMA, must be discontinued from IP and enter into the post-treatment follow-up period (Section 9.3.3.1).

The secondary efficacy endpoint is the rate of hospitalizations due to COPD exacerbations per patient per year during the first year of treatment.

9.5.1.2 Additional Efficacy Assessment(s)

a) Spirometry

One pre-bronchodilator and one post-bronchodilator measurement will be taken at Visits 1A, and two pre-dose measurements at Visit 1B. The assessment of morning pre-dose trough FEV₁ will be obtained at Visits 2, 3, 4, 5, 6, 8, 10, and 12 or EOT.

Measurements to assess eligibility will be taken at Visit 1A. All spirometry results will be transferred via ndd Easy One Spirometer on a monthly basis. Data transfers (values will include: PFT assessment date, time, timepoint, the ATS/ERS criteria met or not, FEV₁, percentage predicted FEV₁, FVC, percentage predicted FVC, FEV₁/FVC ratio, indication of the best effort evaluation per ndd Easy One Spirometer has met ATS/ERS grading) selected to assess Inclusion Criteria (Section 9.3.1)

All spirometry assessments (up to a maximum of 8 PFT maneuvers) will be performed, recorded locally, and will be read by a central vendor (see Appendix III).

The data for each visit must be entered into the electronic data capture system, including patient ID, date, time, visit number, whether spirometry was performed, whether the patient had a bronchodilator in the previous 6 hours, and the reason for visit, if it was unscheduled.

The values for the maneuvers using the sponsor provided ndd Easy One Spirometer will not be entered into the eCRF page anymore, this data will be collected via the ndd Easy One Spirometer and transmitted to the central vendor.

The maneuvers must be reviewed by the PI or qualified designee to ensure ATS/ERS criteria for acceptability and repeatability have been met.

b) COPD Assessment Test (CAT)

Refer to Section 9.5.4, Health Economics and Outcomes.

9.5.2 Safety Assessments

Patients must be seen by a physician or an appropriately trained health professional at every visit and the evaluation must be documented. The procedures discussed below will be completed at the designated visits.

9.5.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), for example, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A).

For the purpose of data collection for this study, any untoward event that was reported from the time the patient signed the ICF until 15 days after the last dose of treatment are to be considered AEs. For patients who prematurely discontinue study drug and enter post-treatment follow-up period, SAEs (including MACE) will be collected until end of study.

Examples of AEs are as follows:

- Changes in the general condition of the patient
- Subjective symptoms offered by or elicited from the patient
- Objective signs observed by the PI or other study center personnel
- All diseases that occur after signing ICF, including any change in severity or frequency of preexisting disease
- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study schedule

Please note medical procedures scheduled prior to consenting, but occurring during the study should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

9.5.2.2 Causality Assessment

For all AEs, the PI must provide an assessment of causal relationship to the investigational product. The causality assessment must be recorded on the appropriate AE reporting page of the patient's eCRF. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility the investigation product caused the event?

Yes: There is evidence to suggest a causal relationship between the investigational product and adverse event; i.e.:

- There is a reasonable temporal relationship between the investigational product and the event, and
- The event is unlikely to be attributed to underlying/concurrent disease, other investigational products, or other factors, and/or

— Positive dechallenge and/or rechallenge exist

No: There is no evidence to suggest a causal relationship between the investigational product and adverse event; i.e.:

- There is no reasonable temporal relationship between the investigational product and the event, or
- The patient did not take the investigational product, or
- The event is likely to be attributed to underlying/concurrent disease, other investigational products, or other factors, or
- The event is commonly occurring in the (study) population independent of investigational product exposure

9.5.2.3 Severity Assessment

The PI will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. *Severity*, which is a description of the intensity of manifestation of the AE, is distinct from *seriousness*, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 9.5.2.4). Severity will be assessed according to the following scale:

- Mild:** Minor awareness of signs or symptoms that are easily tolerated without specific medical intervention
- Moderate:** Discomfort that interferes with usual activities and may require minimal intervention
- Severe:** Significant signs or symptoms that are incapacitating with an inability to work or perform routine activities and/or that require medical intervention

9.5.2.4 Serious Adverse Events

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Important medical event

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of investigational product dependency or drug abuse.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (e.g., elective procedures for preexisting conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

The following events are captured as efficacy endpoints and are therefore excluded from AE/SAE reporting:

- COPD exacerbation
- Signs and symptoms associated with COPD exacerbation
- COPD exacerbation resulting in hospitalization and/or death

For the purpose of data collection for this study, any SAE must be reported from the time the patient signed the ICF until 15 days after the last dose of study drug.

9.5.2.5 Reporting Adverse Events and Serious Adverse Events

Any untoward event that occurs in a patient from the time he or she signs the ICF for the trial until 15 days after the last dose of investigational product has to be collected. Thus, any untoward medical occurrences or unfavorable and unintended signs, symptoms, or diseases that occur in the pretreatment, in treatment, or post treatment period are to be considered AEs and/or SAEs, and consequently recorded and reported as such. For patients who prematurely discontinue study drug and enter post-treatment follow-up period, SAEs (including MACE) will be collected until end of study.

At each visit, patients are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Patients will be asked to volunteer information with a nonleading question such as, "How do you feel since your last visit?" Study center personnel will then record all pertinent information in the patient's eCRF.

Follow-up of unresolved adverse events:

Any AEs that are unresolved at the patients last visit are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AZ retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

All AEs must be recorded on the appropriate AE reporting page of the patient's eCRF whether or not they are considered causally related to the investigational product.

For every AE, the PI must:

- Provide an assessment of the severity, causal relationship to the investigational product, and seriousness of the event (e.g., SAE)
- Document all actions taken with regard to the investigational product
- Detail any other treatment measures taken for the AE

Additional information regarding the immediate reporting required for SAEs is provided in Section 9.5.2.6.

9.5.2.6 Immediate Reporting of Serious Adverse Events

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained. **All SAEs will be recorded in the eDC.**

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study center personnel must report the event to the appropriate AZ representative. The designated AZ representative works with the Investigator to ensure that all the necessary information is provided to the AZ Patient Safety data entry site within 1 calendar day of initial receipt for fatal and life threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AZ representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the electronic data capture (eDC) system, an automated email alert is sent to the designated AZ representative.

If the eDC system is not available, then the Investigator or other study center personnel reports a SAE to the appropriate AZ representative by fax.

The AZ representative will advise the Investigator/study center personnel how to proceed.

The AZ *paper SAE Report Form* should be faxed to the designated AZ representative using the country specific number below.

For U.S: Fax number [REDACTED] CCI

For Canada: Fax number [REDACTED] CCI

The AstraZeneca representative will advise the Investigator/study center personnel how to proceed. As soon as the eDC is available data should be re-entered into the system. If, during

follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

NOTE: For any follow up information pertaining to SAEs occurring prior to the implementation of the updated eDC the information must be faxed to an AZ representative using the process described above. No information should be entered into the eDC.

9.5.2.7 Overdose

Overdose only needs to be reported if leading to an Adverse Event. If the overdose leads to an Adverse Event meeting the criteria of seriousness (SAE), the SAE module must be completed within the same timeframe and following the same routing as for a SAE (see section 2.1). The patient must be followed-up and the investigator will make every effort to obtain information on how the overdose was managed, any treatment administered and the final outcome. This information will be reported, following the same procedure and timeframes as for the initial report.

9.5.2.8 Exposure to Investigational Product During Pregnancy

Study center personnel must report every pregnancy from the time he or she signs the ICF for the trial until the patient's last visit as soon as possible (within 24 hours of learning of the pregnancy) to the appropriate AZ representative.

The designated AZ representative will work with the Investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 9.5.2.8) and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until last visit, if possible, be followed up and documented.

9.5.2.9 Potential Hy's Law Cases

Study center personnel must report every patient that meets potential Hy's law criteria, i.e.:

- ALT or AST \geq 3xULN AND
- Total Bilirubin \geq 2xULN AND
- Alkaline Phosphatase $<$ 2xULN

Within a 24 hour period that occurs anytime from the time he or she signs the ICF for the trial until 15 days after the last dose of investigational product. A potential Hy's law should be reported as an SAE using the most relevant SAE criteria, as judged by the Investigator (see

Section 9.5.2.5). Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the study physician.

Additionally, if a patient meets the above criteria, the presence or occurrence of any of the following will be collected in the eCRF:

- Abnormal liver biochemistry risk factors (e.g. alcohol abuse, increased alcohol consumption within 1 month of a Hy's Law event, IV drug use, tattoo, acupuncture, sexually transmitted disease, toxic/chemical agent exposure, travel to areas at risk, post-partum, parenteral nutrition, excessive physical exercise, changes in diet, fasting episode, weight loss, previous drug reaction associated with an elevation of liver tests, blood transfusion, exposure to anyone with known hepatitis, history of hypotension/shock, history of hepatitis C, history of hepatitis B, history of hepatitis A, history of hepatitis E, history of nonalcoholic steatohepatitis, Wilson's disease, history of diabetes, hemochromatosis, history of α -1 antitrypsin disease, history of Gilbert's disease, known hepatic congestion, cirrhosis, esophageal varices, GI bleeds, recent use of Tylenol/hepatotoxic drugs, and any other relevant abnormal liver biochemistry risk factors)
- Liver disease signs and symptoms (e.g. anorexia, asthenia, pyrexia, pruritus, jaundice, arthralgia, abdominal pain, abdominal tenderness, nausea, vomiting, mucosal inflammation, purpura, hepatomegaly, hepatojugular reflux, splenomegaly, elevated jugular venous distension, ascites, confusional state/encephalopathy, coma, right upper quadrant pain, vascular cutaneous signs, and any other relevant signs and symptoms)
- Liver diagnostic tests (e.g. ultrasound RUQ, abdomen CT, liver MRI/MRCP, endoscopic retrograde cholangiopancreatography/esophagogastroduodenoscopy, liver biopsy, x-ray, and paracentesis)

9.5.2.10 Major Adverse Cardiovascular Events

The primary safety endpoint is time to first MACE.

MACE is a composite of the total of CV death, non-fatal MI and non-fatal stroke.

A Clinical Events Committee (CEC) will be formed to assess and adjudicate all MACE. This committee will be blinded to treatment assignment and composed of independent cardiologists. A charter outlining the communication flow and the criteria to classify and adjudicate MACE will be established.

The committee will adjudicate:

- All death cases
- Myocardial infarction defined as any non-fatal case that was coded to a preferred term (PT) in the standardized MedDRA query (SMQ) "myocardial infarction"
- Stroke defined as any non-fatal case that was coded to a PT in the SMQ "central nervous system hemorrhages and cerebrovascular conditions"

Additionally, the SMQs of cardiac disorders and cerebrovascular disorders will also be assessed by the CEC.

Patients who experience a MACE must be discontinued from IP and enter into the post-treatment follow-up period (Section 9.3.3.1).

Rescue medication use will be collected in the patient diary to assist in the interpretation of patient level safety events, such as MACE or other cardiovascular events. In the event of a MACE or other cardiovascular event, copies of the paper diary may be requested by the Sponsor.

9.5.2.11 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at Visits 1A, 6, 10, and 12 or EOT, for patients who prematurely discontinue IP. At Visit 1B, the PI will assess the clinical significance of any values outside the reference ranges provided by the local laboratory.

Although fasting is not required, the patient should be encouraged to fast prior to each visit. The patient's fasting condition must be consistent at all visits.

Women of childbearing potential will be required to have a serum pregnancy test at Visit 1A and Visit 12 or EOT, for patients who prematurely discontinue IP. For Visits 6 and 10, a urine pregnancy test will be performed for women of childbearing potential.

The following clinical laboratory tests *will* be performed:

Hematology: Absolute and differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), white blood cell count, erythrocyte count, thrombocytes (platelets), hemoglobin, and hematocrit

Chemistry: Sodium, potassium, calcium, chloride, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, aspartate aminotransferase, creatine kinase, inorganic phosphorus, alanine aminotransferase, total cholesterol, triglycerides, uric acid, gamma-glutamyl transferase, and lactate dehydrogenase

Urinalysis: Dipstick analysis will be performed at the center and will include: pH, blood, leukocytes, protein, glucose, bilirubin, ketones, and nitrites. If urine dipstick is abnormal, a urine sample will be sent to local lab for analysis of the sediment

Theophylline: Only if the patient is receiving theophylline

Local laboratories will be used to evaluate all urine and blood samples.

Clinically significant abnormalities in laboratory values as determined by the investigator should be reported as adverse events (Section 9.5.2.1).

9.5.2.12 Vital Signs

Vital sign measurements will be documented at Visits 1A, 2, 3, 4, 5, 6, 8, 10, and 12 or EOT, for patients who prematurely discontinue IP. The parameters are pulse rate, sitting systolic and diastolic blood pressure (BP). Pulse and BP readings will be taken after the subject has been sitting for 10 minutes. Waist circumference will also be taken at Visit 1A according to guidance provided by the National Heart, Lung, and Blood Institute (NHLBI 2000) (See Appendix VI).

9.5.2.13 Electrocardiograms

One 12-lead electrocardiogram (ECG) will be performed at Visit 1A, and 2 hour post-dose ECG will be performed at Visit 1B.

An ECG will be performed 1 hour pre-dose and 2 hours post-dose at Visits 2, 3, 4, 5, 6, 8, 10 and 12. For patients who prematurely discontinue IP (EOT Visit), one ECG assessment will be performed. Patients should be in a supine position for at least 10 minutes prior to the test. All ECGs will be read by a central vendor.

If a clinically significant ECG abnormality persists, the PI must contact the study physician to determine whether the patients should be continued in the study.

The time window for ECGs to be completed is ± 10 minutes from the scheduled time point.

9.5.2.14 Other Safety Assessments

a) Physical Examination

A physical examination will be done at Screening (Visit 1A) and Visits 4, 6, 10, and 12 or EOT by a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations. Height will be collected only at Visit 1A. Body weight will be collected at Visit 1A and Visit 12 or EOT. If a clinically significant finding occurs at Visit 1A, it should be added to the Medical History and any changes thereafter considered AEs.

9.5.2.15 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be established for this study. The DSMB will periodically monitor and review relevant clinical safety data, including adjudicated MACE.

DSMB members comprise a multidisciplinary team, including experts in pulmonary disease, cardiovascular disease, and biostatistics. Ad hoc members from other disciplines may be appointed to the DSMB if deemed necessary by the DSMB Chair and the Sponsor.

Membership and responsibilities of the DSMB as well as meeting frequencies and other details (e.g. communication) will be defined in the DSMB charter.

9.5.2.16 Joint Advisory Committee

The purpose of the ASCENT COPD Joint Advisory Committee (JAC) is to advise the Sponsor Study Team regarding issues related to the conduct of the study (e.g. global enrollment rate,

study patient compliance, screen failure rate, early termination rate), and to establish the scientific strategy, analyses and interpretation of study data and communication of that data. The JAC is comprised of seven (7) expert members, 4 external (2 pulmonologist study investigators, 1 cardiologist, 1 biostatistician), 3 sponsor representatives (2 clinicians and 1 biostatistician).

9.5.3 Investigational Product Concentration Measurements

Not applicable.

9.5.4 Health Economic and Outcomes Research Assessments

The CAT is a validated, patient completed, questionnaire to measure the impact of COPD on a patient's health status. It is comprised of 8 questions to be answered independently by patient via a paper questionnaire (See Appendix V). At Visits 1B, 3, 4, 5, 6, 8, 10 and 12 or EOT, the CAT will be completed at the study site prior to any other study procedures. At Visits 7, 9 and 11, the CAT will be completed at home by the patient during the telephone visit and mailed back to the study site. All data captured on the CAT will be entered into EDC by site staff.

9.5.5 Schedule of Assessments

The schedule of study procedures and assessments is tabulated by visit in the Schedule of Evaluations in Section 2.

The descriptions of the procedures to be performed at each visit are provided below.

All procedures should be performed in the order listed.

9.5.5.1 Informed Consent

Patients must sign the ICF within 30 days prior to any procedures being performed, and before medication washouts are initiated. The following procedures will be performed upon obtaining consent:

- Access IWRS. IWRS will assign Patient Identification Number (PID)
- Obtain patient demographics, medical history, and medication history. Confirmatory documentation for cardiovascular history must be obtained prior to Visit 1B in the form of a historic record, or self-report accompanied by an appropriate treatment regimen as assessed and confirmed by a source (e.g. medically qualified investigator or patient's treating physician).
- If patient requires washout, proceed to Washout/Run-in (Visit 0). If a washout is not required, proceed to Visit 1A (Section 9.5.5.3)

9.5.5.2 Washout/Run-in (Visit 0)

Visit 0 will only occur for patients who are taking a prohibited medication and require a washout. At Visit 0 and prior to the start of the washout period, the following procedures will be performed:

- Access IWRS
- Perform pre-bronchodilator FEV₁ spirometry test (forced maneuver only) (see Section 9.5.1.2 and Appendix III)
- Schedule patient phone contacts during the washout period to assess COPD stability. Contact should be made once per week.
- Dispense rescue medication and rescue medication diary and instructions.
- Schedule patients to return for Visit 1A in approximately 2 weeks

9.5.5.3 Screening (Visit 1A)

For patients who do not require a washout, the ICF must be signed within 30 days prior to Visit 1A, prior to performing any procedures. On the day the ICF is signed, patients will be registered in IWRS, assigned a PID in sequential order (by the IWRS), and dispense albuterol/salbutamol for reversibility testing and rescue medication diary and instructions. Rescue medication dispensing and specific rescue medication will be provided locally.

At Visit 1A, the following procedures will be performed:

- For patients who required a washout, review rescue medication usage per diary.
- Obtain patient demographics, medical history, and medication history. Confirmatory documentation for cardiovascular history must be obtained prior to Visit 1B in the form of a historic record, or self-report accompanied by an appropriate treatment regimen as assessed and confirmed by a source (e.g. medically qualified investigator or patient's treating physician).
- Assess smoking status
- Assess COPD exacerbations (see Section 9.5.1.1)
- Assess any AEs that have occurred since the patient signed the ICF
- Collect concomitant medications (see Appendix II)
- Measure vital signs (see Section 9.5.2.12)
- Perform ECG (see Section 9.5.2.13)
- Perform physical examination (including height and weight) (see Section 9.5.2.14a))
- Perform pre-bronchodilator FEV₁ spirometry test (forced maneuver only) (See Section 9.5.1.2 and Appendix III)

- Reversibility test. Administer 4 puffs (~400 µg) of albuterol/salbutamol from the rescue inhaler within 30 mins of pre-bronchodilator spirometry. Perform qualifying post-bronchodilator assessment 10-15 mins after albuterol/salbutamol administration.
- Perform post-bronchodilator FEV₁ spirometry test (forced maneuver only) and determine FEV₁/FVC ratio (See Section 9.5.1.2 and Appendix III)
- Collect blood and urine samples for local clinical laboratory determinations including serum pregnancy test for women of child bearing potential. Results must be reviewed prior to randomization (see Section 9.5.2.11)
- Confirm patients meet inclusion/exclusion criteria (see Section 9.3)

9.5.5.4 Baseline (Visit 1B)

Within 3-5 days following Visit 1A, upon receipt of clinical laboratory results, the following procedures should be completed at Visit 1B:

- Confirm patient continues to meet inclusion/exclusion criteria (See Section 9.3)
- Administer the CAT (see Section 9.5.4) prior to any other study procedure
- Assess COPD exacerbations (see Section 9.5.1.1). In the event of a Respiratory infection or COPD exacerbation prior to Screening and/or during the Screening period between (Visit 0 and 1B) the screening visit may be extended once only after the last increased additional dose of steroid burst and/or antibiotics is given to ensure patient has recovered from the exacerbation.
- Assess any AEs that have occurred since the patient signed the ICF
- Collect concomitant medications (see Appendix II)
- Perform two pre-dose FEV₁ spirometry tests 30-45 minutes apart (forced maneuver only) (see Section 9.5.1.2 and Appendix III)
- Randomize patients via IWRS
- Dispense IP via IWRS
- Provide and review DPI instructions and IP dosing instructions with patients
- Provide and review diary and diary instructions for IP use with patients
- First dose of IP should be taken in the office and documented in the diary under the supervision of study staff
- Perform post-dose ECG (see Section 9.5.2.13)

- Provide the rescue medication locally if required
- Schedule patients to return for Visit 2 in 1 month (± 7 days) and remind patients not to take their dose of IP on the morning of the next visit

9.5.5.5 Visit 2

At Visit 2, the following procedures will be performed for patients continuing in the treatment period. For patients who discontinue IP, see Section 9.5.5.8 for End of Treatment procedures.

- Confirm that morning dose of IP has not been taken. If morning dose has been taken, the visit must be rescheduled.
- Assess smoking status
- Assess COPD exacerbations (see Section 9.5.1.1)
- Assess any AEs that have occurred since the previous visit
- Assess concomitant medications (see Appendix II)
- Review rescue medication usage per diary
- Measure vital signs (see Section 9.5.2.12)
- Perform pre-dose ECG (see Section 9.5.2.13)
- Perform FEV₁ spirometry test (forced maneuver only) (see Section 9.5.1.2 and Appendix III)
- Collect diary and assess compliance. Provide retraining if necessary (see Section 9.4.9)
- Provide patients with diary and diary instructions for IP use
- Morning dose of IP should be taken in the office and documented in the diary under the supervision of study staff
- Perform post-dose ECG (see Section 9.5.2.13)
- Provide the rescue medication locally, if required
- Schedule patients to return for Visit 3 and remind patients not to take their dose of IP on the morning of the next visit

9.5.5.6 Visits 3, 4, 5, 6, 8, and 10

At Visits 3, 4, 5, 6, 8, and 10, the following procedures will be performed for patients continuing in the treatment period. For patients who discontinue IP, see Section 9.5.5.8 for End of Treatment procedures.

- Confirm that morning dose of IP has not been taken. If morning dose has been taken, the visit must be rescheduled
- Administer the CAT (see Section 9.5.4) prior to any other study procedures
- Assess smoking status
- Assess COPD exacerbations (see Section 9.5.1.1)
- Assess any AEs that have occurred since the previous visit
- Assess concomitant medications (see Appendix II)
- Review rescue medication usage per diary
- Measure vital signs (see Section 9.5.2.12)
- Perform pre-dose ECG (see Section 9.5.2.13)
- Perform physical examination at Visits 4, 6, and 10 only (see Section 9.5.2.14a))
- Perform FEV₁ spirometry test (forced maneuver only) (see Section 9.5.1.2 and Appendix III)
- Collect blood and urine samples for clinical laboratory determinations including urine pregnancy test for women of child bearing potential at Visits 6 and 10 only (see Section 9.5.2.11)
- Collect IP and diary and assess compliance. Provide retraining if necessary (see Section 9.4.9)
- Access IWRS
- Dispense IP
- Provide the rescue medication, if required
- Review and provide patients with DPI instructions and IP dosing instructions
- Provide patients with diary and diary instructions for IP use
- First dose of IP should be taken in the office and documented in the diary under the supervision of study staff

- Perform post-dose ECG (see Section 9.5.2.13)
- Provide CAT and mailing envelope at Visit 6, 8, and 10 for completion at next telephone visit (see Section 9.5.4)
- Schedule patients to return for next visit according to Schedule of Evaluations and remind patients not to take their dose of IP on the morning of the all subsequent in-clinic visits

9.5.5.7 Visits 7, 9, and 11

Visits 7, 9, and 11 will be conducted by telephone for patients continuing in the treatment period. The following information will be collected at each telephone visit:

- Instruct patient to complete CAT (see Section 9.5.4) and remind patient to send CAT back to the site using the pre-addressed, pre-stamped mailing envelope
- Assess smoking status
- Assess COPD exacerbations (see Section 9.5.1.1)
- Assess any AEs that have occurred since the previous visit
- Assess concomitant medications (see Appendix II)

9.5.5.8 Visit 12

At the Final Visit (patients completing the treatment period only), the following procedures will be performed:

- Confirm that morning dose of IP has not been taken. If morning dose has been taken, the visit must be rescheduled.
- Access IWRS
- Administer the CAT (see Section 9.5.4)
- Assess smoking status
- Assess COPD exacerbations (see Section 9.5.1.1)
- Assess any AEs that have occurred since the previous visit
- Collect concomitant medications (see Appendix II)
- Review rescue medication usage per diary
- Measure vital signs (see Section 9.5.2.12)
- Perform pre-dose ECG (see Section 9.5.2.13)

- Complete physical examination (including weight) (see Section 9.5.2.14a))
- Perform FEV₁ spirometry test (forced maneuver only) (see Section 9.5.1.2 and Appendix III)
- Collect blood and urine samples for clinical laboratory determinations including serum pregnancy test for women of child bearing potential (see Section 9.5.2.11)
- Morning dose of IP should be taken in the office and documented in the diary under the supervision of study staff
- Perform post-dose ECG (See Section 9.5.2.13)
- Collect IP and diary and assess compliance (see Section 9.4.9)
- Collect rescue medication and assess usage via diary
- Provide the rescue medication locally if required

Any clinically significant findings obtained during the final examination, including clinically significant laboratory abnormalities, will be documented. A telephone contact will be performed 15 days after the last known dose of IP is taken to assess any AEs that may have occurred and changes to and/or new concomitant medications taken since the last dose taken at the final visit.

Any SAEs that occur within 15 days of the last dose of IP, or that were identified during the telephone contact, will be followed up by the investigator for as long as medically indicated but after 30 days there will be no further recording in the CRF. AZ retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

9.5.5.9 End of Treatment (EOT) Visit

Patients who prematurely discontinue IP will complete the following procedures:

- Access IWRS
- Administer the CAT (see Section 9.5.4)
- Assess smoking status
- Assess COPD exacerbations (see Section 9.5.1.1)
- Assess any AEs that have occurred since the previous visit
- Collect concomitant medications (see Appendix II)
- Review rescue medication usage per diary
- Measure vital signs (see Section 9.5.2.12)

- Perform ECG (see Section 9.5.2.13)
- Complete physical examination (including weight) (see Section 9.5.2.14a)
- Perform FEV₁ spirometry test (forced maneuver only) (see Section 9.5.1.2 and Appendix III)
- Collect blood and urine samples for clinical laboratory determinations including serum pregnancy test for women of child bearing potential (see Section 9.5.2.11)
- Collect IP and diary assess compliance (see Section 9.4.9)
- Collect rescue medication inhaler(s)
- If patient discontinued trial medication before the end of the trial, the patient will be informed that he/she will be contacted every three months for the first two years and then every six months for the third year as per Table 9.3.3–1 via telephone calls, until the subject completes 36 months in the study.
- Schedule next Post-Treatment Follow up Visit according to Table 9.3.3–1. If the EOT occurs within two weeks of the next scheduled visit (telephone contact or on-site) the next visit can be skipped

Any clinically significant findings obtained during the final examination, including clinically significant laboratory abnormalities, will be documented. A telephone contact will be performed 15 days after the last known dose of IP is taken to assess any AEs that may have occurred and changes to and/or new concomitant medications taken since the last dose taken at the final visit. For patients who prematurely discontinue IP, only SAEs will be collected until the last visit/end of study.

AZ retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

9.5.5.10 Contacts between treatment visits

In the event of a patient missing a study visit, the patient will have a documented telephone contact initiated by the PI or designee in accordance with the Schedule of Evaluations (see pages 4-6), approximately every 3 months for the first two years and once every six months for year three following each treatment visit starting after Visit 1B. The PI or designee will ask the patient about any new AEs, COPD exacerbations and concomitant medication changes since the last visit.

9.5.5.11 Vital Status Follow-up

Additionally, patients who discontinue trial medication early will be contacted in accordance with table 9.3.3-1, approximately every 3 months for the first two years and once every six months for year three to obtain vital status information: MACE events, COPD exacerbations, SAEs, and concomitant medications; until the sponsor-defined end of the trial.

9.5.5.12 Completion of Study

The Ethical Committee (EC) / Competent Authority (CA) in the US and Canada needs to be notified about the end of the trial (last patient/patient out, unless specified differently or early termination of the trial).

Based on the number of MACE events, the sponsor will declare the end of the study date and give the study sites at least 3 months' notice. After the announcement of the end of study, the following information will be collected for all patients (these visit procedures also apply for a patient who is discontinuing trial medication before the end of the trial):

- Subjects active on study drug:
 - All assessments listed in Section 9.5.5.9(EOT).
 - Schedule a phone contact for 15 days from visit.

- Subjects in post treatment follow up:
 - All assessments listed for V12 in Table 9.3.3-1

9.6 Data Quality Assurance

9.6.1 Data Monitoring

Before any patient enters the study, a representative of Sponsor, will meet with the PI and the study center staff to review the procedures to be followed during the study. Electronic data capture (EDC) functionality training is provided via computer-based training to train PIs and authorized designees on recording the data in the eCRFs using the electronic data capture EDC system. After the first patient is enrolled, the Sponsor representative, a Regional Site Manager (RSM) or designee, will periodically monitor the progress of the study by conducting on-site visits. This RSM or designee will review query statuses remotely, possibly warranting more frequent communication and/or site visits with the PI and the study center staff. The PI will make available to the RSM or designee source documents (written notes and medical records/ electronic medical records), signed consent forms, and all other study-related documents. The PI and the study center staff will be responsible for data entry of patient data into the eCRFs via the EDC system, resolving data queries generated via the EDC system and providing missing or corrected data. The PI or designee will be responsible for approving all changes performed on the data, and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past.

9.6.2 Data Recording and Documentation

Data collection will involve the use of the AZ EDC system, to which only authorized personnel will have access. Patient's data are to be entered into the EDC system by the PI or designee using their assigned EDC user account. After data entry into the EDC system by the PI or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edits checks, data monitoring and reviews; queries may be electronically issued to the study centers and should be answered electronically via the EDC system.

Each query will carry identifying information (assigned username, date and time) to assist AZ and the PI on the origin of the data clarification request and the response provided by the PI. All data changes made to the patient's data via a data query will be approved by the PI prior to final database lock.

After all data have been reviewed and all issues have been resolved, the database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of eCRFs, laboratory reports, patient diaries, regulatory documents, etc.) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by Sponsor; its authorized representatives; and the FDA or other health authorities.

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Patient Populations

Three populations will be considered in the statistical analysis of the study.

9.7.1.1 Screened Population

The Screened Population will consist of all patients who signed a written informed consent form and received a screening number.

9.7.1.2 Randomized Population

The Randomized Population will consist of all patients in the Screened Population who were randomized to a treatment group in the study.

9.7.1.3 Full Analysis Set Population

The Full Analysis Set (FAS) population will consist of all patients in the Randomized Population who took at least one dose of double-blind investigational product. Patients will be analyzed according to their randomized treatment.

The FAS will be used to carry out the primary analysis of both efficacy and safety data. Efficacy and safety data may be further investigated and sensitivity analyses may be performed using the Randomized Population if more than 1% of patients did not receive one dose of double-blind IP.

9.7.2 Patient Disposition

The number of patients in Randomized, and FAS populations will be summarized by treatment group and study center; the Screened Population will only be summarized overall by study center.

Screen failures (i.e., patients screened but not randomized) and the associated reasons for failure will be tabulated overall. The number and percentage of patients who complete the double-blind treatment period, who prematurely discontinue from IP, and who prematurely discontinue from the study during the same period will be presented for each treatment group and pooled across treatment groups for the FAS Population. The reasons for premature discontinuation as recorded on the termination pages of the eCRF will also be summarized (number and percentage) by treatment group for all randomized patients.

The percentage of premature discontinuations from the study treatment as well as from the study will be compared overall using Kaplan Meier and Log rank test. Each discontinuation reason will be summarized by treatment groups. Additional graphical presentation to illustrate patterns of missing data will be described in the Statistical Analysis Plan.

Handling professional/duplicate patients. Professional patients are individuals who, in violation of protocol entrance criteria enter into the same study more than once and/or enter into different studies at the same time.

Unless otherwise stated, the first incidence of patient entering trial is used in analysis and summary. All data is listed for transparency, with flags for duplicate patients to ensure clarity on the records included/excluded from the analysis.

For handling of AEs, if a patient is randomized to same treatment arm, all data will be included into the analysis. If patient is randomized to a different treatment (i.e., different treatment received at the second incidence vs the first incidence), only the data from the first incidence will be used in analysis.

9.7.3 Demographics and Other Baseline Characteristics

Demographic parameters (including age, age group [≥ 40 and < 60 , ≥ 60 and < 70 , and ≥ 70 years old], race, ethnicity, sex, weight, height, and body mass index) and other baseline characteristics (including duration of COPD in years; patient known to have either chronic bronchitis or emphysema; COPD exacerbation in the previous 12 months; number of COPD exacerbations in the previous 12 months; COPD severity according to degree of airway obstruction: grade I [mild], II [moderate], III [severe], or IV [very severe]; smoking status and history; smoking duration in years; number of cigarettes per day; total pack-years; FEV₁, FEV₁ % predicted, FVC, and FVC % predicted prebronchodilator test; FEV₁, FEV₁ % predicted, FVC, and FVC % predicted, and ratio of FEV₁/FVC postbronchodilator tests; % bronchodilator reversibility; change from prebronchodilator FEV₁ to postbronchodilator FEV₁; reversibility and baseline FEV₁) will be summarized by treatment group for the FAS populations. For continuous variables, the number of nonmissing observations, mean, SD, median, minimum, and maximum will be presented. No statistical tests will be performed.

The World Health Organization Drug Dictionary, enhanced version of March 2011 or newer, will be used to classify prior and concomitant medications by therapeutic class. Prior medication is defined as any medication taken within the period from 15 days before Screening (V0/Visit 1A) to the day before the first dose of double-blind IP. Concomitant medication is defined as any medication taken during the double-blind treatment period between the date of the first dose of IP and the date of the last dose of IP, inclusive.

Prior medications will be tabulated by Anatomical Therapeutic Chemical classification code, preferred name, and treatment group. In addition, the number and percentage of patients who used any prior medication for COPD will be presented by therapeutic categories (i.e., Long-Acting β_2 -Agonists [LABA], Long-Acting Muscarinic Antagonist [LAMA], Short-Acting β_2 -Agonists [SABA], Short-Acting Muscarinic Antagonist [SAMA], Inhaled Corticosteroids [ICS], LABA and ICS Combination, SABA and SAMA combination, leukotriene modifiers, oral phosphodiesterase type 4 [PDE4], systemic corticosteroid, oxygen, methylxanthines, and influenza vaccine) and by treatment groups. Prior medication in the reporting by therapeutic categories is defined as any medication taken within 15 days prior to Visit 0/1A before initiation of a washout period.

All concomitant medications will be classified for each one of the two following periods and listed by treatment groups: 1) medications that the patient started to take before the randomization and continued after the first IP administration, and 2) medications that the patient started to take during the treatment period (from the first IP administration to the last IP administration). Medications that were used between the last IP administration and to the study end will be summarized for the patients who discontinued IP. In addition, the overall number and percentage of patients taking no concomitant medications versus those taking any concomitant medications will be summarized for each of these two periods and by treatment group. Concomitant medications will be tabulated by the third level of the Anatomical Therapeutic Chemical code, preferred name, and treatment group.

The use of prior and concomitant medications will be summarized by the number and percentage of patients in each treatment group for the FAS Population. Multiple medication use by a patient will only be counted once.

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

Exposure to double-blind IP for the FAS Population during the double-blind treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of double-blind IP taken to the date of the last dose taken, inclusive. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented by treatment group.

9.7.4.2 Measurement of Treatment Compliance

Dosing compliance for the double-blind treatment period is defined as the total number of treatment applications (puffs) taken by a patient during that period divided by the number of puffs expected to be taken during that same period multiplied by 100.

Descriptive statistics for IP compliance will be presented by treatment group for each scheduled visit and overall during the double-blind treatment period for the FAS Population. Further information on how to calculate the compliance will be provided in the statistical analysis plan (SAP).

9.7.5 Efficacy Analyses

Efficacy analyses will be based on the FAS Population. All statistical tests will be two-sided hypothesis tests performed at the 0.05 alpha level of significance for main effects. All confidence intervals will be two-sided 95% confidence intervals, unless stated otherwise.

To control for multiplicity, the primary and secondary efficacy variables will be tested sequentially, i.e., the secondary efficacy endpoint will be tested only when both primary and secondary analyses on the primary efficacy endpoint achieved statistical significance, and the secondary analysis on the primary efficacy endpoint will be tested only when the primary analyses on the primary efficacy endpoint achieved statistical significance. Otherwise, nominal p-values will be provided and should be interpreted descriptively.

9.7.5.1 Primary Efficacy Parameter

The primary efficacy parameter is the following:

- Rate of moderate or severe COPD exacerbations during the first year of treatment per patient per year

The primary efficacy endpoint of rate of moderate or severe COPD exacerbation per patient per year during the first year of treatment will be presented for the FAS population. The rate ratio of moderate or severe COPD exacerbation per patient per year due to the effect of aclidinium bromide 400 µg BID relative to placebo will be estimated along with its confidence interval and the corresponding p-value.

Exacerbation rate in aclidinium group will be compared to exacerbation rate in the placebo group using a Negative Binomial regression model. The response variable in the model will be the number of moderate or severe COPD exacerbations experienced by a patient during the first year of treatment. The model will include treatment group, baseline ICS use, baseline COPD severity, history of at least one exacerbation in the past year, and smoking status as factors. In order to adjust for the exposure for each patient, the natural logarithm of the exposure time (in years) during the first year of treatment will be used as an offset variable. When used as the offset variable, the exposure time will be adjusted by subtracting the time when a patient experienced COPD exacerbation(s) (i.e., not at risk during an exacerbation). If the Negative Binomial regression model does not converge, the Poisson regression model with robust variance estimate using sandwich method will be applied.

The primary analysis on the primary efficacy endpoint will be based on on-treatment analysis, i.e. for those patients who prematurely discontinue during the first year of double-blind treatment period and have follow-up assessments, the primary analysis will be based on the data collected before treatment discontinuation. The secondary analysis of this endpoint will be based on on-study analysis using the same model as for the primary analysis of the primary efficacy endpoint. For those patients who prematurely discontinue IP during the first year of treatment and have follow-up assessments, the secondary analysis will include the events collected during the PTFU period up to one year.

The rate ratio of moderate or severe COPD exacerbation per patient per year due to the effect of aclidinium bromide 400 µg BID relative to placebo will be estimated along with its confidence interval and the corresponding p-value. The two-sided p-value for aclidinium bromide 400 µg BID relative to placebo in reducing the rate of exacerbation will be compared to the 0.05 significance level.

Sensitivity analyses

To assess the robustness to variations of the data assumptions underlying the primary and secondary analysis of the primary efficacy endpoint, several sensitivity analyses will be conducted as follows:

- Jump to reference (J2R) approach (see Appendix 1 for details)
- Copy reference (CR) approach (Keene et al, 2014; see Appendix 1 for details)
- Tipping point analysis (see Appendix 2 for details)

9.7.5.2 Secondary Efficacy Parameter

The secondary efficacy variable is rate of hospitalization due to COPD exacerbation per patient per year during the first year of treatment. This will be analysed (on-treatment analysis) using the same model as for the analyses of the primary efficacy endpoint, including on-study analysis as sensitivity analysis.

9.7.5.3 Additional Efficacy Parameters

The additional efficacy parameters are the following (on-treatment analysis):

- COPD exacerbation parameters
 - Rate of moderate or severe COPD exacerbations per patient per year
 - Rate of mild, moderate, or severe COPD exacerbations per patient per year
 - Duration (days) of moderate or severe COPD exacerbations per patient per year
 - Duration (days) of mild, moderate, or severe COPD exacerbations per patient per year

- Number and percentage of patients with at least one COPD exacerbation (any, mild, moderate, severe, and moderate or severe)
- Time (days) to first, second, and third COPD exacerbation (any, and moderate or severe)
- Time (days) to withdrawal due to COPD exacerbation
- Rate of hospitalizations due to COPD exacerbations per patient per year
- Number of days hospitalized due to COPD exacerbations
- Time (days) to first hospitalization due to COPD exacerbation
- Spirometry
 - Change from baseline in morning pre-dose trough FEV₁ at visits 2, 3, 4, 5, 6, 8, 10, and 12

COPD Exacerbations

All additional efficacy parameters will be presented based on the FAS population. The details will be described in the SAP.

The rate of COPD exacerbations per patient per year (any, and moderate or severe) will be analyzed using a Negative Binomial regression model similar the primary analysis of the primary efficacy parameter. For categories that Negative Binomial regression does not converge, the Poisson regression model with robust variance estimate using sandwich method will be applied. The details will be described in the SAP. The durations of all endpoints of COPD exacerbation days will also be summarized for only the patients who had exacerbations during the double-blind treatment period.

The number of patients with at least one COPD exacerbation (any, mild, moderate, severe, and moderate or severe) will be analyzed based on a logistic regression model with treatment group and baseline COPD severity and smoking status as factors.

Time (days) to first COPD exacerbation (any, and moderate or severe) will be analyzed by means of Kaplan-Meier estimators and Cox Proportional Hazards model. The estimates of the hazard ratio comparing aclidinium bromide 400 µg with placebo will be derived using the Cox proportional hazard model for the time in terms of the number of days served as a response and treatment group, baseline ICS use, baseline COPD severity, history of at least one exacerbation in the past year, and smoking status as factors.

Duration of COPD exacerbations per patient per year (any, and moderate or severe) will be summarized descriptively.

Spirometry

The additional efficacy spirometry parameter, change from baseline in morning pre-dose trough FEV₁ at visits 2, 3, 4, 5, 6, 8, 10, and 12, will be analyzed using a mixed model for repeated measures (MMRM). Treatment group will be fitted as the explanatory variable, and pre and post-bronchodilator (albuterol/salbutamol) FEV₁ at screening visit (Visit 1A), and baseline FEV₁ as covariates, and smoking status, baseline ICS use, visit, and treatment group-by-visit interaction as fixed effect factors. The within-patient correlation will be modeled using the unstructured covariance matrix. If the model does not converge, then the compound symmetry covariance structure will be used.

9.7.6 Safety Analyses

The safety analysis will be performed using the FAS Population. For the safety analysis, the safety parameters are AEs including COPD exacerbations, vital sign measurements, ECG parameters, and physical examination findings. For each safety parameter, the last assessment made before the first dose of double-blind IP will be used as the baseline for all analyses of that safety parameter.

9.7.6.1 Primary Safety Parameter

The primary safety parameter is time to first MACE.

The primary safety endpoint of time to first MACE will be presented for the FAS Population and will be based on on-study analysis. The on-study analysis will be used as it provides an overall evaluation of the effect of aclidinium or placebo, as well as reduces the potential bias caused by censoring events and patients as a result of differences in study drug adherence. We are defining on-study analysis as all events that occurred while the patients was in the study, irrespective of treatment exposure (i.e., this includes all events that occurred while a subject was on treatment or off treatment).

In addition, to account for the relation of the occurrence of an event and treatment exposure, an on-treatment analysis will also be conducted and this will include only events that occurred while the patient was exposed to study treatment, i.e., events that occurred after the patient's last treatment dose was censored. Two ascertainment windows, 0 and 15 days, will be evaluated in the on-treatment analyses. The on-treatment and on-treatment +15 days analyses will censor events that occur after and more than 15 days after, respectively, after the last treatment dose.

While a primary method is pre-specified, patterns and timing of discontinuation from study treatment, as well as selected replacement therapy will be carefully evaluated between aclidinium bromide 400 µg BID and placebo. The impact of these explorations in the analysis methods (i.e., the on-study analysis and on-treatment analysis) will be thoroughly assessed. Since both approaches have limitations, the totality of evidence will be carefully weighed regarding the evaluation of MACE.

The choice of on-study and on-treatment analyses (applying different censoring scheme) is consistent with the SAVOR-TIMI 53 trial [Scirica et al, 2013, Geiger et al, 2015] and the TIOSPIR trial assessing all-cause mortality [FDA Briefing Book for Pulmonary-Allergy Drugs Advisory Committee Meeting August 14, 2014 for NDA# 21936].

The primary safety endpoint will be analyzed based on Cox-proportional hazards regression model including, baseline CV severity, smoking status, and treatment group as covariates. The assumption of proportional hazards will be assessed visually using log-cumulative hazard plots. The effect of any departures from proportional hazards will be discussed as part of the presentation of results of the analyses. The CV severity at baseline will be defined as 2 categories: 1) patients who had 2 CV risk factors, and 2) patients who had more than 2 CV risk factors or at least one non-fatal stroke or non-fatal MI. This model will provide point estimate for the hazards ratio (aclidinium over placebo), as well as corresponding 95% confidence interval. The upper bound of the 95% confidence interval (based on Cox regression) for the hazard ratio (aclidinium relative to placebo) of time to first MACE will be used to rule out the null hypothesis of hazard ratio of 1.8 for the primary test on MACE. If the upper bound of the 95% confidence interval is less than the 1.8 margin of the hazard ratio, then the hazard ratio of 1.8 or higher will be ruled out (justification for the hazard ratio of 1.8 is provided in Appendix IV). In addition, the Kaplan-Meier survival curves will be displayed for each treatment group.

The results from the primary safety analysis will also be evaluated considering a superiority hypothesis.

Sensitivity analyses

To account for the relation of the occurrence of an event and treatment exposure, an on-treatment analysis will be conducted and this will include only events that occurred while the patient was exposed to study treatment, i.e., events that occurred after the patient's last treatment dose will be censored. Two ascertainment windows, 0 and 15 days, will be evaluated in the on-treatment analyses. The on-treatment and on-treatment +15 days analyses will censor events that occur after and more than 15 days after, respectively, after the last treatment dose.

Sensitivity analysis of the primary composite endpoint will include analysis with CV death replaced with all-cause mortality.

Sensitivity analysis will also be conducted to assess the impact of change in the inclusion criteria, by including in the model as factor a flag (1=Pre-/2=Post-) to account for the change in the inclusion criteria.

9.7.6.2 Secondary Safety Parameter

The secondary parameter is the following:

- Time to first MACE or other serious cardiovascular events of interest (ie, SMQ of cardiac disorders and SMQ of cerebrovascular disorders)

The analyses of the secondary safety endpoint of the time to first MACE or other serious cardiovascular events of interest and all additional endpoints will not be adjusted for multiple comparisons.

The secondary safety endpoint of time to first MACE or other serious cardiovascular events of interest (ie, SMQ of cardiac disorders and SMQ of cerebrovascular disorders) will be analyzed for the FAS Population using the same method as the primary safety endpoint using a confidence level of 95% and without statistical testing for non-inferiority (non-inferiority margin will not be used). Supportive listings will be provided for all adjudicated events with adjudication conclusions.

9.7.6.3 Additional Safety Parameters

a) Adverse Events

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities, Version 15.0 or newer.

An AE (classified by preferred term) will be considered a treatment-emergent adverse event (TEAE) if it started on or after the date of the first dose of double-blind IP or it started before the date of the first dose of double-blind IP and continued during the double-blind treatment period with increased severity. An AE that occurs more than 15 days after the date of the last dose of double-blind IP will not be counted as a TEAE.

AEs will be collected only once with its maximum intensity, except when the AE started before first IP administration, persisted after it and worsened in intensity any time after first IP. In this latter case, the AE will be collected with each respective intensity. The AE term recorded must be exactly the same in the different intensities collected.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by system organ class, high level term, and preferred term; by system organ class, high level term, preferred term, and severity; by system organ class, high level term, preferred term, and relationship to the IP; and by system organ class, high level term, preferred term, and outcome. If more than one AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by causal relationship to the IP.

For the summary table by system organ class, high level term and preferred term, the distribution of TEAEs in each treatment group will be sorted in decreasing frequency by preferred term for acclidinium bromide 400 µg within each system organ class.

The incidence of common (e.g. $\geq 2\%$ of patients in any treatment group) TEAEs will be summarized by preferred term.

All the incidences will be sorted by decreasing frequency for acclidinium bromide 400 µg.

A SAE that occurs on or after the date of the first dose of double-blind IP and within 15 days of the date of the last dose of double-blind IP will be considered an on-therapy SAE. The number of percentages of patients with on-therapy SAEs, and AEs leading to premature discontinuation of the IP will be summarized by SOC and PT, and treatment group and will be sorted by decreasing frequency for acclidinium bromide 400 µg. In addition, the incidence of fatal on-therapy SAEs (i.e. events that caused death) will be summarized separately by preferred term, and treatment group.

For the Screened Population, separate listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any).

b) Vital Signs

Descriptive statistics for vital signs (pulse rate, sitting systolic and diastolic BP) and changes from baseline values at each visit and at end of study will be presented by treatment group.

Vital sign values will be PCS if they meet both the observed-value criteria and the change from baseline–value criteria. The criteria for PCS vital sign values will be detailed in the SAP. The percentages will be calculated relative to the number of patients with baseline values and at least one postbaseline assessment–The numerator will be the total number of patients with available baseline values and at least one PCS postbaseline value in the treatment period. The denominator will be the total number of patients with available non-PCS baseline values and at least one postbaseline assessment. A supportive listing of patients with PCS postbaseline values will be provided, including the PID number, study center number, and baseline and postbaseline values. A listing of all AEs occurring in patients who have PCS vital sign values will also be provided.

c) Electrocardiogram

Descriptive statistics for ECG parameters (i.e. ventricular heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) and changes from baseline values at each assessment time point will be presented by treatment group. The QTc interval is calculated using both the Bazett ($QTcB = QT/(RR)^{1/2}$) and Fridericia ($QTcF = QT/(RR)^{1/3}$) corrections.

The number and percentage of patients with PCS postbaseline ECG values will be tabulated by treatment group. The criteria for PCS ECG values will be detailed in the SAP. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least one postbaseline assessment. The numerator will be the total number of patients with available baseline values and at least one PCS postbaseline value in the treatment period. A supportive listing of patients with PCS postbaseline values will be provided, including the PID number, study center number, and baseline and postbaseline values. A listing of all AEs for patients with PCS ECG values will also be provided.

d) Other Safety Parameters

i) Physical Examination

A listing of physical examination findings at Screening (Visit 1A) will be provided by treatment group as a part of the medical history listing. Any new physical examination finding or change (worsening) since the previous physical examination will be recorded as an AE in the appropriate AE eCRF form. If any clinically significant change is observed after randomization (Visit 2), it should be recorded in the AE eCRF form.

ii) All-cause mortality

All-cause mortality based on patient's vital status data will be analyzed using the same method as the primary safety endpoint using a 95% CI and without statistical testing for NI (NI margin will not be used).

9.7.7 Health Economics and Outcomes Research Analyses

CAT by Visits

The change from baseline of CAT score will be analyzed with MMRM models. The model may adjust for baseline CAT and history of at least one exacerbation in the past year as covariates, and treatment group, sex, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors.

Descriptive statistics will also be provided.

In addition, changes from baseline in the CAT score will be evaluated in a responder analysis.

Further details for CAT calculation and analysis will be given in the SAP.

9.7.8 Interim Analysis

No interim analysis is planned for this study.

9.7.9 Determination of Sample Size

9.7.9.1 Power for the Primary Safety Endpoint: Time to First MACE Event

For this study, a total of 122 patients with MACE will be needed to have 90% power, at 5% significance level, to rule out a hazard ratio of 1.8 in time to first MACE in aclidinium bromide treated patients relative to placebo, assuming the hazard rate is 1.0 under the alternative hypothesis. The justification for the hazard ratio of margin of 1.8 is provided in Appendix IV.

The study will be stopped when a total of 122 patients with MACE are observed.

The COPD safety database for the new drug application of roflumilast filing included a total of 3,310 patient-years on roflumilast 500 µg and 3,448 patient-years on placebo. That is a total of 6,758 patient years. Based on this exposure a total of 126 MACE were observed leading to ~1.9 MACE per 100 patient years (out of the 126 MACE only 1 patient had 2 MACE). Also the majority of the patients in this program were recruited based on % predicted FEV₁ below 50%.

The placebo group in the UPLIFT study had 2.89 MACE per 100 patient-years while tiotropium group had 2.25 MACE. It should be noted that this was a 4-year study and therefore it is possible more events occurred in the last 2 years of treatment than in the first two years as the health status of the patients could be worse over time (Boehringer Ingelheim, 2009).

This ASCENT COPD study will be recruiting patients with an FEV₁ below 80% and a planned maximum of 3 years double-blind treatment period. The assumption of 1.9 MACE per 100 patient years would be reasonable for this study. To obtain 122 MACE in this study with 1.9 MACE per 100 patient years of treatment, a total of 6,500 patient years of treatment (aclidinium and placebo) would be needed.

Assuming a treatment discontinuation rate of 40% and a study discontinuation rate of 20% at year 2, and following an exponential distributions for time to events and time to discontinuations, a sample size of 4000 is needed to ensure 90% power to observe 122 events applying the on-study analysis, and an 80% power to observe 91 events applying the on-treatment analysis.

9.7.9.2 Power for the Primary Efficacy Endpoint: Rate of Moderate or Severe Exacerbations Per Patient Per Year During First Year of Treatment

The sample size of 4,000 patients after 1 year of treatment will have ~89% power to detect a reduction in the rate of moderate or severe COPD exacerbations per patient per year during the first year of treatment of 14% (rate ratio of 0.86 in aclidinium bromide relative to placebo) at 0.05 alpha level (Table 9.7.9–1.). The 89% power was calculated assuming a discontinuation rate of 30% during the first year, a placebo rate of 0.8 exacerbation per patient per year (reduced from 1 to 0.8 as not all patients will have a history of exacerbation prior to randomization), and an over-dispersion factor k of 0.67 [Keene et al, 2007].

The clinical significance in reduction in the rate of exacerbation is not clearly defined for powering studies. Roflumilast was approved based on average reduction in exacerbation rate per patient per year of 17% relative to placebo averaged across the two pivotal studies. Tiotropium in the Handihaler[®] was approved for exacerbation based on UPLIFT trial along with another 6 months trial. The hazard ratio for time to first moderate or severe COPD exacerbation in UPLIFT was 0.86 (tiotropium relative to placebo) and the rate ratio per patient per year in moderate or severe COPD exacerbation was 0.86, implying a reduction of 14% (Boehringer Ingelheim, 2009).

Table 9.7.9–1. Summary of Statistical Power to Detect a Specific Rate Ratio (Aclidinium Over Placebo) as Statistically Significant for a Range of Rate Ratio: One Study with 4,000 Patients in Total to be Tested at 0.05 Level

	Statistical Power (%)		
	Placebo Rate (event/pt-yr)		
<i>Expected Rate Ratio (Aclidinium over placebo)</i>	0.6	0.8	1.0
0.80	99	99.6	99.9
0.82	96	99	99

	Statistical Power (%)		
	Placebo Rate (event/pt-yr)		
0.84	91	96	98
0.86	81	89	93
0.88	68	77	83
0.90	52	61	67

All calculations assume average exposure time of 0.85 years (30% discontinuation spread uniformly between Day 1 and 1 year) and overdispersion factor k of 0.67. Power was calculated using EAST version 6.3

9.7.10 Computer Methods

Statistical analyses will be performed using version 9.2 (or newer) of SAS on a UNIX operating system.

9.8 Changes in the Conduct of the Study or Planned Analyses

Any amendment to this protocol will be provided to the PI in writing by Sponsor. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/IEC and the signature page, signed by the PI, has been received by Sponsor. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/independent ethics committee (IEC) review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

9.9 Protocol Deviations and Violations

A *protocol deviation* is any change, divergence, or departure from the study design or procedures that is under the PI's responsibility and oversight (as defined by regulations) without prior written IRB/IEC approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, dosing, duration of treatment, failure to perform the required assessments at specified time points, scheduling of visits not in accordance with specifications, or patient safety. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients and must immediately be reported to Sponsor.

Protocol deviations must be reported to the Sponsor either verbally or electronically within 5 working days from the day of discovery.

A *protocol violation* is a form of protocol deviation that has a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data.

Protocol violations must be reported to the Sponsor within 24 hours, if possible. The IRB/IEC must be notified within the time period dictated by the IRB/IEC associated with this study.

10. STUDY SPONSORSHIP

This study is sponsored by AstraZeneca.

10.1 Study Termination

The Sponsor reserves the right to terminate the study in its entirety or at a specific study center before study completion.

10.2 Reporting and Publication

All data generated in this study will be the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the PI will be subject to mutual agreement between the PI and Sponsor.

11. INVESTIGATOR OBLIGATIONS

11.1 Documentation

The PI must provide the following to the Sponsor, before the start of the study:

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the Sponsor, for submission to the FDA
- A fully executed contract
- The curricula vitae for the PI and all Sub-Investigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB/EC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB/IEC, as stated in Section 5.1
- A copy of the IRB/EC-approved ICF
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB/EC members or the DHHS general assurance number
- A copy of the laboratory certifications and reference ranges
- The Investigator's Statement page in this protocol signed and dated by the PI
- Financial disclosure agreement completed and signed by the PI and all Sub-Investigators listed on Form FDA 1572. The PI and all Sub-investigators will provide an updated financial disclosure agreement to the Sponsor 1 year after the completion of the study

11.2 Performance

The PI must demonstrate reasonable efforts to obtain qualified patients for the study.

11.3 Use of Investigational Materials

The PI will acknowledge that the investigational product supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the PI or Sub-Investigators listed on Form FDA 1572. The investigational products must be stored in a safe and secure place. At study initiation, a representative from AZ, will inventory the investigational products at the study center. The PI must maintain adequate records documenting the receipt and disposition of all study supplies. The date investigational products were received and the date of dispensation to each patient will be recorded in IWRS. It is the PI's responsibility to ensure that patients return their investigational product. All unused IP and empty IP packages should be destroyed unless otherwise instructed by AZ.

11.4 Case Report Forms

All patient data relating to the study will be recorded on eCRFs to be provided by AZ through the EDC system. The PI is responsible for verifying that all data entries in the eCRFs are accurate and correct by electronically signing the completed eCRF casebook submitted to AZ. The PI must maintain and retain accurate documentation that supports the information entered into the EDC system for source document verification and possible regulatory inspection.

11.5 Retention and Review of Records

Records and documents pertaining to the conduct of this study, including case report forms, source documents, consent forms, regulatory documents, clinical laboratory results or reports (including, but not limited to, all local laboratory results, spirometry reports and ECG reports), and medication inventory records in all formats (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by the Sponsor.

No study records shall be destroyed without notifying the Sponsor and providing the Sponsor the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of records after the required retention period.

The Principal Investigator must permit access to any documentation relating to the study upon request of the Sponsor or applicable regulatory authorities. If the Principal Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian in advance of the transfer.

For Canadian study sites only: All records and documents pertaining to the conduct of the study must be retained for a 25-year period in accordance with the Canadian Food and Drugs Act and Regulations.

11.6 Patient Confidentiality

All patient records will only be identified by initials and PID number. Patients' names are not to be transmitted to AZ. The PI will keep a master patient list on which the PID number and the full name, address, and telephone number of each patient are listed.

12. INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with this protocol LAS-MD-45 (D6560C00002), dated 25 Jan 2017 and with all applicable government regulations and good clinical practice guidance.

_____/_____/_____
Principal Investigator's Signature Date

Principal Investigator's Name

13. APPENDICES

APPENDIX I. ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from each patient participating in a clinical research study or from the patient's Legally Authorized Representative (LAR). This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA; AZ the IRB; or an authorized contract research organization may inspect the records
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the PI as the contact. The guidance of the IRB/EC may be required)
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled
- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable
- The expected circumstances for which the patient's participation may be terminated by the PI without regard to the patient's consent

- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study
- A statement of consent (e.g., "I agree to participate...")
- A place for the patient's signature and date of signing
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov

A copy of the signed consent form should be given to the patient.

APPENDIX II. CONCOMITANT MEDICATIONS

Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications

<i>Drug Class</i>	<i>Frequency of Use</i>		<i>Restrictions</i>
	<i>Episodic (PRN)</i>	<i>Chronic</i>	
Long-acting β 2-adrenergic agonists and Long-acting muscarinic antagonists (LABA/LAMA) fixed dose combination	N	N	Not allowed within 2 weeks prior to screening Visit 1A and throughout the study. For patients on (LAMA/LABA) fixed dose combination, alternate maintenance bronchodilator therapy should be initiated.
Long-acting muscarinic antagonists (i.e. inhaled anticholinergics) (e.g., tiotropium) and oral, intranasal or parenteral anticholinergics	N	N	Not allowed within 2 weeks prior to Visit 1A and throughout the study. For patients on LAMA, alternate maintenance bronchodilator therapy should be initiated.
Short-acting inhaled anticholinergics (e.g., ipratropium, oxitropium)	N	N	Not allowed within 24 hours prior to Visit 1A and throughout the study.
Short-acting β 2-adrenergic agonists (e.g., fenoterol, terbutaline, albuterol, salbutamol)	Y	N	Episodic use of albuterol HFA or salbutamol sulfate is permitted, however, only Sponsor-provided Albuterol/salbutamol should be used. Should be withheld for 6 hours prior to visits.
Long-acting β 2-adrenergic agonists (e.g., salmeterol, formoterol)	N	Y	Must be stable for at least 2 weeks prior to Visit 1A.
Inhaled corticosteroids	Y	Y	Must be stable for at least 2 weeks prior to Visit 1A. May be initiated or dose may be changed during the course of the study after a COPD exacerbation at the discretion of the investigator.
			Must be a stable schedule at least 2 weeks prior to Visit 1A.

Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications

Drug Class	Frequency of Use		Restrictions
	<i>Episodic (PRN)</i>	<i>Chronic</i>	
Oral or parenteral corticosteroids	Y	Y	May be initiated or dose may be changed during the course of the study after a COPD exacerbation at the discretion of the investigator.
LABA/ICS (e.g., Symbicort, Advair)	N	Y	Must be stable for at least 2 weeks prior to Visit 1A. May also be initiated during the course of the study after a COPD exacerbation at the discretion of the investigator.
Roflumilast	N	Y	Must be stable for at least 2 weeks prior to Visit 1A. May be initiated during the course of the study after a COPD exacerbation at the discretion of the investigator.
Methylxanthines	Y	Y	N/A
Supplemental oxygen	Y	Y	N/A
Leukotriene modifiers (e.g. montelukast, zafirlukast, zileuton)	Y	Y	N/A
Antihistamines	Y	Y	N/A
Vaccinations	Y	Y	N/A
Any other inhaled medications not listed above	N	N	Inhaled medications not listed above (e.g., medications used for nausea and/ or pain control) are prohibited throughout the study. Ingested forms of these medications may be allowed. Please contact the study physician with any questions.

Y = yes, allowed; N = not allowed; PRN = as needed; HFA = hydrofluoroalkane; N/A = not applicable.

APPENDIX III. PULMONARY FUNCTION TESTS

The Investigative site should have the spirometers and all necessary equipment (computer, calibration syringe, printer, paper, ink, etc.), and the proper training from American Association for Respiratory Care (AARC) (for qualification of all technicians in charge of conducting spirometry) is needed in order to conduct this clinical trial per the protocol requirements. Spirometers will measure FVC (maximal volume of air exhaled with maximally forced expiratory effort from a position of maximal inspiration) and FEV₁ (volume of air expressed in liters exhaled during the first second of performance of the FVC) and will meet American Thoracic Society and European Respiratory Society recommendations for accuracy and precision (Miller et al, 2005).

Spirometer recommendations for the study provided devices should be followed to provide accurate and comparable spirometric data, and calibration should be performed every day the system is used. Daily calibration on the day of testing procedures should be conducted with a 3-liter syringe which will allow validation of spirometer accuracy (GOLD, 2017). Spirometry must be performed at temperatures between 17°C and 40°C. Efforts should be made to perform all maneuvers at approximately the same temperature. A notebook must be maintained to document daily (at least for those days spirometric procedures have to be done) ambient temperature. In case of significant changes in temperature and/or barometric pressure within the same day, calibration must be repeated before any other spirometry is done. Daily equipment calibration for days where testing is conducted as well as appropriate staff training records should be kept in the site's regulatory notebook.

Before the first spirometry is conducted for this clinical trial, the trained operator may demonstrate the procedure using a detached mouthpiece and then allow two practice attempts. A copy of the spirometry tracings should be printed and kept in the patient's medical records as source documentation.

The technician performing the test must properly wash his/her hands or use gloves to avoid any possible contamination. Reusable mouthpieces, breathing tubes, valves, and manifolds should be properly disinfected or sterilized regularly in accordance to the recommendations of the American Thoracic Society and European Respiratory Society ATS/ERS (Miller et al, 2005).

Spirometry Maneuvers

Pulmonary function tests will be performed by highly experienced personnel. At each time point, 3 technically adequate measurements should be performed according to the acceptability and repeatability criteria of the American Thoracic Society and European Respiratory Society ATS/ERS (Miller et al, 2005).

Patients should be able to produce repeatable pulmonary function testing (ie, the two best acceptable spirometry efforts must have FEV₁ and FVC values that do not vary by more than 150 mL). If both the acceptability and repeatability criteria are met, the test session may be concluded. If both of these criteria are not met, additional maneuvers should be performed until both criteria are met OR a total of 8 tests have been performed, unless the patient cannot continue. All maneuvers completed, whether deemed acceptable or not, must be retained and provided as source documentation.

The data for each visit must be entered into the electronic data capture system, including patient ID, date, time, visit number, whether spirometry was performed, whether the patient had a bronchodilator in the previous 6 hours, and the reason for visit, if it was unscheduled. The spirometry assessment results should be printed, signed by the technician and PI, and kept in the patient's medical record as source documentation.

Throughout the study, the reading of spirometric values is to be performed by the PI, or appropriately trained designee, to ensure the values meet the American Thoracic Society and European Respiratory Society criteria for acceptability. At each time point, only the greatest acceptable FEV₁ and FVC value will be used for all analyses.

The circumstances of the test should be similar on all occasions with respect to time of the day, temperature and pressure as well as the technician. Smoking and prolonged exposure to cold air, dust, and polluted air should be avoided for at least 1 hour before each visit until the completion of all study procedures. For patients having difficulty not smoking, nicotine gums or patches may be used.

Patients should be at rest for 15 minutes before the test and comfortable; tight or cumbersome clothing should be loosened to allow the thorax to move freely. Measurements are to be made with the patient seated in an upright posture and wearing a nose clip.

The procedure should be carefully described to the patient, with an emphasis on the need to avoid leaks around the mouthpiece. The following order of the spirometric maneuvers must be followed for forced maneuvers for measuring FEV₁ and FVC:

- Breathe in as deeply and quickly as possible.
- Immediately place the mouthpiece in your mouth and seal your lips tightly around it.
- Blow out as hard and as fast as you can, remaining upright and keeping your lips sealed.
- When your lungs are empty, remove the mouthpiece and breathe in normally.

At the time of forced maneuver, the technician performing the measurement should prompt the patient to blast, not just blow, the air from the lungs; continue to encourage him/her to fully exhale. Throughout all complete maneuvers, the technician should enthusiastically coach the patient by word and body language and attempt to obtain 3 acceptable and repeatable efforts with a maximum of 8 attempts for each assessment. The technician should provide the patient with ample time for the patient to rest between each maneuver.

Any bronchoconstriction that appears after consecutive measurements should be noted on the eCRF as an AE.

APPENDIX IV. POWER COMPUTATION DETAILS

ASSESSMENT OF BENEFIT-RISK RATIO AND JUSTIFICATION OF ACCEPTABLE INFERIORITY MARGIN OF HAZARD RATIO

A selected hazard ratio of 1.8 for time to first MACE for aclidinium relative to placebo that would need to be ruled out statistically is the subject of this appendix. The justification will be based on the NNH with 1 MACE per year of treatment compared to Number Needed to Treat (NNT) to reduce 1 exacerbation per patient per year and more importantly compared to NNT to reduce 1 hospitalization due to COPD exacerbation per patient per year. In COPD patients, the event of hospitalization due to COPD exacerbation may be considered comparable to a MACE. As can be seen from [Table 13–1](#) and [Table 13–2](#) below, aclidinium 400 µg BID showed a reduction in the rate of moderate or severe COPD exacerbations of 26.4% across the three Phase III studies (3 to 6 months treatment period in these 3 studies). Also, the effect of aclidinium 400 µg BID on hospitalization due to COPD exacerbation was also strong as can be seen in [Table 13–1](#). Approximately 12% of the moderate or severe exacerbations led to hospitalization. These data are being used to generate the exacerbation hypotheses proposed for this study and to estimate the benefit from aclidinium treatment in terms of reducing both COPD exacerbations and hospitalizations. In addition, the UPLIFT study showed that: tiotropium reduced the rate of moderate or severe COPD exacerbations by 14% over 4 years period; 27% of patients in the placebo group were hospitalized due to COPD exacerbation versus 25.4% of patients in the tiotropium group; the UPLIFT study showed that exacerbations are the largest cause of death in the population of COPD patients (Boehringer Ingelheim, 2009) (see [Table 13–3](#)).

Table 13–1. Summary of Moderate or Severe COPD Exacerbations and of Patients with Exacerbations Leading to Hospitalizations per Patient per Year in the Phase III Placebo Controlled Studies of Aclidinium (Studies LAS-MD-33, LAS-MD-38A, and M/34273/34 Pooled) Intent-to-treat Population

	<i>Placebo</i> (<i>N = 640</i>)	<i>AB400</i> (<i>N = 636</i>)
Total Number of Moderate or severe Exacerbations	83	65
Number (%*) of Patients with ≥ 1 Severe Exacerbations Leading to Hospitalization	13(2%)	5(0.8%)

N = number of patients in ITT Populations of the pooled 3 studies.

*(%) = percent is calculated based on number divided by N.

AB400 = Aclidinium Bromide 400 µg BID.

Table 13–2. Rate of Moderate or Severe COPD Exacerbations per Patient per Year based on the Pooled Phase III Placebo Controlled Studies of acclidinium (Studies LAS-MD-33, LAS-MD-38A, and M/34273/34 Pooled) Intent-to-treat Population

<i>Statistics</i>	<i>Placebo (N = 640)</i>	<i>Acclidinium 200 µg (N = 643)</i>	<i>Acclidinium 400 µg (N = 636)</i>	<i>Rate Ratio for Acclidinium 200 µg relative to Placebo</i>	<i>Rate Ratio for Acclidinium 400 µg relative to Placebo</i>
Rate	0.461	0.319	0.339	0.692	0.736
95% C.I.	(0.39, 0.54)	(0.26, 0.39)	(0.28, 0.41)	(0.55, 0.88)	(0.58, 0.93)
p-value				0.0024	0.0098

Estimate of the rate ratio along with its 95% CI and p-value for comparing Acclidinium versus Placebo or comparing Acclidinium 400 µg versus Acclidinium 200 µg are derived using the Poisson regression model with overdispersion and with the total number of COPD exacerbations during the study as response and with study, sex, and baseline COPD severity as factors along with age as covariate, adjusting for the log of the corresponding total exposure time in years for a patient (as an offset variable in the model).

95% CI = 95% Wald Confidence Interval (lower limit, upper limit) for the rate ratio.

p-value of the rate ratio using the Wald test.

*A new exacerbation will be counted as a separate one only if the patient has been off systemic corticosteroids and antibiotics for ≥14 days since the prior exacerbation.

Table 13–3. Exacerbation Outcomes (Benefit from Tiotropium Treatment in Handihaler®) from the UPLIFT trial

	<i>Placebo (N = 3,006)</i>	<i>Tiotropium (N = 2,986)</i>	<i>Difference in Number of events (Placebo - tiotropium)</i>
Rate of exacerbations per patient year	0.85	0.73	0.12 per patient year (p-value < 0.001)
Number (%) of patients with hospitalization for COPD	811 (27.0)	759 (25.4)	52 hospitalized patients due to COPD (p-value = 0.002 based on time to first hospitalization endpoint)
Number (%) of Death Due to COPD Exacerbation	121 (4.0)	103 (3.4)	18 Deaths

Approach of Benefit Assessment: Expected NNT with Acclidinium to Reduce 1 Exacerbation or Hospitalization

For the purpose of assessing the benefit of reduction in exacerbation or hospitalization per year we assume the placebo group to have a rate of 0.8 event per patient per year and the acclidinium group to have a rate of ~0.69 per patient per year (a reduction of 14%). Based on these assumptions, the acclidinium benefit can be measured by 9 NNT for 1 year to reduce 1 moderate or severe COPD exacerbations, calculated as 1/(1 - 0.89). The NNT to reduce 1 hospitalization due to COPD exacerbation can be predicted to be 42 (this calculation is based on the assumption of 12% of the moderate or severe exacerbation would be hospitalized as observed in Table 13–1, a rate of 0.12 per patient per year for placebo and 0.096 for acclidinium - a reduction of 20%).

It is understood that the reduction in exacerbation of 14% is not known at this point in the planned population. However, since the hypothesis of hazard ratio margin for risk of MACE depends on the benefit magnitude of aclidinium we assume a reasonable expected benefit for the patients from aclidinium treatment for their COPD exacerbation and then compare that to the risk of MACE.

Approach of Risk Assessment: NNH with 1 MACE Per Year

This NNH with 1 MACE per year method for assessment of risk is an alternative approach to the hazard ratio. This is equivalent and easier to compare the benefit based on NNT to reduce 1 exacerbation or hospitalization. The statistical test based on the upper bound of the confidence interval for the hazard ratio being lower than a null hazard ratio margin is the same as using a test based on the lower bound of the confidence interval for the NNH being greater than a null NNH margin. A lower NNH indicates that a product is associated with higher risk to the patient. Conversely, a higher NNH indicates a lower risk to the patient. Likewise a low margin of NNH corresponds to a high hazard ratio margin. These arguments are used to generate the margins for NNH that corresponds to the hazard ratio margins of 1.5, 1.7, 1.8, and 2.0 (See [Table 13–4](#) below for details).

[Table 13–4](#) provides NNT to reduce 1 exacerbation and the margin for NNH with 1 MACE that corresponds to the HR margin of 1.8 along with other useful information. Other important information from [Table 13–4](#) is the maximum point estimate of the hazard ratio that can be observed to rule out the hazard ratio margin of 1.8, which is 1.262. The corresponding minimum point estimate of NNH to rule out the null NNH margin of 66 (with one MACE) is 201 patients per year. (See [Table 13–4](#) for detailed calculations).

In the previously submitted study design, it was proposed to rule out a hazard ratio of 1.5. During the discussion at the aclidinium PADAC, the advisory board was asked to provide the Sponsor with advice on this preliminary study design. Two clear messages emerged:

- The study results should be available as soon as possible, and the study design should be adjusted to allow for this
- In evaluating the risk of MACE, the Sponsor should consider the potential benefit of reduction in exacerbations in addition to assessing risk of MACE, and we should consider adjusting the hazard ratio accordingly. Dr. Mauger pointed out a hazard ratio margin higher than 1.5 could be justified based on the NNH with 1 MACE.

He argued that for such an extremely rare event, you can have a hazard ratio of 1.5 and still be looking at a NNH of over 100, which may lead to accepting the null hypothesis in which the hazard ratio is set too low to be clinically meaningful. A complete discussion by Dr. Mauger and the chair of the PADAC regarding the HR margin is provided in Appendix 12.2. The NNH approach in this document (see [Table 13–4](#)) along with benefit-risk assessment was used to justify a HR margin of 1.8.

The calculations of risk are based on assuming 1.9 MACE per 100 patient years in the placebo group. A value of 201 for minimum point estimate of NNT in column 2 can be obtained as the minimum integer higher than 1 over $((1.262 \times 0.019) - 0.019)$. This calculation assumes the hazard ratio is the same as the rate ratio and this is a valid assumption for low rates as 0.019.

It should be noted that the null hypothesis based on the hazard ratio margin of at least 1.8 is the same as the null hypothesis of at most 66 NNH margin with 1 MACE per year. Therefore, ruling out a hazard ratio of 1.8 or higher is the same as ruling out an NNH of 66 or lower.

The null NNH margin of 105 is calculated as $1/(0.0285 - 0.019)$ where the 0.019 is the assumed placebo mean rate of MACE per 1 patient per year which is the same as 1.9 events per 100 patient years and the 0.0285 is the mean rate of MACE per 1 patient per year in the aclidinium group calculated under the null (the hazard ratio margin of 1.5 = $0.0285/0.019$).

Benefit-Risk Ratio: Justification of Using 1.8 Hazard Ratio

The potential risk of treatment with aclidinium will be assessed in the context of the potential benefit to the patient through reduction of exacerbations and COPD-related hospitalizations. The NNH will define the risk of having a MACE, while the NNT will establish the potential benefit of avoiding an exacerbation or COPD-related hospitalization. This approach is consistent with the advice the Sponsor and the Agency were given at the PADAC. The established benefit of FEV₁ bronchodilator effect of aclidinium bromide in the Pressair® DPI with supporting pulmonary function (ie, FVC, IC), SGRQ and other symptom data provide additional evidence in support of the reduction of exacerbations.

NNT: Reduction in Exacerbations and COPD-related Hospitalizations

The benefit from aclidinium treatment is predicted to be an NNT of 9 patients per year to reduce 1 moderate to severe COPD exacerbation. Also, it can be seen above as an NNT of 42 patients would be expected to eliminate 1 hospitalization per year (Table 13-1 and Table 13-2).

NNH: MACE

The NNH for 1 MACE that will be compared to the above NNT to benefit in reducing 1 exacerbation is the minimum point estimate of NNH of 201 patients with 1 MACE per year of treatment to rule out the null margin of 1.8 for the hazard ratio (or corresponding NNH of 66). The NNH of 201 for 1 MACE is the lowest number of patients needed to reject the null hypothesis (NNH margin of 66 or HR = 1.8 margin). In those 201 aclidinium treated patients, the benefit can be explained by the expected reduction of 22.3 events (201/9) of moderate or severe exacerbations and of those 22.3 events, 4.8 are expected to be COPD hospitalizations (201/42). Therefore, for each reduction of 4.8 hospitalizations due to COPD exacerbations at most 1 additional MACE is allowed for the success of the study based on MACE.

It should be noted in addition to the assumed reduction in exacerbation/hospitalizations benefit, aclidinium has demonstrated robust efficacy as a bronchodilator in COPD, improvement in SGRQ, reduction in the use of rescue medication, and improvement in dyspnea. These benefits justify the selection of the hazard ratio margin of 1.8 for the null hypothesis of time to first MACE for aclidinium relative to placebo that needs to be ruled out statistically.

Rationale for Change in Hazard Ratio Margin From Preliminary Study Synopsis

From Table 13–4, the NNH of 303 patients with 1 MACE is the most extreme point estimate of MACE risk for the study to be successful in ruling out the 1.5 margin of the hazard ratio (this corresponds to a null margin in NNH with 1 MACE of 105 patients). In this 303 acclidinium treated patients, the harm of 1 MACE is best compared to the expected reduction of 33.7 events (303/9) of moderate or severe exacerbations and of those 33.7 events 7.2 are expected to be COPD hospitalizations (303/42).

Based on the null margin of a hazard ratio of 1.5, the study is designed to be too strict with respect to the MACE margin of 1.5 for hazard ratio. The boundary for success is that for harm with 1 additional MACE and a benefit in the reduction of 34 exacerbations (7 of which are expected to be COPD hospitalizations) is required. It would not be appropriate to consider the study a failure if an increase beyond 1 MACE (such as 1.1) is observed despite the expected benefit in the reduction of 34 COPD exacerbations (7 of which are expected to be COPD hospitalizations.)

Table 13–4. Justification of the Selected Margin for Hazard Ratio for this Study Based on Benefit-Risk Approach: Risk Quantified using NNT for 1 year to Harm with 1 MACE and Benefit Quantified Using NNT for 1 Year to Reduce 1 Exacerbation

<i>Point Estimate of NNT† for 1 year to Reduce 1 COPD Exacerbation</i>	<i>Minimum Point Estimate of NNH‡ with 1 MACE to Rule Out its Null Margin</i>	<i>Maximum Point Estimate of HR to Rule out the Null Margin of HR</i>	<i>Total MACE Needed for 90% Power to Rule Out the Null in the Right Columns at 5% Significance Level</i>	<i>Null Hypothesis#: Margin of NNH Per Year with 1 MACE: 1/(acclidinium - placebo)</i>	<i>Null Hypothesis: Hazard Ratio Margin for Increase of MACE: (acclidinium/ placebo)</i>
9	303	1.174	256	105	1.5
9	225	1.234	150	75	1.7
9	201	1.262	122	66	1.8
9	167	1.317	88	53	2.0

† Point estimate of NNT for 1 year to reduce 1 COPD exacerbation was calculated assuming 14% reduction in the rate of exacerbation per patient per year from an average rate of 0.8 event per patient per year in the placebo group.

‡ Minimum point estimate of NNH with 1 MACE to rule out the null margin was calculated by assuming 1.9 MACE per 100 patient years in the placebo group and by using the maximum point estimate of HR to rule out the null margin of HR. For example the 303 value of minimum point estimate of NNT in column 2 can be obtained as the minimum integer higher than 1 over $((1.174 \times 0.019) - 0.019)$. This calculation assumes the hazard ratio is the same as the rate ratio and this is a valid assumption for low rates as 0.019.

It should be noted that the null hypothesis based on the hazard ratio corresponds to the null hypothesis based on NNH with 1 MACE (For example the null hypothesis based on the hazard ratio of at least 1.8 is the same as the null hypothesis of at most 66 NNT with acclidinium to harm with 1 MACE. Therefore, ruling out a hazard ratio of 1.8 or higher is the same as ruling out an NNH of 66 or lower.)

The NNH margin of 105 is calculated as $1/(0.0285 - 0.019)$ where the 0.019 is the assumed placebo mean rate of MACE per 1 patient per year which is the same as 1.9 events per 100 patient years and the 0.0285 is the mean rate of MACE per 1 patient per year in the acclidinium group calculated under the null (the hazard ratio of 1.5 = $0.0285/0.019$).

APPENDIX V. COPD ASSESSMENT TEST - CAT

Your name:	Today's date:
------------	---------------



How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy (0) (1) (2) (3) (4) (5) I am very sad

	SCORE
<div style="display: flex; justify-content: space-between;"> I never cough (0) (1) (2) (3) (4) (5) I cough all the time </div>	<input style="width: 40px; height: 40px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> I have no phlegm (mucus) in my chest at all (0) (1) (2) (3) (4) (5) My chest is completely full of phlegm (mucus) </div>	<input style="width: 40px; height: 40px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> My chest does not feel tight at all (0) (1) (2) (3) (4) (5) My chest feels very tight </div>	<input style="width: 40px; height: 40px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> When I walk up a hill or one flight of stairs I am not breathless (0) (1) (2) (3) (4) (5) When I walk up a hill or one flight of stairs I am very breathless </div>	<input style="width: 40px; height: 40px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> I am not limited doing any activities at home (0) (1) (2) (3) (4) (5) I am very limited doing activities at home </div>	<input style="width: 40px; height: 40px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> I am confident leaving my home despite my lung condition (0) (1) (2) (3) (4) (5) I am not at all confident leaving my home because of my lung condition </div>	<input style="width: 40px; height: 40px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> I sleep soundly (0) (1) (2) (3) (4) (5) I don't sleep soundly because of my lung condition </div>	<input style="width: 40px; height: 40px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> I have lots of energy (0) (1) (2) (3) (4) (5) I have no energy at all </div>	<input style="width: 40px; height: 40px;" type="text"/>
TOTAL SCORE	<input style="width: 40px; height: 40px;" type="text"/>

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APPENDIX VI. WAIST CIRCUMFERENCE MEASUREMENT INSTRUCTIONS

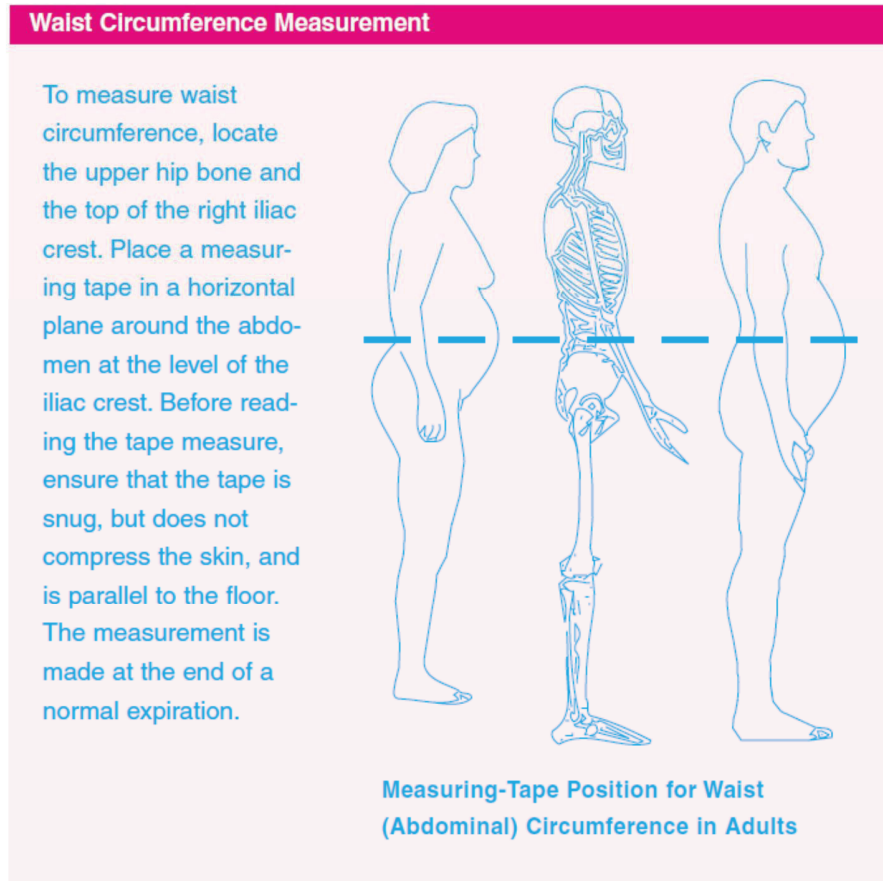


Figure and instructions sourced from:

The Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults

U.S. Department of Health and Human Services

Public Health Service

National Institutes of Health

National Heart, Lung, and Blood Institute

NIH Publication No. 00-4084

October 2000

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