Clinical Study Protocol	
Drug Substance	Aclidinium bromide/ Formoterol fumarate
Study Code	M-AS464-30 (AZ code: D6570C00002)
Version	4.0
Date	08 Jul 2021

A 24-week Treatment, Randomised, Parallel-group, Double blinded, Double-Dummy, Multicenter Study to Assess the Efficacy and Safety of Aclidinium bromide/Formoterol fumarate compared with Individual Components and Placebo and Aclidinium bromide compared with Placebo when Administered to Patients with Stable Chronic Obstructive Pulmonary Disease

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 4.0, 08 Jul 2021

NON-SUBSTANTIAL CHANGES TO THE PROTOCOL

Main changes are summarised below:

- Protocol synopsis (Statistical methods, *Statistical analyses*), Section 8.5: Sex was not included as an adjustment factor in the inferential statistical models, as it is expected that less than 5% of females will be randomised. As a result, inclusion of this factor could lead to imprecision in estimates from statistical models. This is in accordance with a lower prevalence of COPD in females in China. Differences by gender in COPD prevalence in China is most likely to be explained by historic patterns of smoking in Chinese men (Fang et al 2018).

- Section 1.4.1 and Appendix I: New wording was added which would give guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity. The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption. This section describes the measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimising risk to the patient, maintain GCP, and minimising risks to study integrity. These changes will only be initiated at a time of study disruption.

- Section 7.8.1: Inclusion of allowed treatment rules in case of COPD exacerbation or adverse event. These rules were clarified to investigators from study start and are now clearly explained in the protocol.

- Section 7.8.2: Addition of recommendations on COVID-19 vaccinations to study patients. This is done in response to emergency use authorisation of COVID-19 vaccines and to mitigate against any potential risk.

Minor administrative changes were done (see ***bold italicized*** text across the protocol):

- Protocol synopsis (Study site(s) and number of subjects planned) and section 8.2: The target number of randomized patients has been updated to revert the

unintended modification made in CSP V3.0. It is now consistent with CSP V1.0 and V2.0.

- Protocol synopsis (Study period): Estimated date of last subject completed has been updated to Q2 2022 according to the current study plan.
- Section 1.1: SmPC references of Duaklir® and Eklira® Genuair® revised to the most updated available versions.
- Section 4 (Table 2): "review ediary and paper diary" was added to Visit 7 for consistency with section 4.2.6 Visit 7: Week 24.
- Section 5.1.1.1: added statement to clarify that the system configuration can be found in the Project Requirement Specifications, including the spirometry timepoints and time-windows allowed in this study.
- Section 5.1.6: COPD exacerbations collection has been updated to align to the current EDC design, where these episodes are recorded in AE form.
- Section 5.2.1: "Covance" is changed to "central laboratory" to use consistent language across the CSP.
- Section 5.6.1: Language regarding reporting of biomarker results was removed since no biomarker analyses are planned.
- Section 8.5.10: QT interval corrected according to the Bazett formulae is included to align with the planned summaries for ECGs.
- Appendix A: clarification added as any new CSP version will be signed electronically.

Version 3.0, 24 June 2019

Main changes to the protocol are summarised below:

- Section 3.1: The request for a COPD diagnosis for a period of at least 6 months prior to Visit 1 (screening) is not required in other aclidinium COPD studies. If a subject is diagnosed with COPD and does not have documented evidence at hand, the diagnose may be verified before inclusion and it is not considered necessary to wait

for at least six months to participate in the trial. Therefore, Inclusion criteria No. 2 is updated to facilitate for the sites to recruit patients.

- Section 8.5.3: As per ICH guidelines, stratification variables used for the randomisation should be included in the inferential models. Therefore, country is included as a fixed effect in the statistical models.

- Section 8.5: Subjects will be assigned to the actual treatment they received in the Safety Population.

Following minor clarifications are made:

- Synopsis: The target number of randomised patients (Synopsis and Section 8.2) as well as the number of participating sites (Synopsis) have been updated to reflect study recruitment reality.

- Section 3.5: In error, there is a reference to 'a maximum of 320 patients in China' which is not ensured by the central randomisation performed in the study. The sentence is removed.

- Section 3.10.1: a new section "Withdrawal of Informed Consent" is added, as suggested by the new template.

- Section 8.1: A supplementary statistical analysis plan will be produced for the analysis of China subgroup to support the regulatory submission in China.

- Section 8.3: Consistent with previous Aclidinium studies following an FDA recommendation, exacerbation data will be analysed based on Safety Population but not on ITT population.

- Section 8.3: In order to address the discrepancy, with Statistical Analysis section on Page 8, regarding which variables will be analysed using PP population, the text 'and secondary' is added.

- Section 8.5.10: The definition of TEAE is updated as per AZ standards.

Version 2.0, 9 November 2016

Main changes to the protocol are summarised below:

- Synopsis (page 5), Section 1.2 Rational (page 22), Section 1.4. Study Design (page

25), Section 3.3 Subject enrolment and randomisation (page 33), Section 4. Study Plan and Timing of Procedures (Table 2, page 40-41). Section 4.1 Enrolment/screening period (page 43), Section 5.3 Other assessments, Section 8.4.5. Exploratory analysis (page 91): the sub-study for China (CT scan and biomarkers) has been cancelled and therefore any reference to this has been removed from the protocol. • Synopsis (page 3): study timelines have been adjusted • Section 6.5. Overdose (page 78): not only the overdoses leading to AEs but any overdoses will be recorded on the eCRF • Section 7.8 (page 82): clarification on wash-out and restrictions for LABA/ICS • Appendix D, Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law: Updated according to the study design, removed information only applicable for studies with local laboratory and studies of malignant disease.

Version 1.0, 19 August 2015
Initial creation

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.

PROTOCOL SYNOPSIS

A 24-week Treatment, Randomised, Parallel-group, Double blinded, Double-Dummy, Multicenter Study to Assess the Efficacy and Safety of Aclidinium bromide/Formoterol fumarate compared with Individual Components and Placebo and Aclidinium bromide compared with Placebo when Administered to Patients with Stable Chronic Obstructive Pulmonary Disease

International Co-ordinating Investigator:

[redacted]

Study site(s) and number of subjects planned

Approximately 1515 patients will be enrolled to randomise ***1060*** patients (265 patients/treatment arm) considering an estimated ineligibility rate of 30% prior to randomisation.

Approximately 85 sites will participate in China and other Asia countries including India, Taiwan, Vietnam and Philippines.

Study period		Phase of development
Estimated date of first subject enrolled	Q1 2017	III
Estimated date of last subject completed	***Q2 2022***	

Study design

This is a multiple dose, randomised, parallel, double blind, double dummy, multicentre and multinational Phase III study to determine the efficacy and safety of Aclidinium bromide/Formoterol fumarate compared with individual components and placebo and Aclidinium bromide compared with Placebo when administered to patients with stable Chronic Obstructive Pulmonary Disease (COPD).

Patients' informed consent form (ICF) signature must be obtained before performing any procedure related to the trial. ICF must be signed after the patient has received sufficient information about the trial, after he/she has had the opportunity to ask any questions related to the study and considered the options.

At Screening Visit (Visit 1) inclusion and exclusion criteria will be checked by means of patient's medical history review, physical examination, laboratory, electrocardiogram (ECG) measurement and COPD severity stage, according to Global Initiative for Chronic Obstructive Lung Disease (GOLD 2015).

Patients fulfilling inclusion/exclusion criteria at the time of the screening will be entered into a run-in period of 14 ±3 days to assess patient's disease stability. At the Screening Visit (Visit 1) patients are provided with the e-diary to record the use of rescue medication and their COPD symptoms every night.

Patients who meet entry criteria at Randomisation Visit (Visit 2) will be randomised in a ratio 1:1:1:1 to one of the 4 treatment arms. Smoking status (current smokers vs former smokers) and country will be the treatment allocation factors.

At Visit 2, after randomisation, patient will receive investigational product for 24 weeks and will come for scheduled visits at Visit 3 (Week 1), Visit 4 (Week 4), Visit 5 (Week 12), Visit 6 (Week 18), and Visit 7 (Week 24) for assessments of clinical efficacy and safety.

At the on-site visits over the treatment period pre-morning dose assessments will include: two Pulmonary Function Test (PFT) 30 min apart, physical examination, blood pressure and ECG measurement. CAT, Baseline/Transition Dyspnoea Index (BDI/TDI) and St. George´s Respiratory Questionnaire (SGRQ) will be also collected pre-morning dose at visits 2, 4, 5 and 7. Post-morning assessments include +1h post-dose PFT at all visits and +1h post-dose blood pressure and ECG at all visits except Visit 4. At visits 2 and 7, additional PFTs will be performed at +5 min, +30 min, +1h, +2h and +3h post-morning dose.

Laboratory test will be performed at Screening Visit (Visit 1) and at the end of the treatment period (Visit 7).

Patients will be provided with rescue medication, salbutamol pressurised metered dose inhaler (pMDI) 100 µg/puff, to be used on a needed basis, from the time of the informed consent signature until the end of the study.

From Screening Visit (Visit 1) to the end of the study, patients will use an electronic Patient Diary to be completed in the evening to record the intake of rescue medication as well as COPD symptoms by means of the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) questionnaire. Patients will also use a paper Patient Diary to record any AE and the

intake of any concomitant medications from Screening Visit (Visit 1) until the end of the study.

During the entire duration of the study, AEs, COPD exacerbations and the use of any concomitant medication will be assessed and recorded by the investigator.

Patients who prematurely discontinue investigational product (IP) will participate in an End of Treatment (EOT) Visit followed by a post-treatment follow-up period. The EOT visit will include physical examination, laboratory test, ECG and blood pressure to ensure patient´s safety. The IP will be returned at the EOT visit but the paper diary, electronic diary and rescue medication will be redispensed to be used during the post-treatment follow-up. The post-treatment follow-up period will include telephone contacts in place of on-site visits for the remainder of the study duration and an on-site Visit 7 in order to return the study material. During the post-treatment follow-up period the SAEs, COPD exacerbations and concomitant medication will be followed-up.

Patients who prematurely discontinue from the study (withdrawal) will participate in an End of Study (EOS) Visit that will include physical examination, laboratory test, ECG and blood pressure to ensure patient´s safety. The IP, rescue medication, paper diary and electronic diary will be returned at the EOS visit.

For patients that complete the treatment or prematurely discontinue from the study (withdrawals), a follow-up contact will be performed 2 weeks after last IP intake to assess new or ongoing adverse event (AE), as well as any concomitant medication administered to treat the mentioned AE.

Objectives

Primary Objectives:	**Outcome Measures:**
• To assess the bronchodilatory effect of Aclidinium bromide 400 µg /Formoterol fumarate 12 µg compared to individual components and placebo when administered twice daily via inhalation to COPD patients. • To assess the bronchodilatory effect of Aclidinium bromide 400 µg compared to placebo when administered twice daily via inhalation to COPD patients.	• Change from baseline in 1-hour morning post-dose FEV_1 of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to Aclidinium bromide at Week 24. • Change from baseline in morning pre-dose (trough) FEV_1 of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to Formoterol fumarate at Week 24. • Change from baseline in trough FEV_1 of Aclidinium bromide 400 µg compared to placebo at Week 24

Secondary Objectives:	Outcome Measures:
• To assess the benefits of Aclidinium bromide 400 µg /Formoterol fumarate 12 µg in COPD symptoms, disease-related health status and COPD exacerbations compared to placebo, when administered BID via inhalation to COPD patients. • To assess the benefits of Aclidinium bromide 400 µg in COPD symptoms, disease- related health status and COPD exacerbations compared to placebo, when administered BID via inhalation to COPD patients.	• Change from baseline in peak FEV_1 of Aclidinium bromide 400 µg compared to placebo at week 24 • Improvements TDI focal score of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to placebo at week 24 • Improvements TDI focal score of Aclidinium bromide 400µg compared to placebo at week 24 • Change from baseline in SGRQ total score of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to placebo at week 24 • Change from baseline in SGRQ total score of Aclidinium bromide 400µg compared to placebo at week 24
	Additional efficacy variables: • Pulmonary function variables (FEV_1, FVC) at each time point and average (ie Area Under the Curve, AUC_{0-3}) • Symptomatic and health related quality of life outcomes (TDI, SGRQ, CAT, E-RS) • COPD exacerbations (as defined by HCRU and EXACT) • Use of rescue medication

Safety Objective:	Outcome Measure:
• To evaluate the safety profile of Aclidinium bromide 400 µg /Formoterol fumarate 12 µg and Aclidinium bromide 400 µg in the same patient population.	• Adverse events • Clinical laboratory test • Blood pressure • ECG

Target subject population

The study will include patients who are aged ≥40, current or former smokers with a smoking history of ≥ 10 pack-years, and with stable, moderate to severe COPD (GOLD guidelines). Patient must have screening post-bronchodilator test $FEV_1/FVC < 70\%$ and $FEV_1 \geq 30$ and < 80% of the predicted normal value.

Duration of treatment

The total duration of the trial for each patient will be approximately 28 weeks (including Screening Visit and follow up contact). There will be a run-in period of 2 weeks followed by

treatment period of 24 weeks, and a follow up contact that will be performed 2 weeks after last study treatment.

Investigational product, dosage and mode of administration

A double-dummy design will be adopted in the study to achieve blinding. Aclidinium bromide 400 µg /Formoterol fumarate 12 µg, Aclidinium bromide 400 µg and placebo to Aclidinium bromide 400 µg /Formoterol fumarate 12 µg and Aclidinium bromide 400 µg will be administered via the Genuair® device, and Formoterol fumarate 12 µg and placebo to Formoterol fumarate 12 µg will be administered via de Turbuhaler® device. The patient will inhale 1 puff twice daily (12 hours apart, morning and evening), morning dosing at 08:00 to 10:00 am and evening dose at 08:00 to 10:00 pm approximately, from each inhaler.

Note: The strengths are expressed as metered dose.

Substance and strength:	Aclidinium bromide 400µg/Formoterol fumarate 12 µg
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Genuair® Dry Powder Inhaler, DPI)
Substance and strength:	Aclidinium bromide 400 µg
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Genuair® Dry Powder Inhaler, DPI)
Substance and strength:	Formoterol fumarate 12 µg
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Turbuhaler® Dry Powder Inhaler, DPI)
Substance and strength:	Placebo to Aclidinium bromide 400µg/Formoterol fumarate 12 µg and Aclidinium bromide 400 µg
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Genuair® Dry Powder Inhaler, DPI)
Substance and strength:	Placebo to Formoterol fumarate 12 µg
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Turbuhaler® Dry Powder Inhaler, DPI)

The delivered dose of Formoterol fumarate in the mono-formulation used in the study is 9 µg.

Statistical methods

Assumptions for the sample size:

A sample size of 1,060 randomised patients (265 patients per treatment arm) will provide 90% power, after adjusting for multiplicity, to test the following primary endpoints:

- Change from baseline in 1-hour morning post-dose dose FEV_1 of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to Aclidinium bromide at Week 24.
- Change from baseline in morning pre-dose (trough) FEV1 of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to Formoterol fumarate at Week 24.
- Change from baseline in trough FEV1 of Aclidinium bromide 400 µg compared to placebo at Week 24

The same sample size will provide at least 90% power to test the following secondary endpoints:

- Change from baseline in peak FEV1 of Aclidinium bromide 400 µg compared to placebo at Week 24
- Improvements TDI focal score of Aclidinium bromide 400 µg /Formoterol fumarate 12 µg and Aclidinium bromide 400 µg compared to placebo at Week 24
- Change from baseline in St George's Respiratory Questionnaire (SGRQ) total scores of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg and Aclidinium bromide 400 µg compared to placebo at Week 24

Statistical analyses:

The analyses of the primary and secondary variables will be performed on the Intention-to-Treat (ITT) and Per Protocol (PP) populations while all other analyses will be performed for the ITT population. Safety outcomes and COPD exacerbations will be analysed on the Safety population. Moreover, smoking-status and country will be used as a treatment allocation factor during the randomisation process.

The primary efficacy variables will be analysed by means of mixed models for repeated measures (MMRM), adjusted for pre and post bronchodilator (salbutamol) FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group, country, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors. To assess the robustness to variations of the missing data assumptions underlying the primary analysis on the primary efficacy endpoints, sensitivity analyses will be conducted such as copy reference approach.

Improvement in TDI focal score and change from baseline in SGRQ total score at Week 24 will be analysed by means of MMRM, adjusted by the corresponding baseline value (BDI or

SGRQ at baseline) and age as covariates, and treatment group, country, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors.

Additional endpoints like the area under the curve (AUC_{0-3}), COPD exacerbations, symptoms based on CAT and E-RS questionnaires, and rescue medication will be analysed.

Safety outcomes will be summarised by means of descriptive statistics across time by treatment group.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase, also named GPT
AST	Aspartate aminotransferase, also named GOT
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC	Area under the curve
AUC_{0-3}	Area under curve from time 0 to 3 hours
BDI	Baseline Dyspnoea Index
BDRM	Blind Data Review Meeting
BID	Bis In Die (twice daily)
BUN	Blood urea nitrogen
CAT	COPD assessment test
CC-16	Circulating levels of Clara cell secretory protein-16
CDSIC	Clinical Data Interchange Standards Consortium
CI	Confidence intervals
COPD	Chronic obstructive pulmonary disease
CRA	Clinical Research Associate
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organization
CRP	C-reactive protein
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CV	Cardiovascular
CVAC	Cardiovascular Adjudication Committee
DL_{CO}	Carbon monoxide diffusion capacity
DM	Data Management
DMP	Data Management Plan
DPI	Dry Powder Inhaler
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of treatment
ePRO	Electronic Patient Reported Outcomes
ERS	European Respiratory Society
E-RS	EXACT Respiratory Symptoms

EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FDA	U.S. Food and Drug Administration
FDC	Fixed-dose Combination
FEV_1	Forced expiratory volume in 1 second
FSTL1	Follistatin-related protein 1
FVC	Forced vital capacity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GOT	Glutamic Oxalacetic Transaminase, also named AST
GPT	Glutamic Pyruvic transaminase, also named ALT
GREM1	Gremlin1
HBcAg	Hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HRCT	High-resolution computed tomography
HU	Hounsfield units
IATA	International Air Transport Association
ICC	Innovation Center of China
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
IL	Interleukin
IL-6	Interleukin-6
IL-8	Interleukin-8
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
ITT	Intention-to-Treat
IUDRs	Imputation using drop out reasons
IUDs	Intrauterine devices
IUS	Intrauterine system
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting beta2-adrenergic agonist
LAMA	Long-acting muscarinic antagonist/inhaled anticholinergic
LDH	Lactate dehydrogenase
LPCAT1	Lysophosphatidylcholine acyltransferase 1
LSMeans	Least Square means
MACE	Major Adverse Cardiac Events

MedDRA	Medical Dictionary for Regulatory Activities
MIF	Macrophage migration inhibitory factor
MMP	Matrix metalloproteinase
MMP-9	Matrix metalloproteinase-9
MMRM	Mixed model for repeated measures
P	A deflection in an electrocardiographic tracing that represents atrial activity of the heart. The P-wave precedes the QRS complex.
PCT	Procalcitonin
PDE IV inhibitor	Phosphodiesterase type 4 inhibitor
PFT	Pulmonary Function test
PI	Principal Investigator
PK	Pharmacokinetics
pMDI	Pressurised metered dose inhaler
PP	Per Protocol
PR interval	Duration in milliseconds from the beginning of wave P to onset of ventricular depolarisation (Q and R)
PRO	Patient reported outcomes
Pro-BNP	Pro-B-type-Natriuretic Peptide
QRS	ECG interval measured from the beginning of the Q wave (or the R wave if Q is missing) to the J point; the time interval of ventricular depolarisation
QRS interval	Duration in milliseconds of the QRS complex
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QT interval	Duration in milliseconds from the beginning of Q wave to the end of the T wave
QTc	QT corrected
QTc interval	QT interval corrected by heart rate
QTcB interval	QT interval corrected, Bazett formulae
QTcF	QT corrected, Fridericia formulae
QTcF interval	QT interval corrected, Fridericia formulae
RR interval	Duration in milliseconds between two R peaks of two consecutive QRS complexes
RV	Residual volume
SABA	Short-acting beta2-adrenergic agonists
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonist/ inhaled anticholinergics
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard errors

SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SP-B	Surfactant Protein-B
SP-D	Surfactant Protein D
ST segment	Part of an electrocardiogram between the QRS complex and the T wave
TDI	Transition Dyspnoea Index
TEAE	Treatment-emergent adverse event
TLC	Total lung capacity
TNF-α	Tumor Necrosis Factor-alfa
WA%	Wall area percentage
WHO	World Health Organisation
γ-GT	Gamma-glutamyl transferase/ gamma-glutamyl transpeptidase

1 INTRODUCTION

1.1 Background and rationale for conducting this study

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Cigarette smoking is the most common risk factor for COPD. Exacerbation and comorbidities contribute to the overall severity in individual patients. COPD is a major cause of morbidity and mortality worldwide and results in economic and social burden which is both substantial and increasing. In a study of the burden of obstructive lung disease (BOLD Study), the crude prevalence of COPD, all stages, among the study populations ranged from 11.4% in Guangzhou, China to 26.1% in Salzburg, Austria (Buist et al 2007). The prevalence of COPD in China is 8.2% in those aged over 40 years old (Zhong et al 2007).

COPD is characterized by structural changes in the airways resulting from repeated injury and repair and by bronchoconstriction, which is an important target for pharmacologic interventions (GOLD 2015). Dyspnoea, chronic cough and sputum production are the most common clinical symptoms. Adrenergic and cholinergic pathways mediate bronchoconstriction in COPD.

Anticholinergic compounds such as ipratropium, oxitropium, tiotropium, aclidinium, glycopyrronium or umeclidinium have been shown to provide clinical benefit in the treatment of COPD. These therapeutic agents block muscarinic acetylcholine receptors in bronchial smooth muscle and thus decrease cholinergic tone (muscarinic antagonism). β_2-adrenergic agonists such as albuterol, formoterol, salmeterol or indacaterol stimulate β_2-receptors in the bronchial smooth muscle resulting in similar effects to those of anticholinergics. Both anticholinergic drugs and β_2-adrenergic agonists decrease bronchoconstriction (increased FEV_1) and thereby reduce dyspnoea and COPD exacerbations, increase exercise tolerance, and improve quality of life.

As a result of their differing mechanisms of action and similar pharmacodynamic effects, β_2-agonists and muscarinic antagonists have been used simultaneously in the same inhalation device for the treatment of COPD. Administration of an inhaled fixed-dose combination of ipratropium (muscarinic antagonist) and albuterol (β2-agonist) has been shown to produce a significantly greater improvement in pulmonary function than either ipratropium or albuterol monotherapies (Combivent® UDVs® United Kingdom (UK) SmPC). The safety and tolerability profile of ipratropium/albuterol is similar to those of the individual components. However, one significant drawback is the short-lived duration of action of both of the components, which necessitates repeated dosing 3-4 times daily.

Several combinations of LABA and LAMAs have been recently approved worldwide for the treatment of COPD, ie Ultibro (indacaterol/glycopyrronium) and Anoro (vilanterol/umeclidinium). The clinical studies have shown that the combined use of a LABA and a LAMA results in greater improvement of bronchodilation as well as a better symptoms control compared with monotherapies (Pelaia et al 2014, Maltais et al 2014, Maleki-Yazdi et al 2014).

Duaklir® Genuair®/Brimica® Genuair® is a combination product of LAMA (aclidinium bromide) and LABA (formoterol fumarate) approved in Europe for the treatment of COPD at a dose of 400/12 µg (delivered as 340/12 µg) twice daily in November 2014 (Duaklir® Genuair® SmPC 2021).

Aclidinium bromide is a novel LAMA (long acting muscarinic agent) marketed as Eklira® and Bretaris® Genuair® (Eklira® Genuair® SmPC 2021) indicated as a twice daily (BID) maintenance bronchodilator treatment to rescue symptoms of patients with COPD.

The current Phase III study is designed to investigate the long term bronchodilator efficacy of aclidinium bromide 400 µg/formoterol fumarate 12 µg and aclidinium bromide 400 µg delivered by inhalation on a BID schedule in an Asiatic population. The study will also assess the potential benefits of the Investigational Product (IPs) on disease-related health status, COPD symptoms and other outcomes in patients with moderate to severe COPD in China and other Asian countries. In addition, the study will evaluate the safety and tolerability of both products in the same patient population.

1.2 Rationale for study design, doses and control groups

The objectives of this study are to assess the bronchodilator efficacy and safety of Aclidinium bromide 400 µg /formoterol fumarate 12 µg compared to the individual components (Aclidinium bromide 400 µg and Formoterol fumarate 12 µg) and placebo and Aclidinium bromide 400 µg compared to placebo.

The Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 2009) and FDA Code of Federal Regulations, Title 21, Section 300-50, state that each substance of a fixed combination must have a documented contribution within the combination to the claimed effects. Therefore, the objectives of the present trial will be to demonstrate statistically significant bronchodilation of Aclidinium bromide/Formoterol fumarate compared with Aclidinium bromide and Formoterol fumarate in terms of bronchodilation and an acceptable safety profile of the combination compared to the individual components in Asian population. In addition, this study will assess the efficacy and safety of Aclidinium bromide compared with placebo in the same patient population.

The target study population of this study (Stage II or Stage III according to the GOLD 2015: post-bronchodilator FEV_1 ≥30% and < 80% of the predicted normal and FEV_1/FVC < 70%) has been commonly investigated in similar trials.

The proposed trial duration of 24 weeks has been chosen considering the intended indication for Aclidinium bromide/Formoterol fumarate and Aclidinium bromide, ie maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) in accordance to CPMP/EWP/562/98 1999 and the FDA Guidance for Industry Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment (Draft November 2007) that state that any indication for the symptomatic rescue of COPD should be supported by the results from a trial of at least 6 months duration.

The IP doses and dose regimen for the Aclidinium bromide 400µg/Formoterol fumarate 12 µg and the individual components are the approved dose and dose regimen in the EU (Aclidinium bromide 400 µg/Formoterol fumarate 12 µg BID, Aclidinium bromide 400 µg BID and Formoterol fumarate 12 µg BID corresponding to a delivered dose of 9 µg).

The inclusion of a placebo arm is considered the most reliable method to minimise patient and investigator bias and is recommended by FDA Guidance for Industry ICH E10 on Choice of Control Group in Clinical Trials (FDA Guidance for industry ICH-E10 2001), Note for Guidance on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96 2001), CPMP/EWP/562/98 1999 and CHMP/EWP/240/95 2009. Exposure to placebo is deemed necessary to allow a reliable evaluation of the net pharmacological effect of the study drug, as well as of the adverse events caused by the drug compared with those resulting from the COPD natural course or other underlying diseases in this type of population. A placebo control group has been also included in studies with similar patient population and at least the same treatment duration (Donohue et al 2013, Celli et al. 2014, Bateman et al 2013). In addition, the comparison to placebo arm is needed to assess the efficacy and safety of Aclidinium bromide in China where it is not yet approved.

Rescue medication (salbutamol pMDI 100 µg/puff) will be permitted as needed throughout the study duration for all participants. In addition, several background medications for the treatment of COPD (e.g., inhaled corticosteroids, oral or parenteral corticosteroids, oxygen therapy, and oral sustained-release teophyllines) will be permitted. Rescue and background therapies are allowed to help controlling patient's COPD symptoms as well as to minimise the risk of COPD exacerbations.

Inhalers and medication kits containing study drug will present the same external appearance to ensure the double-blind nature of the trial. The blinding and randomisation of study drug will avoid the chance of bias in patient treatment assignation as well as patient management during the study and data interpretation. Additionally, by randomly assigning patients to any

of the possible treatment arms, differences in baseline characteristics of the treatment groups will be minimised. Patient's smoking status at the time of randomisation will be used as treatment allocation factor following the recommendation from CPMP/EWP/562/98 1999.

The parameters to be measured have been selected based on the objectives and outcomes to be assessed. Thus, the study will assess FEV_1 (as a measure of lung function) and other lung function parameters, as well as symptomatic benefits, including the Baseline/Transition Dyspnoea Index (BDI/TDI), COPD Assessment Test (CAT) and St. George Respiratory Questionnaire (SGRQ), COPD exacerbation and use of rescue medication, all previously used in similar studies (Donohue et al 2013, Celli et al. 2014, Bateman et al 2013). Similarly, adverse events and commonly used tolerability assessments (e.g., ECG, blood pressure and clinical laboratory test) will be performed to monitor study drug safety profile and patient's wellbeing throughout the trial.

1.3 Benefit/risk and ethical assessment

The Aclidinium Bromide 400 µg/Formoterol fumarate 12 µg and Aclidinium bromide 400 µg are currently approved in Europe as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) while Formoterol fumarate 12 µg is approved in Europe and indicated for the rescue of broncho-obstructive symptoms in the same population.

The 3 pivotal clinical studies of aclidinium bromide 400 µg have demonstrated a clinically and statistically significant bronchodilatory effect when compared to the placebo throughout the 12 and 24 weeks treatment period. Moreover, treatment with aclidinium bromide 400 µg BID was associated with improvements in dyspnoea, disease-related health status (St. George's Respiratory Questionnaire [SGRQ]) and daily and night-time symptoms (Jones et al. 2012, Kerwin et al 2012). Furthermore, Phase II Studies M/34273/23 (Fuhr et al Chest 2012) and M/34273/29 (Singh et al. 2012) showed the overall bronchodilation of aclidinium bromide 400 µg BID to be broadly comparable to that of commercially available bronchodilators, tiotropium and formoterol. Evidence of the benefits of aclidinium bromide on exercise endurance, lung hyperinflation, exertional dyspnoea and daily physical activity was observed in Study M/34273/40 (Beeh et al. 2014).

The clinical development programme for Aclidinium Bromide 400 µg/Formoterol fumarate 12 µg has shown to provide additional efficacy benefits compared to those associated with aclidinium or formoterol fumarate monotherapies (as assessed by measures of lung function, COPD symptoms and disease-specific health status) and yet the safety and tolerability of aclidinium 400 µg/formoterol fumarate 12µg is generally comparable to that of the component monotherapies (D'Urzo et al. 2014, Singh et al. 2014).

Aclidinium/bromide 400/12 µg appears to have comparable efficacy to other recently approved LABA/LAMA fixed combinations with regard to symptomatic and disease-specific health status benefits. Its symptomatic and disease-specific health status benefits compared to placebo (as assessed by TDI and SGRQ) were comparable to those observed with the recently approved fixed-dose LABA/LAMA combinations of indacaterol/glycopyrronium (Committee for Medicinal Products for Human Us, CHMP Assessment report for Ultibro Breezhaler, EMA/CHMP/296722/2013, 25 July 2013) or umeclidinium/vilanterol (CHMP Assessment report for Anoro, EMA/CHMP/163509/2014, 28 March 2014.). Furthermore, the magnitudes of improvements in breathlessness (TDI), daily symptoms (E-RS), early morning and night-time symptoms, disease-specific health status (SGRQ-C) and exacerbation prevention were comparable with aclidinium 400 µg /formoterol fumarate 12µg and the fixed-dose ICS/LABA combination of salmeterol/fluticasone propionate 50/500 µg BID (Vogelmeier et al. 2015).

LABA/LAMA fixed combinations which are administered once daily have recently received marketing authorisation in the EU and other territories (glycopyrronium/indacaterol and umeclidinium/vilanterol). BID dosing of a LABA/LAMA fixed combination, such as with aclidinium/formoterol fumarate, may be a useful approach to the control of night-time and early morning symptoms, which epidemiological studies indicate are the most troublesome for patients with COPD (Kessler et al. 2011).

The safety profile for Aclidinium Bromide 400 µg/Formoterol fumarate 12 µg is based on the clinical experience after exposure at the recommended therapeutic dose for up to 12 months. No relevant post-marketing experience data is available. The safety profile of Aclidinium bromide 400 µg and Formoterol fumarate 12 µg are based on clinical and post-marketing experience.

As the IP contains Aclidinium bromide and Formoterol fumarate, the type and severity of adverse reactions associated with each of the components are the ones expected with Aclidinium Bromide 400 µg/Formoterol fumarate 12 µg.

Common adverse events which may be expected with aclidinium bromide treatment includes sinusitis, nasopharyngitis, headache, cough and diarrhoea. Common adverse event to be expected with formoterol fumarate are palpitations, headache and tremor.

The most frequently reported adverse reactions with Aclidinium bromide 400 µg/Formoterol fumarate 12 µg were nasopharyngitis (7.9%) and headache (6.8%).

Other commonly reported adverse reactions with Aclidinium bromide 400 µg/Formoterol fumarate 12 µg are urinary tract infection, sinusitis, tooth abscess, insomnia, anxiety, headache, dizziness, tremor, cough, diarrhoea, nausea, dry mouth, myalgia, muscle spasms, oedema peripheral and blood creatine phosphokinase increased.

Hypokalaemia, hyperglycaemia, agitation, dysgeusia, tachycardia, electrocardiogram QTc prolonged, palpitations, rash, pruritus, blurred vision, dysphonia, throat irritation, urinary retention and blood pressure increased are uncommon adverse reactions that could be observed with the Aclidinium bromide 400 µg/Formoterol fumarate 12 µg or the individual components, while bronchospasm and hypersensitivity could rarely occur when administering the individual components.

There is limited evidence on the management of overdose with Duaklir® Genuair®, Eklira® Genuair®. High doses may lead to exaggerated anticholinergic and/or β_2-adrenergic signs and symptoms; the most frequent of which include blurred vision, dry mouth, nausea, muscle spasm, tremor, headache, palpitations and systolic hypertension.

For more details on the safety and tolerability profile of the aforementioned compounds, please see the approved Investigator´s Brochures.

Based on the study drug safety profile, no specific risk is anticipated with the doses and the dose regimen proposed in this trial. Still, investigators will ensure adequate medical care of the trial participants at all times throughout the course of the study.

1.4 Study Design

This is a multiple dose, randomised, parallel, double blind, double dummy, multicentre and multinational Phase III study to determine the efficacy and safety of Aclidinium bromide/Formoterol fumarate compared to individual components and placebo and Aclidinium bromide compared to placebo when administered to patients with stable Chronic Obstructive Pulmonary Disease.

The study will consist of a Screening Visit (Visit 1) conducted after signature of the informed consent form, where medical history, COPD history, physical examination, laboratory analysis, ECG and COPD severity stage (post-bronchodilator FEV_1 according to Global Initiative for Chronic Obstructive Lung Disease, GOLD guidelines) will be conducted.

Patients fulfilling inclusion/exclusion criteria at the time of the screening will be entered into a run-in period of 14 ±3 days to assess patient's disease stability.

Patients who are still meeting entry criteria at Visit 2 will be randomised in a ratio 1:1:1:1 to one of the 4 treatment arms to start a 24 weeks treatment period. Smoking status (current smokers vs former smokers) and country will be the treatment allocation factors.

- Aclidinium bromide 400 µg/Formoterol fumarate 12 µg
- Aclidinium bromide 400 µg
- Formoterol fumarate 12 µg

– Placebo

After randomisation, patients will be assigned one medication kit with 4 Genuair® inhalers containing Aclidinium bromide 400 µg/Formoterol fumarate 12µg, or Aclidinium bromide 400 µg or matching placebo and 4 Turbuhaler® inhalers containing formoterol fumarate12 µg or matching placebo. At Visit 5 a second kit will be dispensed with 4 additional Genuair and 4 Turbuhaler inhalers.

Each Genuair® inhaler will contain at least 60 doses (and a maximum of 68 doses). Each Turbuhaler inhaler will contain at least 60 doses.

Patients will be instructed to take 1 puff from the Genuair® and 1 puff from the Turbuhaler® in the morning (09:00 ± 1 h) and 1 puff from the Genuair® and 1 puff from the Turbuhaler® in the evening (21:00 ± 1 h) during the 24 weeks of treatment. It is important that the evening administrations are consistently performed approximately 12 hours after morning administrations. During the double-blind treatment period, patients will visit the site to assess clinical efficacy and safety on 5 more occasions, after 1 week of treatment (Visit 3), after 4 weeks of treatment (Visit 4), after 12 weeks of treatment (Visit 5), after 18 weeks of treatment (Visit 6) and after 24 weeks of treatment (Visit 7). A follow-up contact will be performed 2 weeks after the last IP administration for patient that complete the treatment and patient that discontinue from the trial (withdrawals). Patients completing the trial will be the patients on treatment up to Visit 7, even if they do not complete the follow-up contact.

Patients who prematurely discontinue investigational product (IP) will perform an EOT visit and will participate in a post-treatment follow-up period. The follow-up period will include phone calls to collect COPD exacerbations, concomitant medications, and SAEs for the remainder of the study duration and an on-site visit in place of Visit 7 (EOS visit). Moreover, the EXACT (E-RS) questionnaire will be completed by patients every night during the post-treatment follow-up period.

Figure 1 Study flow chart

<table>
<tr><th>Visit 1</th><th>Visit 2</th><th>Visit 3</th><th>Visit 4</th><th>Visit 5</th><th>Visit 6</th><th>Visit 7</th><th>Follow Up Contact</th></tr>
<tr><td>~ -2 weeks</td><td>Week 0</td><td>Week 1</td><td>Week 4</td><td>Week 12</td><td>Week 18</td><td>Week 24</td><td>Week 26</td></tr>
<tr><td rowspan="5">Screening (Run-in period) 14 ± 3 days</td><td colspan="6">Treatment Phase (24 weeks)</td><td rowspan="5">Follow Up 14 + 3 days</td></tr>
<tr><td colspan="6">Aclidinium bromide/Formoterol Fumarate 400/12 µg (BID)</td></tr>
<tr><td colspan="6">Aclidinium bromide 400 µg (BID)</td></tr>
<tr><td colspan="6">Formoterol fumarate 12 µg (BID)</td></tr>
<tr><td colspan="6">Placebo</td></tr>
</table>

Rescue medication (salbutamol pMDI 100 µg/puff) will be permitted as needed throughout the study, for all participating patients. In addition, several maintenance medications for the treatment of COPD (inhaled corticosteroids, oral or parenteral corticosteroids up to a maximum of 10 mg of prednisone/day or 20 mg every other day, and oral sustained release teophyllines at a maximum dose of 400 mg/day) are permitted if the dose is stable for at least 4 weeks prior to entering the study (Visit 1). Rescue and maintenance therapies listed above will be allowed to help minimise the risk of COPD exacerbations.

The use of the following medication is not allowed during the study: anticholinergics (long and short acting), inhaled $ß_2$ agonists (long and short acting agents except salbutamol used as rescue medication), methyl-xanthines other than oral sustained release teophylline, continuous oral and parenteral corticosteroids used at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day, intra-muscular depot corticosteroids, mast-cell stabilizers, leukotriene modifiers, phosphodiesterase IV inhibitors and non-selective $ß_1$-blocking agents. Patients on combination therapies involving any of the prohibited medications can participate in the trial provided medications are discontinued prior to Visit 1 (Screening).

1.4.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (e.g. during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-Cov-2 or similar pandemic infection) which would prevent the conduct of the study-related activities at study sites, thereby compromising the study staff or the patient's ability to conduct the study. The

investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of the study participants, maintain compliance with Good Clinical Practice, and minimise risks to study integrity.

Where allowable by local authorities, ethics committees, healthcare provider guidelines (e.g. hospital policies) or local government, these changes may include the following options:

- Pausing recruitment and screening of new patients
- Rescheduling of visits
- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form (ICF) should be signed as soon as is feasible ie at the patient's next visit).
- Telemedicine visit: Remote contact with the patient using telecommunication technology including phone calls, virtual or video visits.
- Home delivery of Investigational Product

Further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix I.

2 STUDY OBJECTIVES

Primary and secondary objectives are to be assessed regardless the adherence to the randomised treatment.

2.1 Primary objective

Primary Objective:	**Outcome Measure:**

• To assess the bronchodilatory effect of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to individual components and placebo when administered twice daily via inhalation to COPD patients. • To assess the bronchodilatory effect of Aclidinium bromide 400 µg compared to placebo when administered twice daily via inhalation to COPD patients.	• Change from baseline in 1-hour morning post-dose dose FEV_1 of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to Aclidinium bromide at Week 24. • Change from baseline in morning pre-dose (trough) FEV_1 of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to Formoterol fumarate at Week 24. • Change from baseline in trough FEV_1 of Aclidinium bromide 400 µg compared to placebo at Week 24

2.2 Secondary objectives

Secondary Objectives:	**Outcome Measures:**
• To assess the benefits of Aclidinium bromide 400 µg /Formoterol fumarate 12 µg in COPD symptoms, disease-related health status and COPD exacerbations compared to placebo, when administered BID via inhalation to COPD patients. • To assess the benefits of Aclidinium bromide 400 µg in COPD symptoms, disease- related health status and COPD exacerbations compared to placebo, when administered BID via inhalation to COPD patients.	• Change from baseline in peak FEV_1 of Aclidinium bromide 400 µg compared to placebo at week 24 • Improvements TDI focal score of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to placebo at week 24 • Improvements TDI focal score of Aclidinium bromide 400µg compared to placebo at week 24 • Change from baseline in SGRQ total score of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to placebo at week 24 • Change from baseline in SGRQ total score of Aclidinium bromide 400µg compared to placebo at week 24
	Additional efficacy variables: • Pulmonary function variables (FEV_1, FVC) at each time point and average (ie Area Under the Curve, AUC_{0-3}) • Symptomatic and health related quality of life outcomes (TDI, SGRQ, CAT, E-RS) • COPD exacerbations (HCRU and EXACT) • Use of rescue medication

2.3 Safety objectives

Safety Objective:	**Outcome Measure:**

• To evaluate the safety profile of Aclidinium bromide 400 µg /Formoterol fumarate 12 µg and Aclidinium bromide 400 µg in the same patient population.	• Adverse events • Clinical laboratory test • Blood pressure • ECG

3 SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Adult male or non-pregnant, non-lactating female patients aged ≥40
   - Explanatory notes: A female is considered to be of childbearing potential unless is at least one year post-menopausal or permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy). Women of childbearing potential are allowed to enter the trial if they show to have a negative pregnancy test at the Screening Visit and are using, during the last two months before the Screening Visit and during the whole duration of the trial, at least one medically approved and highly effective method of birth control defined as those, alone or in combination, which result in a low failure rate (ie less than 1% per year) when used consistently and correctly. Male participants are not requested to use contraception methods during their participation on the trial.
2. Patients with a diagnosis of COPD (GOLD 2015) prior to Visit 1 (screening).
3. Patients with moderate to severe stable COPD (Stage II or Stage III, according to GOLD 2015) at Visit 1: post-bronchodilator FEV1 ≥30% and < 80% and post-bronchodilator FEV1/FVC < 70%
   - Explanatory note: "post" means FEV1 and FVC between 10 to 15 minutes after inhalation of 400 µg of salbutamol from acceptable and repeatable pulmonary function testing according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 criteria. Predicted normal values to be used for calculation purposes are based on the Global Lung Function Initiative predicted values (Quanjer et al 2012).
4. Current or former smokers with a smoking history of ≥ 10 pack-years.
   - Explanatory notes:
     a. Former smoker condition defined as having quit smoking ≥ 6 months before Visit 1 (Screening).

b. Pack-years is calculated by dividing the number of cigarettes smoked per day by 20 (the number of cigarettes in a pack) and multiplying this figure by the number of years a person has smoked. For example, a person who smokes 40 cigarettes a day and has smoked for 10 years would have a 20 pack-year smoking history (40 cigarettes per day ÷ 20 cigarettes per pack = 2; 2 × 10 years of smoking = 20 pack-year history). In case of intermittent smoking/non-smoking periods, pack-years is calculated by summing all periods pack-years.

c. Patients smoking other tobacco types will not be allowed, unless they meet the cigarette criterion as well.

5. Patients able to perform repeatable pulmonary function testing for FEV1 according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 criteria at Visit 1 (screening).
6. Patients who understand the study procedures and are willing to participate in the study as indicated by signing the informed consent.

3.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff and/or site staff) or patients employed by or relatives of the employees of the site or sponsor.
2. Previous enrolment or randomisation in the present study
3. History or current diagnosis of asthma.
4. Any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation (including the mild COPD exacerbation) within 6 weeks prior to screening or during the run-in period.
5. Patients hospitalized for COPD exacerbation (an emergency room visit for longer than 24 hours will be considered a hospitalization) within 3 months prior to screening and during the run-in period.
6. Clinically significant respiratory conditions other than COPD
   - Explanatory note: Clinically significant respiratory conditions, some examples are:
     a. Known active tuberculosis.
     b. History of interstitial lung disease or massive pulmonary thromboembolic disease.
     c. Pulmonary resection or lung volume reduction surgery.
     d. History of lung transplantation.

e. Patients who in the Investigator's opinion might have needed thoracotomy or other lung surgery during the study.

f. Clinically significant bronchiectasis.

g. Known α1-antitrypsin deficiency.

7. Patients who in the Investigator's opinion may need to start a pulmonary rehabilitation program during the study and/or patients who started/finished it within 3 months prior to screening.
8. Use of long-term oxygen therapy (≥15 hours/day).
9. Patient who does not maintain regular day/night, waking/sleeping cycles including night shift workers.
   - Explanatory note: patients with symptomatic sleep apnoea syndrome, any disease related to sleep disturbances such as restless-legs syndrome or somnambulism are to be excluded from the study. However, the use of continuous positive airway pressure is not an exclusion criterion
10. Clinically significant cardiovascular conditions:
    - Explanatory note: Clinically significant cardiovascular conditions, some examples are:
      a. Myocardial infarction within the 6 months prior to screening.
      b. Thoracic surgery within 12 months prior to Visit 1 (screening).
      c. Unstable angina or unstable arrhythmia which had required changes in the pharmacological therapy or other intervention within 12 months prior to Visit 1 (screening), or newly diagnosed arrhythmia within the 3 months prior to screening.
      d. Hospitalization within 12 months prior to screening for heart failure functional classes III (marked limitation of activity and only comfortable at rest) and IV (need of complete rest, confinement to bed or chair, discomfort at any physical activity and presence of symptoms at rest) as per the New York Heart Association.
11. Patients with Type I or uncontrolled Type II diabetes, uncontrolled hypo-or hyperthyroidism, hypokalaemia, or hyperadrenergic state, uncontrolled or untreated hypertension.
12. Patients with QT corrected interval (QTc) using Fridericia formula (QTcF) (QTc=QT/RR1/3) >470 msec as indicated in the centralised reading report assessed at Screening (Visit 1).
13. Patients with clinically significant abnormalities in the clinical laboratory tests, ECG parameters (other than QTcF) or in the physical examination at Visit 1 (screening).

14. Patients with abnormal liver function tests defined as AST, ALT, or total bilirubin ≥ 2.5 times upper limit of normal ranges at screening
15. Patient with known non-controlled history of infection with human immunodeficiency virus and/or active hepatitis
    - Explanatory note: Active hepatitis is defined as clinical symptoms associated with chronic portal inflammation with regional necrosis and fibrosis, which may progress to nodular postnecrotic cirrhosis or patients with antibody to hepatitis B core antigen (HBcAg) and hepatitis B surface antigen (HBsAg) test with positive results or antihepatitis C virus (HCV) antibody and HCV recombinant immunoblot assay HCV positive tests or genetic material (ribonucleic acid) testing positive results.
16. Patient with a history of hypersensitivity reaction to inhaled anticholinergic drugs, sympathomimetic amines, inhaled medication or any component thereof.
17. Patient with known narrow-angle glaucoma, symptomatic bladder neck obstruction, acute urinary retention, or patients with symptomatic non-stable prostatic hypertrophy.
    - Explanatory note: Patients with well-controlled, stable, asymptomatic benign prostatic hypertrophy are not excluded.
18. History of malignancy of any organ system (including lung cancer), treated or untreated, within the past 5 years other than basal or squamous cell skin cancer.
    - Explanatory note: Patients are excluded whether or not there is evidence of local recurrence or metastases.
19. Any other serious or uncontrolled physical or mental dysfunction.
    - Explanatory note: as judged by the Investigator, the dysfunction could place the patient at a higher risk as a result of his/her participation in the study, or confound the results of the study, or would be likely to prevent the patient from complying with the requirements of the study or completing the study
20. Patients with a history (within 2 years prior to Visit 1 (screening) of drug and/or alcohol abuse that may prevent study compliance based on the Investigator judgment.
21. Patients unlikely to be cooperative or cannot comply with the study procedures
    - Explanatory note: patients who may have difficulties following the treatment, completing the patient diary, or attending the clinic at the required times, or unable to properly use a DPI or pressured metered dose inhaler device, or performing spirometry measurements.
22. Patients treated with any investigational drug within 30 days (or 6 half-lives, whichever is longer) prior to screening.
23. Patients who intended to use any concomitant medication not permitted by this protocol or who had not undergone the required washout period for a particular prohibited medication.

24. Patients unable to give consent, or patients of consenting age but under guardianship, or vulnerable patients.
25. Any other conditions that, in the Investigator's opinion, might have indicated the patient to be unsuitable for the study.

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.

3.3 Subject enrolment and randomisation

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject or their guardian/legal representative before any study specific procedures are performed.
2. Call/access IVRS/IWRS to assign potential a unique Patient Identification number consisting of 2 parts, the site number (4-digits) and the screening number (3 digits).
3. At Randomisation Visit (Visit 2), the investigator will determine subject eligibility. See Section 3.
4. For patients fulfilling the eligibility criteria, the investigator will call/access IVRS/IWRS to assign eligible subject unique randomisation code and first medication kit number.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

Randomisation codes will be assigned strictly sequentially as subjects become eligible for randomisation.

3.4 Procedures for handling incorrectly enrolled or randomised subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician/CRO immediately, and a discussion should occur between the AstraZeneca study physician/CRO and the investigator regarding whether to continue or discontinue the patient

from treatment. The AstraZeneca study physician/CRO must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Subjects will be allocated to the four treatment groups in a 1:1:1:1 ratio:

- Aclidinium bromide 400 µg/Formoterol fumarate 12 µg administered via Genuair inhaler
- Aclidinium bromide 400 µg administered via Genuair inhaler
- Formoterol fumarate 12 µg administered via Turbuhaler inhaler
- Placebo

The randomisation will be stratified by country and smoking status (smoker or former smoker) and the randomisation numbers will be grouped in blocks. The block size will not be communicated to the investigators.

The randomisation will be performed using a centralized Interactive Voice/Web Response System (IVRS/IWRS) at Visit 2 (Day 1). Specific information concerning the use of the IVRS/IWRS will be provided in a separate manual. Randomised subjects who discontinue from the treatment will not be replaced.

At the randomisation, the IVRS/IWRS will inform the site about the first medication kit number to be administered and dispensed to each particular patient.

3.6 Methods for ensuring blinding

All medication kits will have identical appearance regardless of the investigational product contained and will be labelled using a unique medication identification number (Kit ID) that is linked to a treatment arm. IVRS/IWRS will assign the study medication to be dispensed to each subject at Visit 2 and Visit 5 (after 12 weeks of treatment).

Active compounds have no perceivable taste, appearance, odour or colour that could unmask the blinded design.

This is a double-dummy study because the Aclidinium bromide 400µg/Formoterol fumarate 12 µg and the Aclidinium bromide 400 µg will be administered via Genuair inhaler and the Formoterol fumarate 12 µg will be administered via Turbuhaler inhaler. Therefore, in order to ensure the double blind nature of the trial, patients will have to inhale from both inhalers twice daily following the schema below.

Table 1 Schema of IP administration to ensure double-blind trial

Treatment arm	Morning inhalation (8-10 AM)	Evening inhalation (8-10 PM)
Aclidinium bromide /Formoterol fumarate 400/12 µg	1 puff of Aclidinium bromide/Formoterol fumarate 400/12 µg via Genuair 1 puff of placebo via Turbuhaler	1 puff of Aclidinium bromide/Formoterol fumarate 400/12 µg via Genuair 1 puff of placebo via Turbuhaler
Aclidinium bromide 400 µg	1 puff of Aclidinium bromide 400 µg via Genuair 1 puff of placebo via Turbuhaler	1 puff of Aclidinium bromide 400 µg via Genuair 1 puff of placebo via Turbuhaler
Formoterol fumarate 12 µg	1 puff of placebo via Genuair 1 puff of Formoterol fumarate 12 µg via Turbuhaler	1 puff of placebo via Genuair 1 puff of Formoterol fumarate 12 µg via Turbuhaler
Placebo	1 puff of placebo via Genuair 1 puff of placebo via Turbuhaler	1 puff of placebo via Genuair 1 puff of placebo via Turbuhaler

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Only authorised personnel at the research site will receive unblinding permits in IVRS/IWRS. Patient will be immediately withdrawn from the study once his/her treatment has been unblinded.

Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca/CRO, without revealing the treatment given to subject to the AstraZeneca/CRO staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

3.8 Restrictions

– Donation of blood is not allowed throughout the study

– Patient should keep regular night/day shifts.

The activities that should preferably be avoided prior to lung function testing are:

– Smoking within at least 1 h of testing
– Consuming alcohol within 4 h of testing
– Performing vigorous exercise within 30 min of testing
– Wearing clothing that substantially restricts full chest and abdominal expansion
– Eating a large meal within 2 h of testing
– Subjects should avoid taking inhaled bronchodilators prior to spirometry (see Section 7.7)
– Restrictions regarding concomitant medication are described in Section 7.

Any event likely to interfere with the objectives of the trial will be communicated to the investigator and reported without delay to AstraZeneca.

3.9 Patient discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

- Adverse Event: if a patient experiences an AE, its premature discontinuation will be considered at the discretion of either the investigator or the patient regardless of the causal relationship to the IP. AE should be indicated as the reason for discontinuation in the eCRF.
- Progressive disease: if at investigator's or patient's discretion the severity of the COPD exacerbation episode jeopardises the current medical condition of the patient, the patient should be discontinued from the treatment and progressive disease should be indicated as the reason for discontinuation in the eCRF.
- Protocol deviation: This will include patients that have been wrongly randomised: not fulfilling inclusion/exclusion criteria but detected after randomisation. After randomisation, any protocol deviations detected should be corrected when possible and the patient should be allowed to continue. The following major deviations could lead to patient discontinuation after discussion between the AstraZeneca study physician/CRO and the investigator (see section 3.4): those which could affect patient's safety (e.g., illness requiring treatment(s) which in the clinical judgement of the investigator [or after discussion with the trial monitor might invalidate the trial by interfering with the IP) or which are due to patient unwillingness to comply with the trial activities or those violations of inclusion and/or exclusion criteria detected after randomisation.
- Lack of efficacy: only if at the investigators discretion the response to the treatment is considered as unsatisfactory
- Pregnancy

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue investigational product, without prejudice to further treatment. A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events.

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 for the full study period. The reason for premature discontinuation of IP will be documented in the source documentation.

If possible, subjects who discontinue investigational product will be seen and assessed by an Investigator(s) in an End of treatment (EOT) visit.

From the EOT visit on the patients will start a post-treatment follow-up period where the on-site visits will be replaced by telephone calls in order to follow-up the SAEs, COPD exacerbations and Concomitant Medication. During this post-treatment follow-up period the patients will not have IP but they will keep the paper diary to record the concomitant medication and the e-diary to continue recording the use of rescue medication and EXACT questionnaire.

The Visit 7 will be performed as an on-site visit in order to return the e-diary, paper diary and rescue mediation and to follow-up any new SAE, COPD exacerbation and Concomitant medication.

For any patient who withdraws from the IP, the investigator will:

1. Ask the patient to undergo the End of Treatment (EOT) visit **AS SOON AS POSSIBLE** after discontinuation of IP.
2. Arrange for alternative medical care of the withdrawn patient.
3. Appoint the telephone contacts replacing on-site visits and on-site Visit 7.

The date and cause of discontinuation from IP will be collected in the eCRF.

If the patient decides to discontinue from the study after having discontinued from the IP, an EOS visit should be performed so that the patient returns the e-diary, paper diary and rescue mediation and to follow-up any new SAE, COPD exacerbation and Concomitant medication. The date and cause of discontinuation from the study will also be collected in the eCRF.

3.10 Patient discontinuation from the study (withdrawal)

Subjects may be discontinued from the study in the following situations:

- Screen failures: patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Screen Failure (Non-fulfilment of inclusion/exclusion criteria)' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).
- Adverse Event (ex: death, long-term disability/hospitalization): if a patient experiences an AE, its premature discontinuation will be considered at the discretion of either the investigator or the patient regardless of the causal relationship to the IP. AE should be indicated as the reason for discontinuation in the eCRF.
- Progressive disease (ex: death, long-term disability/hospitalization): if at investigator's or patient's discretion the severity of the COPD exacerbation episode jeopardises the current medical condition of the patient, the patient should be discontinued from the treatment and progressive disease should be indicated as the reason for discontinuation in the eCRF.
- Protocol deviation: This will include patients that have been wrongly randomised: not fulfilling inclusion/exclusion criteria but detected after randomisation. After randomisation, any protocol deviations detected should be corrected when possible and the patient should be allowed to continue. The following major deviations could lead to patient discontinuation after discussion between the AstraZeneca study physician/CRO and the investigator (see section 3.4): those which could affect patient's safety (e.g., illness requiring treatment(s) which in the clinical judgement of the investigator [or after discussion with the trial monitor might invalidate the trial by interfering with the IP) or which are due to patient unwillingness to comply with the trial activities or those violations of inclusion and/or exclusion criteria detected after randomisation.
- Lack of efficacy: only if at the investigators discretion the response to the treatment is considered as unsatisfactory
- Pregnancy
- Lost to follow-up: Non-attendance to visits. In these cases, every effort should be made by the investigator to ascertain the reason and to assure patient's attendance as soon as possible. Every effort (at least three documented attempts) should be made to contact the patient and documented in the medical records. If patient could not be reached after that, a registered mail letter will be sent to the patient and documented in the medical records.
- Withdrawal by the subject: The patient is permitted to stop his/her participation at any time during the trial without incurring any loss in his/her medical care. The investigator should ensure that such withdrawal is not due to AEs or COPD exacerbation, in which case the corresponding reason should be selected.
- Others: At the investigator´s or Sponsor's request, study cancellation or any other reason not described above.

3.10.1 Withdrawal of the informed consent

Subjects are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. The subject will return electronic PRO (ePRO) devices.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

3.10.2 Procedures for discontinuation of a subject from the study

For any patient who withdraws from the study, the investigator will:

1. Ask the patient to undergo the End of Study visit AS SOON AS POSSIBLE after discontinuation.
2. Arrange for alternative medical care of the withdrawn patient.
3. Appoint the follow-up call within 14+3 days after the last IP (if applicable)

The date and cause of discontinuation from the study will be collected in the eCRF.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

3.11 Premature termination of the study

The “end of trial” is defined as the date when all patients randomised in the trial performed the last contact (either Visit 7 or Follow-up contact) and will be communicated to Regulatory Authorities and Ethics Committees on due time according to local regulations.

Sponsor reserves the right to prematurely terminate (ie, suspend) the trial for reasons such as:

- The principal investigator and the sponsor feel that the type, number and /or severity of AEs justify discontinuation of the trial.
- Data not known before becoming available and raising concern about the safety of the study drug so that continuation would pose potential risks to the patient.
- The sponsor decides to discontinue the study.

If the study is terminated or suspended, the sponsor will promptly inform the investigators/institutions and the Regulatory Authorities and provided with the reason(s) for the termination or suspension. Independent Ethics Committee (IEC) will be informed by the investigator or sponsor, according to local regulations.

The investigator will inform the patients and will collect and keep all the data up to the date of discontinuation.

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

If the trial is terminated or suspended, study results will be reported according to the requirements outlined in this protocol as far as applicable.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4 STUDY PLAN AND TIMING OF PROCEDURES

Table 2 Study Plan detailing the procedures

Period	**Run -in**	**Treatment**						**Follow-up**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EOT[12]/ EOS**	**Phone contact [13]**
Week	**-2**	**0**	**1**	**4**	**12**	**18**	**24**	**NA**	**26**
Day	**-14 (±3)**	**1**	**7 (±3)**	**28 (±3)**	**84 (±3)**	**126 (±3)**	**168 (±3)**	**NA**	**182 (+3)**
Informed Consent[1]	X								
Medical and COPD History	X								
Laboratory analysis (haematology and biochemistry) and serum pregnancy test (for women of childbearing potential only)	X						X	X	
Physical exam[2]	X						X	X	
Bronchodilator test[3]	X								
Inclusion/exclusion criteria	X	X							
Randomisation		X							
IP kit assignment and dispensing		X			X				
IP administration at the clinic		X	X	X	X	X	X		

Period	**Run -in**	**Treatment**						**Follow-up**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EOT[12]/ EOS**	**Phone contact [13]**
Week	**-2**	**0**	**1**	**4**	**12**	**18**	**24**	**NA**	**26**
Day	**-14 (±3)**	**1**	**7 (±3)**	**28 (±3)**	**84 (±3)**	**126 (±3)**	**168 (±3)**	**NA**	**182 (+3)**
CAT, BDI/TDI and SGRQ[4]		X		X	X		X		
ECG and Blood Pressure[5]	X	X	X		X	X	X	X	
Pre-dose spirometry[6]	X	X	X	X	X	X	X		
Post-dose spirometry[7]		X	X	X	X	X	X		
Provide ediary[8] and paper diary[9]	X	X	X	X	X	X			
Review ediary and paper diary		X	X	X	X	X	***X***	X	
EXACT and rescue medication	Daily since Screening Visit (Visit 1) (in the evening)								
Provide rescue medication, if needed	X	X	X	X	X	X			
Collect IP and drug accountability[10]					X		X	X	
Collect rescue medication, ediary and paper diary[11]							X	X	
Adverse Events and COPD Exacerbations	X	X	X	X	X	X	X	X[11]	X
Concomitant medications	X	X	X	X	X	X	X	X	X[12]

1. Patients requiring the washout of prohibited COPD medications before performing the Screening Visit should sign the informed consent before starting the washout period (one day to one month before, depending on the length of wash-out period required). Patients will be registered in IVRS/IWRS at the moment of the ICF signature.
2. Height and Weight only at Visit 1 1 (screening).
3. Bronchodilator test will be done 10-15 minutes after the inhalation on 400 mcg of salbutamol through a Spacer device.
4. Questionnaires will be completed in the following order: The preferred order for completing the questionnaires will be: first BDI/TDI, second CAT and finally the SGRQ. For BDI/TDI: BDI will be used at Visit 2 and TDI at succeeding visits. Questionnaires should be assessed before any study procedures or IP administration. Questionnaires cannot be repeated.
5. ECG and Blood Pressure will be performed once at Visit 1 to determine patient eligibility. Afterwards, ECG and Blood Pressure will be performed pre-morning dose and 1 hours post-morning dose at the above indicated visits. At EOT/EOS visit, only one ECG will be performed.
6. From Baseline (Visit 2) onwards, 2 sets of pre-dose forced manoeuvres will be performed 30 minutes apart.
7. Post-morning dose spirometry at Visit 2 and Visit 7: at 5 and 30 min, and at 1, 2, 3 hours. At Visits 3, 4, 5 and 6 at 1h post-dose.

8. Electronic Patient Diary: patients will record the number of doses taken of study drug and rescue medication every morning and evening; EXACT questionnaire will be filled in every evening.
9. Paper Patient Diary: patients will record any adverse event and/or concomitant medication taken. Paper diary should be dispensed to the patients starting at Visit 1 and at every visit to record any AEs and changes on the concomitant medications.
10. IP dispensed at Randomisation will be collected when dispensing a new kit at Visit 5.
11. Rescue medication: Empty inhalers will be collected throughout the study treatment, as applicable, if dispensed more than once.
12. In case of premature discontinuation of IP or discontinuation from study, End of Treatment (EOT) or End of Study (EOS) visit should be performed as soon as possible in order to check the patient safety. Compliant subjects who are discontinued from the IP should be encouraged to continue to undergo the post-treatment follow-up period. The post-treatment follow up period will include phone calls to collect COPD exacerbations, concomitant medications, and SAEs for the remainder of the study duration as well as an on-site Visit 7 to return the study material. During this post-treatment follow-up period the patients will not have IP but they will keep the paper diary to record the concomitant medication and the e-diary to continue recording the use of rescue medication and EXACT questionnaire.
13. Only concomitant medication related to AEs must be recorded at follow-up contact.

4.1 Enrolment/screening period

This period will start with the signature of the Informed Consent Form (ICF) and subject registration in IVRS/IWRS, will follow with Visit 1 (Screening) and will end at the randomisation visit (Visit 2).

Prior to ICF signing, investigators will evaluate suitability of patients for entry in the trial by comparing past and current medical status, as documented in the patient's medical records, to the inclusion/exclusion criteria of this study protocol.

Patients' informed consent signature must be obtained before performing any procedure related to the trial. ICF must be signed after the patient has received sufficient information about the trial, after he/she has had the opportunity to ask any questions related to the study and considered the options.

Patients who require a washout period from prohibited concomitant treatments should be seen and sign the ICF prior to Visit 1, to ensure the necessary washout before this visit. No trial assessments will be performed that date, and Visit 1 will be scheduled later according to the wash-out length required for the specific medication stopped. Patient will be dispensed one inhaler of rescue medication and trained on its use.

If no wash-out period is required, Visit 1 assessments will start after signing the ICF. Any patient signing the ICF should be recorded in IVRS/IWRS and should be assigned a patient ID number.

4.1.1 Visit 1 (screening)

Screening Visit will be scheduled in the morning, at a similar start time of all the other visits if the patient was enrolled in the study. The following assessments and processes will be performed and data reviewed:

- Prior medication and concomitant medication review: Confirm that no prohibited medication was taken during the washout period and that the appropriate withholds have been made. Record in the eCRF Prior and Concomitant medications.
- Review of any Adverse Event during wash-out period.
- Sign the ICF and register patient in IVRS/IWRS (if not done yet). Note: patients must be registered in IVRS/IWRS at the moment of the ICF signature.
- Review medical history, demographic, COPD history (date of COPD diagnosis, number of COPD exacerbations during last year and date of last COPD exacerbation and if hospitalization) and smoking information (ie, date of smoking initiation, current smoker or former smoker, date of smoking cessation and total-pack years).

- Physical examination including body weight (in light indoor clothes, without shoes) and height measurement
- Blood pressure.
- 12-lead ECG.
- Blood sampling for haematology and biochemistry analysis and, when appropriate, pregnancy test.
- Spirometry Forced manoeuvre test (FEV1 and FVC measurement): 1 set of tests will be performed.
- Bronchodilator test (Reversibility test): administer inhaled salbutamol (100 µg x 4 puffs) through a spacer device at least 10 minutes after previous spirometry test. Afterwards, 10 to 15 minutes after salbutamol inhalation, perform again 1 set of Spirometry Forced manoeuvre.
- Review inclusion/exclusion criteria.

Only patients who meet all inclusion/exclusion criteria at this point will be allowed to continue. Otherwise, the screening failure will be recorded in the IVRS/IWRS. When patient fulfilled inclusion/exclusion criteria, the following will occur:

- Patient will be trained and dispensed the rescue medication inhaler (if not done pre-wash-out).
- Patient will be trained on the use of Genuair® and Turbuhaler® with the empty training inhalers.
- Patient will be trained and provided with the electronic Patient Diary and will be asked to start its recording that night onwards.
- Patient will be trained and provided with the paper Patient Diary and will be asked to start its recording as needed.
- Next protocol visit will be scheduled. Patient will be reminded to avoid the intake of rescue medication for at least 6 hours before attending the next visit, and to bring back the rescue medication inhaler, the electronic and the paper Patient Diary.

4.2 Treatment period

4.2.1 Visit 2 (Randomisation Visit)

The following assessments will be performed pre-randomisation and pre-morning IP dose:

- Paper Patient Diary review: Adverse events, COPD exacerbation, and concomitant medication review.
- Electronic Patient Diary review. In case of low compliance with the e-diary (e.g. less than 75% of entries), patient should be retrained on how to use the e-diary and, if possible, visit 2 should be rescheduled in order to get minimum baseline data.

- Confirmation of inclusion/exclusion criteria.

Only patients who meet all inclusion/exclusion criteria at this point will be allowed to continue. Otherwise the screening failure will be recorded in the IVRS/IWRS.

When patient fulfils inclusion/exclusion criteria, the following assessments will be performed:

A. Randomisation
   - Randomise the patient via the IWRS/IVRS, and obtain kit number assignment. Document the randomisation date on the medical notes.

B. Pre-dose assessments (baseline)
   - BDI by an independent interviewer unaware of available patient status (if possible this questionnaire should be complete before the others).
   - CAT
   - SGRQ
   - Blood pressure.
   - 12-lead ECG.
   - Spirometry forced manoeuvre tests (FEV1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning IP dose, allowing approximately 30 min between them.

C. Morning IP administration
   - Patient will be re-trained on the use of Genuair® and Turbuhaler® with the empty training inhalers. The investigator will evaluate proper use of the device by the patient and provide additional training if needed.
   - Dispense the kit number assigned by IWRS/IVRS and record the kit number dispensed on the Drug Accountability Log.
   - Administer the first dose of IP at approximately 09:00±1h by inhalation of 1 puff from the Genuair® inhaler #1 and 1 puff from the Turbuhaler® inhaler #1. The investigator or study personnel should check that the patient has correctly used the inhaler.
   - Instruct the patient to inhale from both inhalers every morning and evening until the last evening before next visit. Remind the patient to come to next visit with the medication kit to assess the drug accountability.
   - Record the date and time of the first IP administration in the Masterscope CT.

D. Post-dose assessments
   - Post-dose PFT (FEV1 and FVC): at +5min, +30 min, +1h, +2h, and +3h.
   - Blood pressure: at +1h
   - 12-lead ECG: at +1h

Note: for T+1h the ECG and blood pressure should be measured before the PFT manoeuvre.

The following procedures will be performed at any time after post-morning IP dose:

- IP kit will be given to the patient and reminded about the correct dose regimen and timing.
- Rescue medication will be dispensed, as needed.
- Patient will be provided with a paper patient diary.
- The electronic Patient Diary will be re-dispensed.
- Next protocol visit will be scheduled. Patient will be reminded to hold the morning IP dose that day, avoid the intake of rescue medication for at least 6 hours before attending the next visit, and to bring the IP kit, the rescue medication inhaler, the electronic and the paper Patient Diary to the clinic.

4.2.2 Visit 3: Week 1

A. Pre-dose assessments (baseline)
   - Paper Patient Diary review: Adverse events, COPD exacerbation, and concomitant medication review.
   - Electronic Patient Diary review.
   - Check appropriate wash-out before visit (at least 6h since last rescue medication intake).
   - Blood pressure.
   - 12-lead ECG.
   - Spirometry forced manoeuvre tests (FEV1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning IP dose, allowing approximately 30 min between them.

B. Morning IP administration
   - If needed, patient will be re-trained on the use of Genuair® and Turbuhaler® with the empty training inhalers. The investigator will evaluate proper use of the device by the patient and provide additional training if needed.
   - Administer IP at approximately 09:00±1h by inhalation of 1 puff from the Genuair® inhaler and 1 puff from the Turbuhaler® inhaler. The investigator or study personnel should check that the patient has correctly used the inhaler.
   - Remind the patient to inhale from both inhalers every morning and evening until the last evening before next visit. Remind the patient to come to next visit with the medication kit to assess the drug accountability.
   - Record the date and time of the IP administration in the Masterscope CT.

C. Post-dose assessments

- Blood pressure: at +1h
- 12-lead ECG: at +1h
- Post-dose PFT (FEV1 and FVC): at +1h.

The following procedures will be performed at any time after post-morning IP dose:

- Same IP kit will be redispensed to the patient and reminded about the correct dose regimen and timing.
- Rescue medication will be dispensed, as needed.
- Patient will be provided with a paper patient diary.
- The electronic Patient Diary will be re-dispensed.
- Next protocol visit will be scheduled. Patient will be reminded to hold the morning IP dose that day, avoid the intake of rescue medication for at least 6 hours before attending the next visit, and to bring the IP kit, the rescue medication inhaler, the electronic and the paper Patient Diary to the clinic.

4.2.3 Visit 4: Week 4

A. Pre-dose assessments (baseline)

- Paper Patient Diary review: Adverse events, COPD exacerbation and concomitant medication review.
- Electronic Patient Diary review.
- Check drug accountability and record it in the paper Drug Accountability Log. Collect locked Genuair® and empty Turbuhaler® inhalers.
- Check appropriate wash-out before visit (at least 6h since last rescue medication intake).
- TDI by an independent interviewer unaware of available patient status.
- CAT
- SGRQ
- Spirometry forced manoeuvre tests (FEV1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning IP dose, allowing approximately 30 min between them.

B. Morning IP administration

- If needed, patient will be re-trained on the use of Genuair® and Turbuhaler® with the empty training inhalers. The investigator will evaluate proper use of the device by the patient and provide additional training if needed.
- Administer IP at approximately 09:00±1h by inhalation of 1 puff from the Genuair® inhaler and 1 puff from the Turbuhaler® inhaler. The investigator or study personnel should check that the patient has correctly used the inhaler.

- Remind the patient to inhale from both inhalers every morning and evening until the last evening before next visit. Remind the patient to come to next visit with the medication kit to assess the drug accountability.
- Record the date and time of the IP administration in the Masterscope CT.

C. Post-dose assessments

- Post-dose PFT (FEV1 and FVC): at +1h.

The following procedures will be performed at any time after post-morning IP dose:

- IP kit will be redispensed to the patient and reminded about the correct dose regimen and timing.
- Rescue medication will be dispensed, as needed.
- Patient will be provided with a paper patient diary.
- The electronic Patient Diary will be re-dispensed.
- Next protocol visit will be scheduled. Patient will be reminded to hold the morning IP dose that day, avoid the intake of rescue medication for at least 6 hours before attending the next visit, and to bring the IP kit, the rescue medication inhaler, the electronic and the paper Patient Diary to the clinic.

4.2.4 Visit 5: Week 12

A. Pre-dose assessments (baseline)

- Paper Patient Diary review: Adverse events, COPD exacerbation, and concomitant medication review.
- Electronic Patient Diary review.
- Check appropriate wash-out before visit (at least 6h since last rescue medication intake).
- Collect ALL Genuair® and Turbuhaler® inhalers and check them in order to assess drug accountability
- TDI by an independent interviewer unaware of available patient status.
- CAT
- SGRQ
- Blood pressure.
- 12-lead ECG.

- Spirometry forced manoeuvre tests (FEV1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning IP dose, allowing approximately 30 min between them.

B. Morning IP administration

- If needed, patient will be re-trained on the use of Genuair® and Turbuhaler® with the empty training inhalers. The investigator will evaluate proper use of the device by the patient and provide additional training if needed.
- Call IVRS/access IWRS to assign a new medication kit and record the kit number in the drug accountability log
- Administer IP at approximately 09:00±1h by inhalation of 1 puff from the Genuair® inhaler and 1 puff from the Turbuhaler® inhaler. The investigator or study personnel should check that the patient has correctly used the inhaler.
- Remind the patient to inhale from both inhalers every morning and evening until the last evening before next visit. Remind the patient to come to next visit with the medication kit to assess the drug accountability.
- Record the date and time of the IP administration in the Masterscope CT.

C. Post-dose assessments

- Blood pressure: at +1h
- 12-lead ECG: at +1h
- Post-dose PFT (FEV1 and FVC): at +1h.

The following procedures will be performed at any time after post-morning IP dose:

- IP kit will be dispensed to the patient and reminded about the correct dose regimen and timing.
- Rescue medication will be dispensed, as needed.
- Patient will be provided with a paper patient diary.
- The electronic Patient Diary will be re-dispensed.
- Next protocol visit will be scheduled. Patient will be reminded to hold the morning IP dose that day, avoid the intake of rescue medication for at least 6 hours before attending the next visit, and to bring the IP kit, the rescue medication inhaler, the electronic and the paper Patient Diary to the clinic.

4.2.5 Visit 6: Week 18

A. Pre-dose assessments (baseline)

- Paper Patient Diary review: Adverse events, COPD exacerbation, and concomitant medication review.
- Electronic Patient Diary review.

- Check appropriate wash-out before visit (at least 6h since last rescue medication intake).
- Check drug accountability and record it in the paper Drug Accountability Log.
- Collect locked Genuair® and empty Turbuhaler® inhalers.
- Blood pressure.
- 12-lead ECG.
- Spirometry forced manoeuvre tests (FEV1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning IP dose, allowing approximately 30 min between them.

B. Morning IP administration

- If needed, patient will be re-trained on the use of Genuair® and Turbuhaler® with the empty training inhalers. The investigator will evaluate proper use of the device by the patient and provide additional training if needed.
- Administer IP at approximately 09:00±1h by inhalation of 1 puff from the Genuair® inhaler and 1 puff from the Turbuhaler® inhaler. The investigator or study personnel should check that the patient has correctly used the inhaler.
- Remind the patient to inhale from both inhalers every morning and evening until the last evening before next visit. Remind the patient to come to next visit with the medication kit to assess the drug accountability.
- Record the date and time of the IP administration in the Masterscope CT.

C. Post-dose assessments

- Blood pressure: at +1h
- 12-lead ECG: at +1h
- Post-dose PFT (FEV1 and FVC): at +1h.

The following procedures will be performed at any time after post-morning IP dose:

- Same IP kit will be redispensed to the patient and reminded about the correct dose regimen and timing.
- Rescue medication will be dispensed, as needed.
- Patient will be provided with a paper patient diary.
- The electronic Patient Diary will be re-dispensed.
- Next protocol visit will be scheduled. Patient will be reminded to hold the morning IP dose that day, avoid the intake of rescue medication for at least 6 hours before attending the next visit, and to bring the IP kit, the rescue medication inhaler, the electronic and the paper Patient Diary to the clinic.

4.2.6 Visit 7: Week 24

A. Pre-dose assessments (baseline)

- Paper Patient Diary review: Adverse events, COPD exacerbation and concomitant medication review.
- Electronic Patient Diary review.
- Check appropriate wash-out before visit (at least 6h since last rescue medication intake).
- Collect ALL Genuair® and Turbuhaler® inhalers and check them in order to assess drug accountability and record it in the paper Drug Accountability Log.
- TDI by an independent interviewer unaware of available patient status.
- Blood sampling for haematology and biochemistry analysis and, when appropriate, pregnancy test.
- CAT
- SGRQ
- 12-lead ECG.
- Blood pressure.
- Physical examination (any new or worsened finding will be recorded in the AE form of the EDC).
- Spirometry forced manoeuvre tests (FEV1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning IP dose, allowing approximately 30 min between them.

B. Morning IP administration

- If needed, patient will be re-trained on the use of Genuair® and Turbuhaler® with the empty training inhalers. The investigator will evaluate proper use of the device by the patient and provide additional training if needed.
- Administer IP at approximately 09:00±1h by inhalation of 1 puff from the Genuair® inhaler and 1 puff from the Turbuhaler® inhaler. The investigator or study personnel should check that the patient has correctly used the inhaler.
- Record the date and time of the IP administration in the Masterscope CT.

C. Post-dose assessments

- Blood pressure: at +1h
- 12-lead ECG: at +1h
- Post-dose PFT (FEV1 and FVC): at +5min, +30 min, +1h, +2h, and +3h.

The following procedures will be performed at any time after post-morning IP dose:

- Review and retrieve paper and electronic Patient Diary.

- Retrieval of rescue medication.
- Research personnel will register patient´s completion of the treatment in IVRS/IWRS.
- The follow-up call will be scheduled.
- Patient will be instructed by study personnel to resume the COPD medication taken before trial start, or any other treatment deemed appropriate according to medical judgement.

4.2.7 End of Treatment (EOT)

The following procedures will be performed for patients that discontinue from the IP and accept to participate in the post-treatment follow-up period:

- Paper Patient Diary review: Adverse events, COPD exacerbation and concomitant medication review.
- Electronic Patient Diary review.
- Collect ALL Genuair® and Turbuhaler® inhalers and check them in order to assess drug accountability and record it in the Drug Accountability Log.
- Blood sampling for haematology and biochemistry analysis and, when appropriate, pregnancy test.
- 12-lead ECG.
- Blood pressure.
- Physical examination (any new or worsened finding will be recorded in the AE form of the EDC).
- If deemed appropriate by the investigator, one forced spirometry test may be performed to assess patient lung condition.
- Research personnel will register patient´s discontinuation of the treatment in IVRS/IWRS and will complete the corresponding EOT visit in the EDC.
- Patient will be instructed by study personnel to resume the COPD medication taken before trial start, or any other treatment deemed appropriate according to medical judgement.

At the end of the visit the investigator will:

- Redispense the paper diary and electronic diary. Patients will be followed up for SAEs and concomitant medication and they will be requested to record daily the EXACT questionnaire in the e-diary.
- Inform the patient that he/she will be contacted as per the planned study visits via telephone calls until the 24 weeks of treatment are completed (if the EOT occurs within two weeks of the next scheduled visit (call) the next visit (call) can be skipped). The Visit

7 must always be done as an on-site visit in order to return the paper and electronic diary as well as the rescue medication.

– Schedule telephone calls and on-site Visit 7 after 24 weeks of treatment.

Patients that discontinue from the treatment and accept participation on the post-treatment follow-up should complete the EXACT questionnaire in the ediary every night and should attend phone calls instead of regular visits up to Visit 7, that will always be an on-site visit. During the phone calls patient will be asked about adverse events.

Patients attending Visit 7 will be considered patients discontinued from the treatment but completed the follow-up so they will have a date and reason for treatment discontinuation collected in the EOT visit and a date of study completion to be collected at Visit 7.

If any patient accepting the participation in the post-treatment follow-up period decided to discontinue from the follow-up before performing Visit 7, an EOS visit should be scheduled in order to return the paper and electronic diaries as well as the rescue medication (see section 4.2.8). These patients will be considered patients discontinued from the treatment and discontinued from the follow-up so they will have a date and reason for treatment discontinuation collected in the EOT visit and a date and reason for follow-up discontinuation collected in the EOS visit.

4.2.8 End of Study (EOS) visit

The procedures to be performed during the EOS visit will be different depending on whether the patient decides to discontinue from the study (patient discontinued from the treatment who does not accept to enter in the post-treatment follow-up period) or whether the patient decides to discontinue from the post-treatment follow-up (patient discontinued from the treatment who accept to enter in the post-treatment follow-up period but discontinue from the follow-up before performing Visit 7).

4.2.8.1 EOS visit for patients that discontinue from the study

Patients that discontinue from the treatment and do not accept to participate in the post-treatment follow-up period will be considered as “discontinued from the study” and will have to perform a visit that will be a combination of the EOT visit and EOS visit.

The following procedures will be performed for patients that discontinue from the study:

– Paper Patient Diary review: Adverse events, COPD exacerbation and concomitant medication review.
– Electronic Patient Diary review.
– Collect ALL Genuair® and Turbuhaler® inhalers and check them in order to assess drug accountability and record it in the Drug Accountability Log.

- Blood sampling for haematology and biochemistry analysis and, when appropriate, pregnancy test.
- 12-lead ECG.
- Blood pressure.
- Physical examination (any new or worsened finding will be recorded in the AE form of the EDC).
- If deemed appropriate by the investigator, one forced spirometry test may be performed to assess patient lung condition.
- Research personnel will register patient´s discontinuation of the study in IVRS/IWRS and will complete the corresponding EOS visit in the EDC respectively.
- Patient will be instructed by study personnel to resume the COPD medication taken before trial start, or any other treatment deemed appropriate according to medical judgement.
- Retrieve paper and electronic Patient Diary.
- Retrieval of rescue medication.
- Schedule the follow-up call 14+3 days after the last IP (if still applicable)

4.2.8.2 EOS visit for patients that discontinue from the post-treatment follow-up period

If a patient discontinue from the post-treatment follow-up for any reason (ie withdrawal of informed consent), an EOS visit should be performed as soon as possible in order to retrieve the study material (paper diary, electronic diary and rescue medication).

No additional tests are required in this visit unless the investigator considers them necessary to ensure the patients safety.

The activities to be performed in the EOS visit for patients that had previously discontinued from the IP are:

- Research personnel will register patient´s discontinuation from the follow-up in IVRS/IWRS and will complete the corresponding EOS visit in the EDC respectively.
- Retrieve paper and electronic Patient Diary.
- Retrieval of rescue medication

4.3 Follow-up period

A follow-up should be performed for patients completing the treatment or discontinued from the study by means of a visit or a phone contact, as considered appropriate, 14 (+ 3) days after last IP intake in order to assess new or ongoing AE (as well as any concomitant medication administered to treat the mentioned AE) and COPD exacerbations.

4.4 Re-scheduling visits rules and repeated tests

At Visit 1 (screening) any individual test(s) might be repeated before randomisation e.g., in case of impaired results (e.g., blood sample haemolysed) or results requiring confirmation (to ensure patient eligibility or results inconsistent with patient's known past medical conditions), etc. The full Visit 1 will not be repeated. If any of the specific tests of the Screening Visit needs to be repeated, and more than 28 days has elapsed since first test date, the patient will be screen failed.

As deemed necessary by the investigator, ECGs and laboratory test can be repeated at any time during the study in order to follow-up the progress of any clinically relevant abnormal finding, investigate any potential new adverse event, etc. Also for monitoring purposes, additional spirometry tests may be performed in between protocol visits.

However, individual spirometry tests within a protocol visit (PFT scheduled timepoints) as well as CAT, BDI/TDI, and SGRQ must not be repeated.

Before starting any visit procedure, research personnel will review the data recorded on the electronic and paper Patient Diary and will ask the patient about his/her overall status. The following rules with respect to postponing the visit will be adhered to:

- The occurrence of any COPD exacerbation episode.
- The maintenance of the relevant wash-out (6 hours (six) for salbutamol: the visit will be postponed unless it can be slightly delayed, that is morning IP dose can still happen before 10:00 am.).
- The intake of any prohibited medication (except when related to treat a COPD exacerbation): the visit will be postponed (no assessment performed) according to the wash-out length required for the specific prohibited medication taken as long as delay fits the protocol allowed time window. If the delay is longer than the protocol allowed time window, please contact your Clinical Research Associate (CRA).
- For logistic reasons: Patient or Investigator are not able to perform the visit on the scheduled date due to technical or personal issues by site/patient.

After visit assessments have started:

- In case of intake of salbutamol during the course of a visit before morning IP dose, the visit may be re-scheduled if at all possible. Should this happen, all assessments (except CAT, BDI/TDI, and SGRQ) planned for the visit must be (again) performed, even if this results in the repetition of some assessments. If visit re-schedule is not possible, safety assessments will be performed and spirometries skipped.

- In case of intake of salbutamol during the course of a visit after morning IP dose, all planned safety assessments will be performed and spirometry assessments will be skipped. After IP intake, re-scheduling of visits is not allowed.

See Appendix I for re-scheduling rules due to civil crisis, natural disaster, or public health crisis disruption.

5 STUDY ASSESSMENTS

The Electronic Data Capture (EDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Pulmonary function test (spirometry)

5.1.1.1 General Conditions

A centralized spirometry company (ERT) will provide the spirometers and all necessary equipment (computer, calibration syringe, printer, paper, ink, etc.), a detailed study manual and training to the technicians and principal investigator (as needed) in charge of conducting the spirometries for this clinical trial. Spirometer will measure:

- FVC (maximal volume of air exhaled with maximally forced expiratory effort from a position of maximal inspiration).
- FEV1 (volume of air expressed in litres exhaled during the first second of performance of the FVC).

The ATS and ERS guidelines should be followed to provide accurate and comparable spirometric data. Spirometer will be configured to meet ATS/ERS recommendations for accuracy and precision (Standardisation of Lung Function Testing, Miller et al 2005). The computerised spirometer will generally check the consistency between tests and some of the requirements set out in the ATS/ERS spirometry guidelines, and will automatically alert the technician to the presence of some deviations from some ATS/ERS requirements. However, the technician must ensure that tests are performed with the correct technique, manually deselecting efforts which do not meet minimum standards. **The technician must use their**

judgement to ensure that the optimum spirometry data is gained from the patient at each test session.

The technical details about the system set up are part of the Project Requirement Specifications, including the spirometry's timepoints described in section 4 and the time-windows allowed in this study.

These data will be electronically transmitted by the investigator to ERT at least at the end of each patient protocol visit. Throughout the study, a centralised reading of spirometric values will be performed by an independent spirometric expert at ERT, blinded to patient's IP allocation and patient's identity, in a two-steps quality control:

- "Over-Read" process: The first review of the spirometry data (including review of tests that rejected by the technician) qualifies spirometric curves according to ATS/ERS criteria. No changes are made to the data.
- "Best Test Review" process: During this procedure, the acceptability of tests is assessed first followed by repeatability. If problems are encountered on the spirometric curve identified by the technician as the "best test", ERT will check if there is another curve that is acceptable. If a better "best test", the sites will be queried. If the site accepts the proposed new "best test" (as indicated by the investigator signing a query form), this newly accepted measure will represent the "best test" in all analysis and reporting. No identification of "best test" will be made without the approval of the investigator. All tests will be saved.

Inclusion of patient in the study will be based on the post Best Test Review values.

5.1.1.2 Practical Considerations

Prior to the first spirometry, the trained technician should demonstrate the procedure to the patient by using a detached mouthpiece then, allow some practise attempts. Demonstration should be repeated and the patient should practise the procedure as many times during the trial course as deemed necessary.

Patients who are unable to produce acceptable spirometry tests must not be included in the study. Investigators should pay particular attention to the geometry of a patients flow loop. This should be reasonably constant for a specific patient over time. There is often a learning component to spirometry and the investigator should ensure that the patient technique is stable prior to randomisation.

The activities that should preferably be avoided prior to lung function testing are:

- Smoking within at least 1 h of testing
- Consuming alcohol within 4 h of testing

- Performing vigorous exercise within 30 min of testing
- Wearing clothing that substantially restricts full chest and abdominal expansion
- Eating a large meal within 2 h of testing

Testing may be performed either in the sitting or standing position. Sitting is preferable for safety reasons in order to avoid falling due to syncope. The chair should have arms and be without wheels. If a wheelchair is used, the wheels should be locked. If the standing position is used, a chair can be placed behind the patient/subject, so that they can be quickly and easily moved into a sitting position if they become lightheaded during the manoeuvre.

Each manoeuvre at each timepoint comprises one "set of tests": 3 measurements (curves) technically adequate are needed according to the acceptability and repeatability criteria of the ATS/ERS spirometry guidelines. If both the acceptability and repeatability criteria are met, the manoeuvre session can conclude after 3 measurements. If one or both of these criteria are not met, additional tests should be performed.

In case a patient becomes fatigued during the procedure due to the intensive serial repetitions, patient will rest for approximately 10 minutes and the affected timepoint will be skipped until patient recovers. Salbutamol use will be avoided if at all possible by letting patient rest as needed.

Any bronchoconstriction that appears after consecutive measurements should be recorded on the AE form of the EDC.

The paragraph below describes the process to perform forced manoeuvres to measure FEV_1 and FVC:

- Place the mouthpiece in the mouth and close the lips around the mouthpiece.
- Breathe normally approximately 3 times.
- Inhale completely and rapidly with a pause of <1 second at total lung capacity.
- Exhale maximally during at least 6 seconds taking care that lips are sealed around the mouthpiece and while maintaining an upright posture.
- Breathe in again and relax.

At the time of forced manoeuvre, the technician performing the measurement should prompt the patient to blast, not just blow the air from their lungs, and then continue to actively encourage him/her to fully exhale. Throughout all manoeuvres, the technician should enthusiastically coach the patient by word and body language.

Investigator must print every spirometry test, sign and date them.

5.1.2 COPD Assessment Test (CAT)

The CAT is an 8-item questionnaire designed to assess and quantify the impact of COPD symptoms on health status. The validation studies show that it has properties very similar to much more complex health status questionnaires such as the Saint George Respiratory Questionnaire (SGRQ, Jones et al 2009).

Based on the strong correlation between the CAT and SGRQ, a difference or change of 2 or more units in the CAT score has been suggested as a clinically significant difference or change in health status (Jones et al 2011).

The CAT has a scoring range of 0-40, and it is calculated as the sum of the responses given for each of the 8 items (Scores ranging from 0 to 5, Appendix E), with higher scores indicating a higher impact of COPD symptoms on health status.

A validated electronic version of the questionnaire will be used, in the relevant validated language versions. Data will be recorded by the patient in the e-diary (logpad) provided by ERT. Data will be transferred after each session. During the study CAT data will be accessible to investigators on an online website. The electronic entries on the logpad are considered a source document and will be kept at site in a CD/DVD sent by ERT at the end of the trial.

5.1.3 Evaluation of Dyspnoea through BDI-TDI questionnaire

Evaluation of dyspnoea (both at baseline and during treatment) **MUST be performed by an independent interviewer** experienced in taking history of respiratory disease who must be not aware of other parameters evaluated for this patient in order to avoid any bias. This information includes any data which could reveal patient status (e.g. CAT, SGRQ, spirometric data, AEs, etc).

In addition, the assessment must take place always BEFORE the IP dose.

The objective of the Baseline and Transition Dyspnoea Indexes (BDI/TDI) (Appendix F) is to measure the severity of breathlessness in symptomatic patients. The BDI measures the severity of dyspnoea at the beginning of the trial and the TDI evaluates changes from this baseline (Mahler et al 1984).

Each index (BDI and TDI) contains an arbitrary rating for three categories which are major factors affecting the development of dyspnoea:

- Functional impairment which determines the impact of breathlessness on the ability to carry out activities
- Magnitude of task which determines the type of task that causes breathlessness
- Magnitude of effort which establishes the level of effort needed to evoke breathlessness

To evaluate the status in each domain, the interviewer will ask open-ended questions concerning patient's breathlessness. Based on patient's response, a grade reflecting the degree of impairment related to dyspnoea in each category will be selected in the e-diary (logpad) provided by ERT.

The logpad will be set-up to restrict the access to the BDI/TDI questionnaire only to the independent interviewer.

Baseline Dyspnoea Index (BDI)

The BDI includes three categories, each one with five grades of severity from zero (severe) to four (unimpaired) and the categories are summed to create the focal score (zero to twelve). The lower the focal score (total score), the worse the severity of dyspnoea.

Provision is made for circumstances when dyspnoea cannot be rated: "W" if no information on the severity can be obtained, "X" if there is generally insufficient information, or "Y" if the patient's capacity is compromised by factors other than respiratory.

Transition Dyspnoea Index (TDI)

This index includes three categories, each one with ranges from minus three (major deterioration) to plus three (major improvement) including a zero score to indicate "no change". Also for the TDI the three categories are added to obtain a focal score ranging from minus nine, including zero, to plus nine.

Provision is made for circumstances when dyspnoea cannot be rated: "Z" if reduction of activities, effort or functional impairment is caused by reasons other than respiratory.

A change of 1 unit in TDI has been defined as a minimal meaningful improvement (Witek and Mahler 2003).

Full BDI and TDI is located in Appendix F. The validated version in local language for each participating country will be used. Official instructions for the administration of BDI and TDI will be provided to the investigators in a separate manual.

BDI/TDI grade will be recorded in the logpad provided by ERT to each research site. Data recorded will be transferred to ERT after each session. During the study BDI/TDI data will be accessible to investigators on an online website. The electronic entries on the logpad are considered a source document and will be kept at site in a CD/DVD sent by ERT at the end of the trial.

5.1.4 St. George's Respiratory Questionnaire (SGRQ)

The disease-specific health status will be evaluated by means of a self-administered instrument, the SGRQ (Jones et al 1992). This questionnaire is a standardised self-completed tool for measuring impaired health and perceived well-being ("quality of life") in respiratory diseases (Jones et al 1991).

A validated electronic version of the questionnaire will be used, in the relevant validated language versions. Data will be recorded by the patient in the e-diary (logpad) provided by ERT. Data will be transferred to ERT after each session. During the study SGRQ data will be accessible to investigators on an online website. However, after randomisation, patients will NOT be provided with any information on the data recorded at the previous visits. The electronic patient's entries on the logpad are considered a source document and will be kept at site in a CD/DVD sent by ERT at the end of the trial.

The questionnaire contains 50 items divided into three dimensions:

- Symptoms which contains items concerned with the level of symptomatology, including frequency of cough, sputum production, wheeze, breathlessness, and the duration and frequency of attacks of breathless or wheeze. A typical question in this dimension is "In an average week, how many good days (with little chest trouble) have you had?". There are 5 possible responses to this item (ie, 5-point Likert scale): none; one or two; three or four; nearly every day; and every day.
- Activity which is concerned with physical activities that cause or are limited by breathlessness. A typical item in this dimension is "Because of my breathing, jobs such as house work take a long time or I have to stop for rests?". Responses in this dimension are dichotomous (ie, either true or false).
- Impacts which covers a range of aspects related to social functional and psychological disturbances resulting from the disease, such as employment, being in control of health, panic, stigmatisation, the need for medications and its side effects, expectations for health and disturbances in daily life. An example of these items is "I get afraid or panic when I cannot catch my breath". Responses to items in this dimension are dichotomous (ie, either true or false).

Each of the three dimensions of the questionnaire is scored separately in the range from 0 to 100%, zero score indicating no impairment of life quality. A summary score utilising responses to all items is the total SGRQ score which also ranges from 0 to 100%. The SGRQ scores are calculated using weights attached to each item of the questionnaire which provides an estimate of the distress associated with the symptoms or state described in each item. Higher scores indicate poorer health.

A decrease of 4 units in the SGRQ total score has been established as the criterion for minimal meaningful improvement (Jones 2005). SGRQ responders will be those with a SGRQ total score ≥4 unit decrease.

The SGRQ and further instructions is located in Appendix G. The official manual with instructions for the administration of SGRQ will be provided to the investigators in a separate manual.

5.1.5 Exacerbations of Chronic Pulmonary Disease Tool (EXACT) and EXACT- Respiratory Symptoms (E-RS)

The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) is a single patient-reported outcome (PRO) measure to evaluate the effects of pharmacologic treatment (preventive and curative) on exacerbations of COPD, including chronic bronchitis presence/frequency, severity, duration and resolution (Leidy et al 2010, Leidy et al 2010, Jones et al 2010). It captures the cardinal symptoms of COPD (dyspnoea, cough, sputum production).

The EXACT questionnaire consists of 14 questions that will be recorded by the patient in an electronic Patient Diary (logpad) provided by ERT validated in different languages (see Appendix H) each day in the evening before going to bed, starting at Screening Visit night. The recall period is “today”.

An EXACT Total score is computed for each day of diary collection. The EXACT Total score is computed across the 14 items and has a theoretical range of 0 to 100, with higher values indicating a more severe condition. An EXACT-identified event will be defined as a persistent increase from baseline in total EXACT score of ≥9 points for ≥ 3 days or ≥ 12 points for ≥ 2 days.

The EXACT-Respiratory Symptoms (E-RS) is a reliable, valid and responsive measure of respiratory symptoms of COPD suitable for use in clinical trials (Leidy et al 2014). The E- RS is based on the 11 respiratory symptom items from the 14-item EXACT. The E-RS yields a total score (ranging from 0 to 40), quantifying respiratory symptom severity overall, and 3 subscale scores assessing breathlessness (derived sum of 5 items); cough and sputum (derived sum of 3 items); and chest symptoms (derived sum of 3 items). A change of 2 units in the RS-total score has been proposed as cut off to define responder definition for symptomatic improvement (Leidy et al 2014).

Data recorded will be transferred to ERT after each session. During the study EXACT data will be accessible to investigators on an online website.

The electronic entries on the electronic Patient Diary (logpad) are considered source document and will be kept at site in a CD/DVD sent by ERT at the end of the trial.

5.1.6 COPD Exacerbation

For this study purposes, a COPD exacerbation is defined according to the following severity categories:

Severity	Definition
Mild	Increase of COPD symptoms during at least 2 consecutive days, self-managed by the patient at home by increasing usual COPD medication (short-acting bronchodilator and/or inhaled corticosteroid use)
Moderate	Increase of COPD symptoms during at least 2 consecutive days, which does not lead to hospitalisation but is treated with antibiotics and/or systemic corticosteroids or an increase in dose of systemic corticosteroids.
Severe	Increase in COPD symptoms during at least 2 consecutive days, which leads to hospitalisation (overnight stay at hospital or emergency room) or death

COPD exacerbation according to the health care utilisation definition will be evaluated by the investigator at each visit on the basis of the information registered by the patient (and subsequently checked by the investigator at each visit) into the electronic Patient Diary and paper Patient Diary. COPD exacerbation episodes ***will be recorded in the AE form*** of the EDC.

Information to be recorded in the COPD Exacerbation includes start and stop date, treatment received (antibiotics, systemic corticosteroids, increase in rescue medication), outcome, need of hospitalisation, etc. The onset of an exacerbation will be defined by the onset of symptoms worsening. The end of the exacerbation will be defined by the investigator based on symptoms recovery or stabilization and end of treatment received for the episode.

A new COPD exacerbation episode is defined as the patient being off oral steroids and antibiotics for ≥7 days since prior exacerbation. If the patient is off oral steroids and antibiotics for less than 7 days, then it will be considered as a “relapse” of the previous exacerbation, and it will be treated as the same COPD exacerbation episode within the COPD exacerbation form of the EDC.

In case of a COPD exacerbation after randomisation:

– The next study visit (Va, other than Visit 7) must be postponed until 4 weeks after the resolution of a moderate to severe episode, or 2 weeks after a mild episode. If the re-scheduled visit (Va) date falls within less than 2 weeks from the following per protocol visit (Va+1), then the first (visit Va) will be skipped. Subsequent visits should be

scheduled and performed as indicated in the protocol (ie, with respect to Randomisation Visit day).

- The next study visit is Visit 7 and patient keeps on IP dosing: Visit 7 will never be skipped, since the whole assessments for study completion are due to be performed, nor it will be postponed, since it would extend study treatment exposure. Thus, Visit 7 will be maintained on the scheduled day but only safety assessments will be performed.
- The next study visit is Visit 7 and patient interrupted IP dosing due to exacerbation treatment/interventions: Premature Discontinuation Visit will be performed

COPD exacerbations will be analysed in this study on the basis of EXACT questionnaire (section 5.1.5) as well as on the basis of health care utilisation definition (increase of COPD symptoms during at least 2 consecutive days that require a change in COPD treatment).

5.1.7 Rescue medication

Patients will record once daily in the electronic Patient Diary (logpad) the number of inhalations (puffs) of rescue medication (salbutamol) taken during the last 24h. The question displayed on the device will be: “How many puffs of rescue medication (salbutamol) have you inhaled in the last 24 hours (from yesterday when you went to bed until now)?”

The electronic Patient Diary recording will start at Visit 1 (screening) night and will end the night before Visit 7.

Data recorded will be transferred to ERT on ongoing basis during the study. Data will be accessible to investigators on an online website.

The electronic entries on the electronic Patient Diary (logpad) are considered source document and will be kept at site in a CD/DVD sent by ERT at the end of the trial.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the times indicated in the Study Plan (see Section 4).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry and haematology will be performed by ***the central laboratory*** which will provide the report to sites. A specific manual will be distributed by ***the central laboratory***.

The following laboratory variables will be measured:

- Haematology: Haematocrit, haemoglobin, erythrocytes (red blood cells), leucocytes (white blood cells), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils and basophils), thrombocytes (platelets).
- Biochemistry:
  - Electrolytes: Sodium, potassium, calcium, chloride and inorganic phosphorus.
  - Enzymes: GOT (AST), GPT (ALT), alkaline phosphatase, γ-GT, LDH and creatine kinase and isoenzymes (CK-MM, CK-MB, or CK-BB).
  - Substrates: Glucose, total cholesterol, triglycerides, creatinine, total bilirubin, total protein, albumin, uric acid and BUN.
- Pregnancy: Serum pregnancy test only for women of childbearing potential.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be retained at centre as source data for laboratory variables.

All along the trial, clinically relevant new findings or worsening of a pre-existing finding in the laboratory results must be considered an adverse event and must be recorded on the Adverse Event EDC form. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

In case of technical problems, or if the investigator considers that a result is clinically relevant or doubtful, additional blood samples may be collected within a reasonable time and will be sent to the central laboratory for analysis.

Should pregnancy occur during the participation in the trial, the patient must immediately discontinue from the trial. The pregnancy should be reported as described in section 6.6.

5.2.1.1 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law

5.2.2 Medical History/Physical examination

A medical history of screened patients will be obtained at the Visit 1, recording only the relevant demography and medical data, as required in the Medical History /Physical examination EDC form and excluding the target indication (i.e COPD).

A complete physical examination will be performed at Visit 1 and Visit 7. Only relevant findings, detected at Screening Visit, will be recorded in the Medical History/Physical examination EDC form.

Body weight and height will be measured only at Visit 1 (screening) (allowing calculation of Body Mass Index) and will be recorded on the MasterScope® CT. Patients should be in light indoor clothes without shoes.

5.2.3 ECG

Standard 12-lead ECG evaluations will be recorded after approximately 5 minutes resting in supine position before any blood sampling and spirometry test. 12-lead ECGs will be recorded preferably always by the same technician for each patient.

ERT, as the responsible company for the centralized electrocardiographic assessments, will provide the research sites with the 12-lead ECG equipment and supplies, specific training and written instructions.

Following an acquisition of a quality ECG tracing, the investigator or designee will electronically transfer the data to ERT.

Within 72 hours of reception, a specialized cardiac safety technician and cardiologist at ERT will read and interpret the ECG tracings according to the ERT internal processes ("manual reading") and will make available the ECG report to the research personnel on an online website.

When any 12-lead ECG result exceeds normal ranges alert reports will be immediately sent by ERT by e-mail to the investigator.

The personnel in charge or the reading an interpretation of the ECG tracings at ERT will be blinded to patient's IP allocation and patient's identity.

The investigator will review the "manual reading" reports to assess the clinical relevance of any abnormal findings and/or to decide if the patient is or remains eligible for the study.

However, the responsibility for inclusion or continuation of the subject in the study will lie within the investigator in consultancy with the sponsor.

The 12-lead ECG will be recorded at 25 mm/sec and will consist of a recording of leads I, II, III, aVR, aVL, aVF and V1 to V6 and 10 seconds recording of lead II (rhythm strip). At least 3 complete evaluable complexes per lead will be recorded. The following ECG parameters will be determined: Heart rate, RR interval, PR interval, QRS interval, QT interval, QTc interval, QTcB interval and QTcF interval.

At Visit 1 (screening), the 12-lead ECG should be recorded at a similar time to that to be obtained pre-dose during the course of the trial. Investigators will assess patients' eligibility according to the manual reading report of Visit 1.

Any abnormal finding in the ECG tracing (rhythm, ectopy, conduction, morphology, myocardial infarction, ST segment, T wave and U wave observations) will be evaluated by the investigator and will be specifically documented.

Throughout the trial, clinically relevant new findings or worsening of a pre-existing finding in the ECGs (parameters or abnormal findings in the tracing) must be considered an adverse event and must be recorded on the Adverse Event EDC form.

In case of technical problems, the investigator considers any result is clinically relevant or doubtful, additional 12-lead ECGs may be performed, using the same equipment, within a reasonable time.

5.2.4 Blood pressure

Systolic and diastolic pressure (in mmHg) will be measured after at least 5 minutes resting, and also, before taking any blood sample and conducting any spirometry. Measurements will be carried out with patient in the supine position and preferably always on the same arm. Data will be recorded on the EDC.

If there is any suspicion of unreliable measurement, blood pressure will be measured again. The value obtained on the second measurement will be considered as definitive and will be the one recorded on the EDC.

Throughout the trial, clinically relevant new findings or worsening of a pre-existing finding in the medical history/physical examination/blood pressure must be considered an adverse event and must be recorded on the AE form of the EDC.

5.2.5 Adverse Events

Procedures for recording and assessing adverse events are included in section 6.6.

5.2.5.1 MACE (major adverse cardiac event) adjudication

MACE (major adverse cardiac event) is a composite of the total of cardiovascular (CV) death, non-fatal myocardial infarction and non-fatal stroke.

A Cardiovascular Adjudication Committee (CVAC) will provide independent and objective review and adjudication of MACE and will also adjudicate all deaths. The CVAC chair will also choose additional serious and non-serious adverse events for adjudication.

An external vendor will be used to manage dossier compilation and communication between AstraZeneca and CVAC members.

For the procedures related to the MACE adjudication, please refer to the specific charter.

5.3 Other assessments

5.4 Pharmacokinetics

Pharmacokinetic samples will not be taken during the study

5.5 Pharmacodynamics

Pharmacodynamic samples will not be taken during the study

5.6 Pharmacogenetics

Pharmacogenetic samples will not be taken during the study.

5.6.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed.

5.6.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

5.6.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at participating sites keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca Biobank or Innovation Center of China (ICC) during the entire life cycle.

5.6.4 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an optional part of the study, then the subject may continue in the study.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6 SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The investigator will closely monitor any adverse event and will adopt the necessary clinical measures to ensure the safety of the patient.

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition

can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period (ie 2 weeks after the last IP).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca 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.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped

- Assessment of intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of AE.

6.3.3.1 Assessment of intensity

For grading the intensity of an AE, the following intensity rating scale will be used:

1. Mild - awareness of sign or symptom, but easily tolerated (acceptable)
2. Moderate - discomfort sufficient to cause interference with normal activities (disturbing)
3. Severe - incapacitating, with inability to perform normal activities (unacceptable)

AEs will be collected only once with its maximum intensity.

For grading the intensity of a COPD exacerbation, please refer to section 5.1.6.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures and additional study drug. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: '*Have you had any health problems since the previous visit/you were last asked*?',or revealed by observation will be collected and recorded in the eCRF.

Patients should be instructed to record AEs in the Patient Diary on a daily basis between visits. Any AE recorded on the Patient Diary will be transcribed in standard medical terms as AE on the eCRF AE page by the investigator.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report.

Medical disorders present at the time of signing the informed consent that are part of the patient's medical history will only be considered AEs if they worsen after this time.

Relevant abnormalities detected before IP administration in physical exam, laboratory value/vital sign, ECGs will not be considered AEs **if already known** as part of the medical history or **in relation to prior medical conditions**, and will be recorded on the eCRF Medical History/physical examination form/page. However, abnormalities detected in screening/run-in/baseline tests, thought to be due to a study procedure, will be considered AEs.

During the trial, abnormalities (newly occurring or worsening of previously known abnormalities) detected in laboratory values, vital signs, ECGs and physical examination

which are considered clinically relevant by the investigator or which require an intervention or a diagnosis test, or may result in the IP discontinuation, should be reported as AEs.

In addition, when an AE meets the criteria of seriousness (SAE), it must also be recorded on the SAE form and reported following the defined timelines (section 6.4).

6.3.7 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease.

Any worsening of chronic COPD symptoms which do not meet clinical criteria for a COPD exacerbation as determined by the investigator, should not be recorded as an adverse event unless the study drug was discontinued, the worsening meets the criteria of a Serious Adverse Event, or the patient showed clear deterioration from baseline.

COPD exacerbations that meet the criteria for seriousness will be reported in the SAE form according to procedure detailed in section 6.4 below.

6.4 Reporting of serious adverse events

Serious Adverse Events will be collected from time of signature of informed consent form (ICF) throughout the treatment period and including the follow-up period (ie, 2 weeks after last IP administration). For patients who discontinued the IP, SAEs will be collected during the post-IP discontinuation follow-up period.

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca 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 AstraZeneca representatives of any follow-up information on a previously reported SAE

within one calendar day ie, 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 EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone, fax or email.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The minimum information that has to be included in the initial report is:

- An event meeting the criteria of SAE.
- A qualifiable reporter, defined as an investigator of this trial or his/her delegate.
- A qualified patient defined as a patient who has consented to this trial.
- A suspect medicinal product
- The investigator's causality assessment.

Unless the SAE has been sufficiently documented in the initial report, the investigator will provide all available additional information in follow-up reports by updating the EDC form and adhering to the same time frames as defined for the initial report. This will be continued until the event has been fully documented and reported.

An event reported to the AztraZeneca representative which does not meet the SAE criteria shall be nullified by the investigator by a follow up report.

A regulatory report of the SAE (depending on the local requirements) will be produced by AztraZeneca and submitted to the Regulatory Authorities, Ethics Committee and/or investigators when applicable according to local regulations.

SAEs NOT considered to be reported to the sponsor will be:

- Hospitalisation for a treatment/surgical procedure which was elective or pre-planned for a pre-existing condition that did not worsen during the participation in the trial.
- Hospitalisation or prolongation of an existing hospitalisation for respite care (e.g. patient lives too far from the hospital or has no caregiver at home).

6.5 Overdose

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel should inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study, the investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) 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.

6.6.2 Paternal exposure

Provided that nonclinical data with aclidinium and formoterol fumarate based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential and toxicity to reproduction and development do not reveal special hazard for humans, male participants are not requested to use contraception methods during their participation on the trial.

In case of pregnancy of the subject's partners, the participant will not be necessarily discontinued from the trial but the partner's pregnancy should be reported on the Pregnancy form following the same timeframe and routing as described for any participant's pregnancy. These pregnancies will be also followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be obtained and documented.

6.7 Management of IP related toxicities

There will be no dose reductions in this study.

6.8 Study governance and oversight

Not applicable

7 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

The IP (Aclidinium Bromide 400 µg/Formoterol fumarate 12 µg inhalation powder) consists of a fixed dose combination of long-acting anticholinergic drug, namely aclidinium bromide, combined with the long-acting β_2-agonist formoterol fumarate.

The drug product is an inhalation powder comprising of micronized aclidinium bromide and micronized Formoterol fumarate with α-lactose monohydrate as the carrier.

The Aclidinium bromide/Formoterol fumarate will be compared to the individual components, aclidinium bromide and formoterol fumarate and placebo. Note: The strengths are expressed as metered dose.

Substance and dosage:	Aclidinium bromide/Formoterol fumarate 400/12 µg
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Genuair® Dry Powder Inhaler, DPI)
Manufacturer:	Industrias Farmacéuticas Almirall, S.L. (IFA) Barcelona, Spain

Substance and dosage:	Aclidinium bromide 400 µg
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Genuair® Dry Powder Inhaler, DPI)
Manufacturer:	Industrias Farmacéuticas Almirall, S.L. (IFA) Barcelona, Spain
Substance and dosage:	Formoterol fumarate 12 µg*
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Turbuhaler® Dry Powder Inhaler, DPI)
Manufacturer:	AstraZeneca
Substance and dosage:	Placebo to Aclidinium bromide/Formoterol fumarate 400/12 µg and Aclidinium bromide 400 µg
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Genuair® Dry Powder Inhaler, DPI)
Manufacturer:	Industrias Farmacéuticas Almirall, S.L. Barcelona, Spain
Substance and dosage:	Placebo to formoterol 12 µg
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Turbuhaler® Dry Powder Inhaler, DPI)
Manufacturer:	AstraZeneca

*Placebo to Aclidinium bromide/Formoterol fumarate 400/12 µg and Aclidinium bromide 400 µg
Note: The delivered dose of Formoterol fumarate in the mono-formulation used in the study is 9 µg.

7.2 Additional Drug

Rescue medication Salbutamol pMDI (100 µg/puff) is considered as additional study drug and the accepted standard brand available in the country will be sourced. If required by country regulations or procedures, CRO/AstraZeneca will locally source or provide reimbursement for the cost incurred of this additional study drug

7.3 Dose and treatment regimens

Run-in period

At the moment of the ICF signature or Visit 1 (screening) subjects will receive rescue medication (see Section 7.7) to be administered as needed until Visit 2 (randomisation).

Instructions will be given to the subject on how to use the pMDI inhaler (inhalation technique and priming instructions). In order to inhale properly according to instructions the subject will

practice inhalation technique, as many times as judged necessary by the supervising study personnel. Instructions on how to use the pMDI will be provided to the subjects in local language.

Double-blind treatment period

Before taking the first dose of double-blind medication the subject will be instructed by the study personnel on how to use the Genuair inhaler and Turbuhaler inhaler. Subject will practice inhalation technique with empty training devices provided for this purpose. Instructions on how to use the Genuair and Turbuhaler inhalers will be provided to the subjects in local language.

The Aclidinium bromide/Formoterol fumarate 400/12 µg, the Aclidinium bromide 400 µg and the matching placebo will be administered via Genuair inhaler and the formoterol fumarate12 µg as well as matching placebo will be administered via Turbuhaler. In order to ensure the double blind nature of the trial, patients will have to inhale from both inhalers twice daily following the schema below:

Treatment arm	Morning inhalation (8-10 AM)	Evening inhalation (8-10 PM)
Aclidinium bromide /Formoterol fumarate 400/12 µg	1 puff of Aclidinium bromide/Formoterol fumarate 400/12 µg via Genuair 1 puff of placebo via Turbuhaler	1 puff of Aclidinium bromide/Formoterol fumarate 400/12 µg via Genuair 1 puff of placebo via Turbuhaler
Aclidinium bromide 400 µg	1 puff of Aclidinium bromide 400 µg via Genuair 1 puff of placebo via Turbuhaler	1 puff of Aclidinium bromide 400 µg via Genuair 1 puff of placebo via Turbuhaler
Formoterol fumarate 12 µg	1 puff of placebo via Genuair 1 puff of Formoterol fumarate 12 µg via Turbuhaler	1 puff of placebo via Genuair 1 puff of Formoterol fumarate 12 µg via Turbuhaler
Placebo	1 puff of placebo via Genuair 1 puff of placebo via Turbuhaler	1 puff of placebo via Genuair 1 puff of placebo via Turbuhaler

At all study visits, subjects will receive enough double-blind medication and rescue medication to cover for treatment need until the next study visit.

7.4 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

IP will be supplied in the form of medication kits (medication box). Every medication kit will contain Genuair® inhalers, each inserted in a bag, and Turbuhaler® inhalers.

Every medication kit will be identified with a unique kit number. Each bag, Genuair® and Turbuhaler® included in the kit will show on the label the kit number they belong to.

In order to allow drug reconciliation and dispensation control, research personnel will record the patient number on the labels of every kit dispensed, as well as on the bags label and inhalers labels.

The label will include, but not limited to, the following information:

- Name of sponsor (AstraZeneca)
- Investigational product/study drug dosage form, route of administration, and quantity of dosage units
- Storage conditions
- Study code
- Kit number
- Directions for use
- The name of the Principal Investigator, where applicable (this may be pre- printed or to be added on the label when the investigational product / study drug is dispensed)
- The period of use e.g., expiry date.
- The following standard statements:
- ‘for clinical study use only’
- ‘keep out of reach of children’

7.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the study drug specifies the appropriate storage.

The person responsible for the IP at the drug distribution centre and hospital pharmacy (or any facility at the research site) will inventory and acknowledge receipt of all IP supplies received as well as its dispensation.

7.6 Compliance

Each subject is required to comply with the prescribed treatment regimen throughout the study. Subjects will be instructed on how to use the inhalers correctly. Any subject found to be noncompliant would be counselled on the importance of taking their study medication as prescribed.

In order to ensure correct inhalation technique, training devices will be available at each study site for instructional purposes as well as for subjects to practice the correct inhalation technique. Instruction and practice should occur prior to dispensing study medication. These devices will be used in the clinic only and will not be dispensed to subjects for use at home.

The treatment compliance will be calculated for each device (Genuair and Turbuhaler) by the Statistical programmer of AstraZeneca as number of doses taken respect to the number of doses expected (expressed in percentage). The formula and the cut point will be established in the Statistical Analysis Plan (SAP).

To consider a patient as “treatment compliant”, she/he must be compliant with both inhalers, Genuair and Turbuhaler. Patients non-compliant will be reported as protocol deviations.

7.7 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the subject.

Subjects will be asked to bring all used and unused inhalers to the site at each on-site visit. The Investigator or delegate will review the inhalers and will record if they are used or unused in the Drug Accountability Log.

Any study medication deliberately or accidentally destroyed must be recorded. Any discrepancy between dispensed and returned study medication should be explained.

Study site personnel, if applicable, or the AstraZeneca monitor/representative will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

Study Drug is destroyed once there are satisfactory records of product accountability by the Monitor and the Study Leader has given authorization.

At the end of the trial and after reconciliation all the study medication (IP and rescue medication), both used ad unused, will be destroyed in authorized locations/sites. The destruction will be document appropriately and the certificate of destruction will be filed in the Trial Master File.

7.8 Concomitant and other treatments

7.8.1 Restricted and prohibited concomitant treatment

It is the responsibility of the Investigator to initiate treatment in case of COPD exacerbations and adverse events, as he/she deems appropriate. For safety purposes, the use of prohibited

and restricted medications listed below to treat a COPD exacerbation or an adverse event is allowed during the study.

Unless the use of prohibited or restricted medication meets the criteria outlined in sections 3.9 and 3.10, it will not constitute a reason for discontinuation of IP nor withdrawal from study.

Restricted Medication /Class of drug:	Restrictions	Stabilization period
Inhaled corticosteroids*	• Patients who were following a stable regimen of the combination for at least 4 weeks can be switched to the same inhaled corticosteroid (at the same dose and dose regimen) as monotherapy at least 48 hours before Visit 1 (screening).	No stabilization period is required in this case.
	• If treatment is switched to a different inhaled corticosteroid as monotherapy at an equivalent therapeutic dose to the one used for the fixed inhaled combination, a stabilisation period of at least 14 days or longer, until patient is considered stabilised, should occur before Visit 1 (Screening). The patient will be considered stabilised if, according to the investigator's judgement, during the second week of observation there are no changes in symptoms beyond the day to day variation, or symptoms experienced remain at a similar level of those existing before medication change.	2 weeks
	• If treatment is switched to a different inhaled corticosteroid as monotherapy at different therapeutic dose to the one used for the fixed inhaled combination, a stabilisation period of at least 28 days or longer, until patient is considered stabilised, should occur before Visit 1 (Screening) . The patient will be considered stabilised if, according to the investigator's judgement, during the last week of observation there are no changes in symptoms beyond the day to day variation, or symptoms experienced remain at a similar level of those existing before medication change.	4 weeks
Continuous oral or parenteral corticosteroids*	Dose equivalent of 10 mg of prednisone per day or 20 mg every other day or lower that this.	4 weeks
Selective β-blocking agents (eg. Atenolol, metoprolol, nebivolol)	-	2 weeks
Oxygen therapy*	• < 15 hours a day	4 weeks

Restricted Medication /Class of drug:	Restrictions	Stabilization period
Oral sustained-release theophyllines (less than 400mg/day)*	• Theophylline should be avoided the morning of study visits and begin after visit completion.	4 weeks

*Change in daily dose, dosing schedule, formulation or treatment is unlikely during the course of the trial (the exception being the treatment of a COPD exacerbation).

Prohibited Medication/Class of drug:	Wash-out before V1
Oral, intra-nasal or parenteral anticholinergic agents such as atropine, glycopyrrolate or biperiden	7 days
Long-acting inhaled anticholinergics, LAMAs (e.g. aclidinium bromide, umeclidinium)	72 h
Long-acting inhaled anticholinergics, LAMAs (e.g. tiotropium bromide, glycopyrrolate)a	7 days
Short-acting inhaled anticholinergics, SAMAs (e.g.ipratropium, oxitropium)	12 h
Inhaled and short acting β2-agonists, SABAs (eg, fenoterol or albuterol, except for salbutamol)	6 h
Oral* and twice-daily long acting β2-agonists, LABAs (eg, terbutaline*, formoterol or salmeterol)	48 h
Once daily long-acting β2- agonists (LABAs) (eg, indacaterol, oladaterol)	7 days
Combination of LABAs+ICS (eg Advair, Symbicort, Seretide) *Note: Patients can be switched to the same or a different inhaled corticosteroid as monotherapy (see restricted medication section for stabilization period)*	4 weeks
Once daily combination of LABAs+ICS (eg Breo)	7 days
Combination of SABAs+SAMA (eg Combivent)	12 h
Combination of LABA+LAMA (eg Ultibro, Anoro Ellipta)	7 days
Methyl-xanthines (eg. Theophylline, theobromine tablets)	72 h
Cromolyn sodium, nedocromil	5 days
Leukotriene modifiers (eg montellukast)	48 h
PDE IV inhibitors (eg, roflumilast)	4 weeks
Continuous oral or parenteral corticosteroids used at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day *Note: can be switched to dose equivalent of 10 mg of prednisone per day or 20 mg every other day as long as they are at stable dose for at least 4 weeks prior to V1*	4 weeks
Non-selective β-blocking agents (eg. Carvedilol, alprenolol, nadolol, propranolol, sotalol, timolol) *Note: can be switched to selective β1-blocking agents, as long as they are at stable dose for at least 2 weeks prior to V1*	2 weeks
Herbal or traditional medicine.	2 weeks

7.8.2 Rescue medication

Rescue/Supportive Medication/Class of drug:	Usage:
Salbutamol pMDI (100 µg/puff) *Note: marketed salbutamol available in the participating countries will be supplied in their original box and with its original instructions leaflet (local languages). Where needed according to local regulations, salbutamol boxes will be provided labelled for the purposes of this trial.*	• Administration should be on "as needed" basis, as per the investigator's instructions from the ICF signature until the end of the trial • 6h of wash-out is needed before each study visit

7.8.3 Other concomitant treatment

Medications other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

7.8.4 Vaccination Against COVID-19

The sponsor accepts that vaccination against COVID-19, when and where available, and when patients are eligible according to the applicable guidelines, should be based on the risks and benefits for each individual patient and on what is in the patient's best interest according to the Investigator's clinical judgement. Consequently, vaccination during the study, is in general permitted and any delays in receiving the vaccination due to study participation should be minimised.

To avoid potentially confounding the interpretability of safety data, it is recommended that patients are not randomised for at least 7 days from the receipt of the COVID-19 vaccine (either the first dose or subsequent dose) or as considered appropriate in the clinical judgement of the investigator. Similarly, COVID-19 vaccination should be at least 7 days apart from a study assessment visit.

If and when a patient receives a COVID-19 vaccination, the vaccine information (e.g. vaccine type/brand, route, date of administration) will be recorded in the Case Report Form as a concomitant medication.

Any AEs suspected to be due to the vaccination should be captured as per Section 6.3 of this CSP.

8 STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.

- Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first subject randomised and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

A supplementary statistical analysis plan (SAP) will be produced to specify the analyses required for China subgroup.

8.2 Sample size estimate

Approximately 1515 patients will be screened in this study in order to achieve ***1060*** randomised patients, considering an estimated ineligibility rate of 30% prior to randomisation.

Based on previous data, a sample size of 265 randomised patients per group will provide at least 90% power to detect a statistically significant difference at week 24 of 100 mL between Aclidinium bromide 400 µg/Formoterol fumarate 12 µg and Aclidinium bromide 400 µg in change from baseline at 1-hour morning post-dose FEV_1, 65 mL between Aclidinium bromide 400 µg/Formoterol fumarate 12 µg vs Formoterol fumarate 12 µg in change from baseline morning pre-dose (trough) FEV_1, 100 mL between Aclidinium bromide 400 µg vs placebo in trough FEV_1, and 175 mL between Aclidinium 400 µg vs. placebo in peak FEV_1. Previous studies on the same drug and for the same spirometric endpoints showed a standard deviation of 230 mL.

The sample size is driven by the comparison between Aclidinium bromide/Formoterol fumarate 400/12 µg vs. Formoterol fumarate 12 µg in morning pre-dose FEV_1, and the minimal detectable difference is 39 mL.

The same sample size will provide at least 90% power to detect a statistically significance difference at week 24 of at least 1-unit between Aclidinium bromide 400 µg/Formoterol fumarate 12 µg and Aclidinium bromide 400µg vs placebo in TDI focal score, assuming a SD of 3.5-units, and at least 4-unit difference in change from baseline in SGRQ total score assuming a SD of 13.5-unit for the same treatment comparisons.

All tests will be performed using two-sided tests at 5% significance level.

Nominal powers for primary and secondary efficacy variables are as follow:

	Step	Endpoint	Treatment Comparison	Nominal power (%)
Primary Endpoints	1	1-hour postdose FEV_1	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. Aclidinium bromide 400 µg	99
	2	Morning predose FEV_1	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. Formoterol fumarate 12 µg	90
	3	Morning predose FEV_1	Aclidinium bromide 400 µg vs. placebo	99
Secondary Endpoints	4	Peak FEV_1	Aclidinium bromide 400 µg vs. placebo	99
	5	TDI	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. placebo	90
	6	TDI	Aclidinium bromide 400 µg vs. placebo	90
	7	SGRQ	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. placebo	92
	8	SGRQ	Aclidinium bromide 400 µg vs. placebo	92

The order of the hierarchy of endpoints and treatment comparisons is detailed in section 8.5.

8.3 Definitions of analysis sets

Demographic and other baseline (screening) characteristics will be analysed using the Safety population. The analysis of all efficacy variables will be performed on the ITT population, except for COPD exacerbations, which will be analysed using the Safety Population. In addition, the primary and secondary efficacy variables will be also analysed using the PP Population to assess the robustness of the findings from the ITT Population. All safety outcomes and other variables will be analysed using the Safety population.

For the randomised analysis, ITT and PP analyses sets, subjects will be classified to treatment arms according to their randomised treatment. For the Safety Population, subjects will be classified using the actual treatment they received. Any major deviations from the randomised treatment assignment will be listed and considered when interpreting the safety data.

8.3.1 Screening analysis set

The Screened population is defined as all subjects who attended screening visit and received a subject number.

8.3.2 Randomised analysis set

The randomised population is defined as all subjects in the screened population who were randomised to a treatment group in the study.

8.3.3 Safety analysis set

The safety population is defined as all randomised patients who took at least one dose of IMP.

8.3.4 Patient disposition

Frequency and percentages of patient disposition and reasons for discontinuation of investigational product will be presented. Patients who prematurely discontinue the investigational product will be listed along with the reason for discontinuation.

8.3.5 Efficacy analysis set

The Intention-to-Treat (ITT) population is defined as all randomised patients who take at least one dose of IP and have at least a baseline FEV_1, under the ITT principle and regardless the adherence to the randomised treatment.

The Per-Protocol (PP) population is defined as a subset of the ITT population consisting of patients who:

a. met all inclusion/exclusion criteria liable to affect the efficacy assessment
b. have sufficient treatment compliance
c. did not present serious deviations of the protocol that may affect efficacy. The precise reasons for excluding patients from the study populations will be fully defined and documented in the Blind Data Review Meeting (BDRM).

8.3.6 PK analysis set

Not applicable

8.3.7 PRO analysis set

Not applicable

8.4 Outcome measures for analyses

8.4.1 Primary efficacy variables

The primary efficacy variables are the following:

- Change from baseline in 1-hour morning post-dose dose FEV_1 of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to Aclidinium bromide at Week 24.

- Change from baseline in morning pre-dose (trough) FEV1 of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to Formoterol fumarate at Week 24.
- Change from baseline in trough FEV1 of Aclidinium bromide 400 µg compared to placebo at Week 24.

Morning pre-dose (trough) FEV_1 is defined as the average of the corresponding -30 and 0 minute timepoints values before the morning IP administration at Week 24. If one time-point is missing then the available one will used as morning pre-dose. Baseline for both variables is defined as the average of the two FEV_1 values measured just prior to the administration of the first dose of IP at Visit 2. If one of the two is missing, then the available one will be used as baseline value.

8.4.2 Secondary efficacy variables

- Change from baseline in peak FEV1 of Aclidinium bromide 400 µg compared to placebo at week 24.
- Improvements TDI focal score of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to placebo at week 24.
- Improvements TDI focal score of Aclidinium bromide 400µg compared to placebo at week 24.
- Change from baseline in SGRQ total score of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg compared to placebo at week 24.
- Change from baseline in SGRQ total score of Aclidinium bromide 400µg compared to placebo at week 24.

8.4.3 Additional efficacy variables:

- Pulmonary Function Tests:
  - Change from baseline in morning pre-dose FEV1 and FVC at all visits, except for primary variables at Week 24.
  - Morning pre-dose FEV1 and FVC at all visits.
  - Change from baseline in FEV1 and FVC by time point at all visits, except for the primary variable.
  - FEV1 and FVC by time point at all visits.
  - Change from baseline in normalised area under curve from time 0 to 3 hours (AUC0-3) FEV1 and FVC at Day 1 and at Week 24.
  - Change from baseline in peak FEV1 and FVC at Day 1 and at Week 24.
- Signs and Symptoms and Health-related Quality of Life:
  - Improvements in TDI focal score and three component scores at Weeks 4, 12, and 24 (except for focal score at Week 24).

- Number (%) of patients who achieved a clinically meaningful difference in TDI focal score (improvement of ≥1 unit) at Weeks 4, 12, and 24.
- Change from baseline in SGRQ total score and three dimension scores at Weeks 4, 12, and 24 (except for total score at Week 24).
- Number (%) of patients achieving a clinically meaningful improvement (≥4 units) compared with baseline in SGRQ total score at Weeks 4, 12, and 24.
- Number (%) of patients achieving a clinically meaningful improvement ≥2 units) in CAT total score at Weeks 4, 12 and 24.
- Change from baseline in the CAT score at Weeks 4, 12 and 24.

- COPD Exacerbations
  - Analysed based on Health Resource Utilization definition (worsening of symptoms requiring a change in COPD treatment and/or hospitalization and/or emergency room treatment)
    - Rate of COPD exacerbations per patient/year (any, and moderate or severe).
    - Time (days) to first COPD exacerbation (any, and moderate or severe).
    - Number (%) of patients with at least 1 COPD exacerbation (any, mild, moderate, severe and moderate or severe).
  - Derived from the EXACT questionnaire:
    - Rate of COPD exacerbations per patient/year.
    - Time (days) to first COPD exacerbation.
    - Number (%) of patients with at least 1 COPD exacerbation.
- Daily COPD Symptoms and use of rescue medication:
  - Change from baseline in E-RS total score and breathlessness, cough & sputum and chest domains at all visits and over 24 weeks.
  - Number (%) of patients with a clinically meaningful improvement in E-RS total score, and by domain at all visits (more details in the SAP). Rescue medication:
  - Change from baseline in the use of rescue medication at all visits and over 24 weeks.

8.4.4 Safety outcomes

- Adverse events
- Clinical laboratory test (haematology, biochemistry and pregnancy test)
- Blood pressure
- 12-lead ECG

8.5 Methods for statistical analyses

Statistical analyses of demographic, baseline characteristics, efficacy and safety and tolerability data will be performed by the sponsor. A fully specified Statistical Analysis Plan

(SAP) will be prepared by the statistician before data base lock. The Statistical Analysis System, SAS v. 9. 3 will be the statistical software used to analyse the data sets. Tables, figures and listings will be compiled in the statistical report and appended to the CSR.

For primary and secondary variables, the "estimand" will assume that all patients adhere to treatment, ie. missing data will be modelled based on what it was observed during treatment using direct likelihood approaches. This assumes data is missing-at-random (MAR). Sensitivity analyses will be performed under Missing-Not-At-Random (MNAR) assumptions. Further details will be provided in the SAP.

Estimands for all additional variables will be derived "on-treatment". Missing data will be modelled through direct likelihood approaches.

For all patients exacerbations, SAEs and concomitant medication data up to the final time point will be collected, even if a patient stops treatment early, therefore, a sensitivity "estimand" based on this data will also be derived and analyses will be performed based on this data.

The study population will be described using demographic and baseline characteristics recorded during the run in period. Analyses of demographic and baseline characteristics will be based on the Safety population.

8.5.1 Exposure

Mean exposure to the study medication (in days), and number and percentage of patients exposed during the double-blind study period will be summarised by treatment group. Treatment exposure is defined as the number of days between the date of first dose of the double-blind medication taken and the date last dose taken plus one.

8.5.2 Prior and Concomitant Medication

The prior and concomitant medications, categorized according to the WHO Drug Reference List dictionary which employs the Anatomical Therapeutic Chemical (ATC3 class) classification system, and preferred name, will be summarized by treatment group as frequency and percentage of patients reporting usage. Multiple medication use by a patient will only be counted once. In addition, prior COPD medications will be grouped and tabulated by treatment group, and by therapeutic categories.

8.5.3 Analysis of the primary variable (s)

The analyses of the primary variables will be performed on the Intention-to-Treat (ITT) and Per Protocol (PP) populations while all other analyses will be performed for the ITT

population. Moreover, smoking- status and country will be used as a treatment allocation factor during the randomisation process.

The primary efficacy variables, change from baseline in 1-hour morning post-dose FEV_1 at Week 24 and change from baseline in morning pre-dose (trough) FEV_1, will be analysed by means of mixed model for repeated measures (MMRM), adjusted for pre and post bronchodilator (salbutamol) FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group, country, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors.

8.5.4 Analysis of the secondary variable(s)

Change from baseline in peak FEV_1 at Week 24 will be analysed with the same statistical model than for the primary endpoints.

Improvement in TDI focal score and change from baseline in SGRQ total score at Week 24 will be analysed by means of MMRM, adjusted by the corresponding baseline value (BDI or SGRQ at baseline) and age as covariates, and treatment group, country, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors.

The within-patient correlation will be modelled using the unstructured covariance matrix. The analysis will be performed based on all post baseline measurements using only the observed cases without imputation of missing values. If the model does not converge, then the compound symmetry covariance structure will be used. Restricted maximum likelihood method will be used.

Each treatment effect and treatment comparisons will be estimated by the Least Square means (LSMeans) and their differences in LSMeans on the treatment-by-visit interaction at Week 24, along with their standard errors (SE) and two-sided 95% confidence intervals (CI), and the p-value corresponding to the between-treatment group difference. Statistical comparisons will be two-sided hypothesis tests, and the overall significance level will set at 0.05.

8.5.5 Multiplicity control

Multiplicity adjustment for the control of family-wise type I error will be carried out for primary and secondary endpoints. Each endpoint will be tested hierarchically at the 5% level as long as the previous one is significant at the 5% level.

Pre-specified Sequence of Testing for Multiplicity Adjustment

Testing Order in Hierarchy	**Endpoint (at Week 24)**	**Treatment Comparison**

1	1-hour morning post-dose FEV_1	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. Aclidinium bromide 400 µg
2	Morning pre-dose FEV_1	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. Formoterol fumarate 12 µg
3	Morning pre-dose FEV_1	Aclidinium bromide 400 µg vs. placebo
4	Peak FEV_1	Aclidinium bromide 400 µg vs. placebo
5	TDI	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. placebo
6	TDI	Aclidinium bromide 400 µg vs. placebo
7	SGRQ	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. placebo
8	SGRQ	Aclidinium bromide 400 µg vs. placebo

8.5.6 Subgroup analysis (if applicable)

The efficacy and safety in China subgroup will be analysed to facilitate a benefit-risk assessment for regulatory submission in China.

In addition, to explore the homogeneity of the aclidinium/formoterol treatment over placebo, the following subgroups will be explored (but not limited): country, sex, age group, smoking-status, race, BMI group, COPD severity, bronchodilator reversibility, and inhaled corticosteroid use.

For each subgroup the analysis of the primary and secondary analyses will be carried out.

Details of the Subgroup analysis will be specified in SAP.

8.5.7 Interim analysis

Not applicable

8.5.8 Sensitivity analysis (if applicable)

For most variables, missing data will be dealt with direct likelihood approach. In this case, no imputation is to be performed; the profile of the patient is used instead to adjust the estimates of the parameters when data are not available.

Sensitivity analyses based on imputation using drop out reasons (IUDR) will be explored and added to the SAP if deemed appropriate. To assess the robustness to variations of the missing

data assumptions underlying the primary analysis on the primary efficacy endpoints, sensitivity analyses will be conducted using a copy reference approach.

For COPD exacerbations and concomitant medication, for those patients who prematurely discontinue the IP but have follow-up assessments, data that include events collected during the follow-up period will be analysed.

8.5.9 Analysis of additional efficacy variables

Continuous variables defined as change from baseline or absolute values will be analysed by using the same mixed models as for primary and secondary endpoints. Dichotomous variables will be analysed by means of logistic regression models.

Rate of COPD exacerbations per patient/year will be modelled through negative binomial regression models. Time to first COPD exacerbation will be analysed through Cox regression models. Number of patients with at least 1 COPD exacerbation will be analysed through logistic regression models. The primary analysis described above will be based on the data collected before treatment discontinuation. In addition, for those patients who prematurely discontinue the IP but have follow-up exacerbation assessments, data that include events collected during the follow-up period will be analysed to assess the robustness to variations of the missing data assumptions underlying this primary analysis. In this case, the exposure time will be re-calculated based on the last data collection.

The number and percentage of patients with any prior and concomitant medication will be described by ATC text and preferred name and, where applicable, by treatment group. Concomitant medication will be analysed following the same criteria described in the previous paragraph for COPD exacerbations.

Exposure and compliance to the study medication during the study period will be summarised using descriptive statistics and will be presented by treatment group.

More details on how additional efficacy variables will be analysed will be provided in the SAP.

8.5.10 Analyses of safety and tolerability outcomes

Adverse events will be coded using the MedDRA dictionary. An adverse event will be considered as treatment-emergent (TEAEs) if it started at the time of or after the first IP administration. Adverse events that occurred more than 15-days (2 weeks) after last IP intake will not be considered a TEAE.

A comprehensive summary of AEs will be presented; Summaries of the number and percentage of patients with non-TEAE, Treatment Emergent Adverse Events (TEAE), AE

leading to discontinuation, Serious Adverse Events (SAE), Fatal Adverse Events will be presented by treatment using descriptive statistics. SAE will be also collected post-discontinuation and interpretation in the data provided pre- and post- discontinuation analysed.

Additionally, TEAEs will be tabulated for all treatments by system organ class, preferred term, intensity, causality, seriousness; and outcome and SAEs will be tabulated for all treatments by system organ class, preferred term, intensity and causality.

Laboratory data will be summarized by presenting shift tables using normal ranges (baseline to most extreme post-baseline value) and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges). The incidence of clinically notable lab abnormalities will be summarized.

Blood pressure data will be summarized by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital sign abnormalities will be summarized.

ECG intervals will be summarized by presenting summary statistics of observed and change from baseline values. The (uncorrected) QT interval will be corrected according to the ***Bazett*** and Fridericia's formulas. The incidence of clinically notable ECG abnormalities will be summarized.

8.5.11 Exploratory analysis

Additional efficacy endpoints will be exploratory. In addition, all subgroup analysis specified in the Section 8.5.4. will be also exploratory.

8.5.12 Deviations from the planned analyses

Any additional analyses will be detailed in the SAP that will be included in the Final Clinical Study Report. Any deviation from the planned analyses will be justified and detailed in the Final Clinical Study Report.

9 STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative or delegate will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the EDC/and/or ePROs system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative or delegate will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative or delegate will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca/CRO and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in Q1 2016 and to end by Q3 2017.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with aclidinium bromide or formoterol fumarate.

9.4 Data management

DataManagement (DM) of the study will be performed by Parexel and supervised by DM at AstraZeneca according upon agreed Standard Operating Procedures.

Main DM activities and procedures will be accurately described in the Data Management Plan (DMP), created by Parexel and meeting the sponsor requirements.

An EDC system will be used to collect and manage clinical data in electronic format (eCRF or electronic forms). Parexel will be responsible for EDC and database creation (including all data sources) according to the Sponsor structure specifications, following CDSIC standards.

In addition to the AstraZeneca eCRF data, Parexel DM will receive electronic records for external data processed by external providers (vendors). A reconciliation will be performed by Parexel of the eCRF data and against the rest of data sources to ensure consistency of the common data. Consistency and structural checks to be run in the data and listings for Parexel data cleaning and review will be defined in a Data Validation Plan which will be created by Parexel to meet sponsor requirements and standards.

Interactive checks on the EDC will provide a first level of filters. Checks will run when data has been inserted, informing the research personnel through a flag when data must be verified.

The need of additional queries may also be identified during the study as per the listings review by the Parexel DM staff, data coding, SAEs reconciliation process, etc.

Database, checks, programmes for data visualisation, listings programming (for data review and data visualisation) and any programming implying data conversions will be appropriately validated by Parexel.

Parexel DM will oversee the status of queries performed by the third party providers.

Reconciliation of SAEs between the clinical database and Drug Safety database will be performed by Parexel DM on ongoing basis and before database soft lock. Procedures to follow will be detailed in the DMP.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to WHO Drug Dictionary Enhanced extended with Herbal. All coding will be performed by medical coding team at the CRO. MedDRA and WHO DRUG Enhanced will be used, version number of each dictionary will be documented in the DMP.

Data will be collected during the study execution and transferred to the study data repository at the CRO, where data will be mapped into SDTM datasets on an ongoing basis.

Transfers of SDTM datasets from the study data repository will be periodically received at AstraZeneca during the study and after Database lock. Frequency of these transfers will be agreed between AstraZeneca and the CRO.

All the processes will be carried out according to the specific pre-established processes and timelines documented in the DMP.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, locked and signed, clinical database lock will be declared. Any treatment revealing data (random, PK data, etc) may thereafter be added and after clinical database will has been locked.

An audit trail of all databases will be maintained in order to protect the authenticity and integrity of the clinical data.

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable

regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca/CRO before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca/CRO will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca/CRO will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorised representatives of AstraZeneca/CRO, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good

Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca/CRO immediately if contacted by a regulatory agency about an inspection at the centre.

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Appendix A Signatures

Use e-signature instead of wet ink signature for CSP V3.0 ***and any subsequent versions***.

Appendix B Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix C IATA 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry

1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:
- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

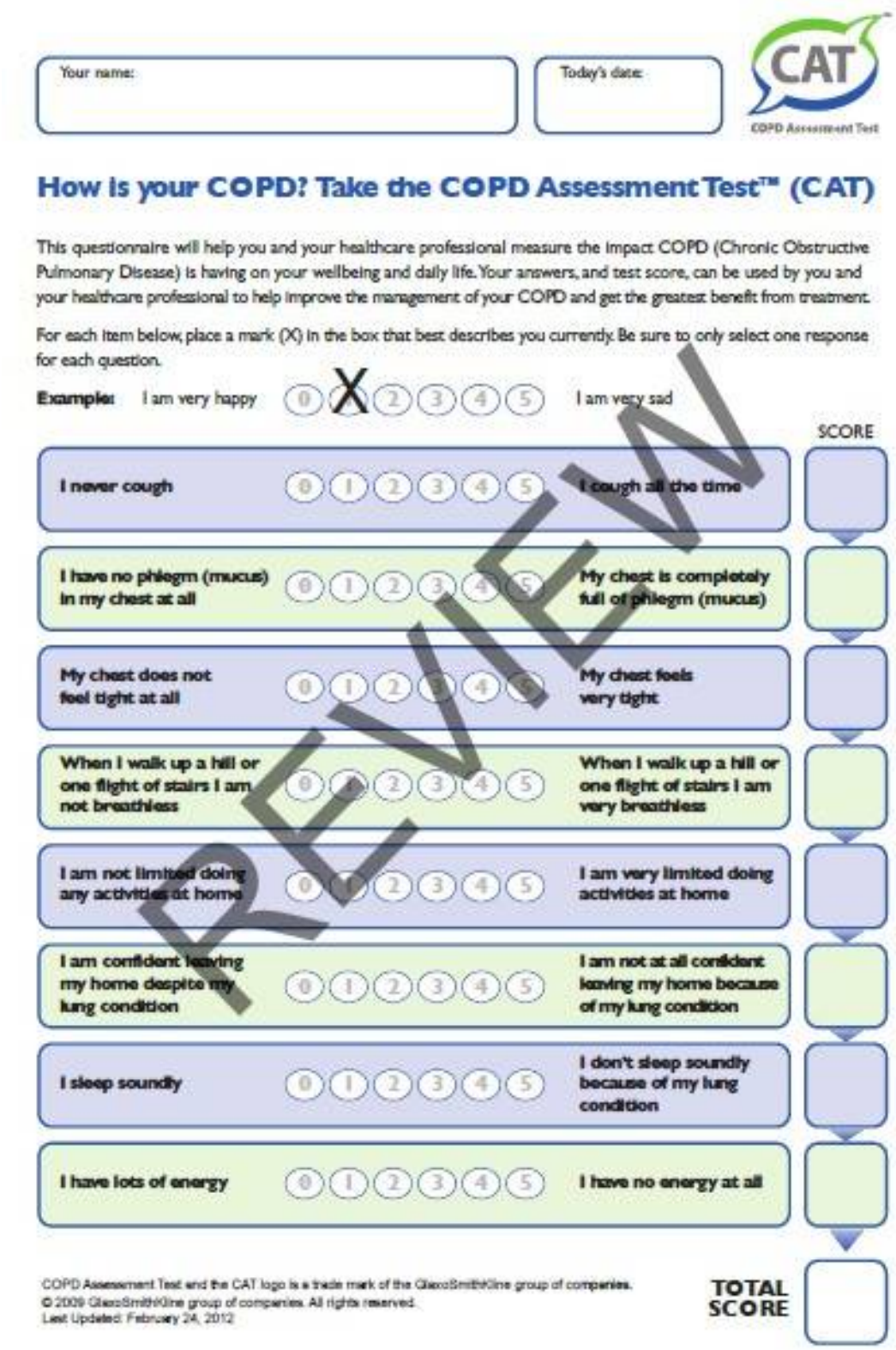
If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix E COPD ASSESSMENT TEST (CAT)



Your name:

Today's date:

CAT
COPD Assessment Test

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 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
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	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
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	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

Last Updated: February 24, 2012

Appendix F BDI-TDI

Baseline/Transition Dyspnea Index (BDI/TDI)

BASELINE DYSPNEA INDEX

Baseline Functional Impairment

_____Grade 4	*No Impairment*	Able to carry out usual activities and occupation without shortness of breath.
_____Grade 3	*Slight Impairment*	Distinct impairment in at least one activity but no activities completely abandoned. Reduction, in activity at work *or* in usual activities, that seems slight or not clearly caused by shortness of breath.
_____Grade 2	*Moderate Impairment*	Subject has changed jobs and/or has abandoned at least one usual activity due to shortness of breath.
_____Grade 1	*Severe Impairment*	Subject unable to work or has given up most or all usual activities due to shortness of breath.
_____Grade 0	*Very Severe Impairment*	Unable to work and has given up most or all usual activities due to shortness of breath.
_____W	*Amount Uncertain*	Subject is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorised.
_____X	*Unknown*	Information unavailable regarding impairment.
_____Y	*Impaired for Reasons Other than Shortness of Breath*	For example, musculoskeletal problem or chest pain.

Usual activities refer to requirements of daily living, maintenance or upkeep of residence, yard work, gardening, shopping, etc.

Baseline Magnitude of Task

_____Grade 4	*Extraordinary*	Becomes short of breath only with extraordinary activity such as carrying very heavy loads on the level, lighter loads uphill, or running. No shortness of breath with ordinary tasks.
_____Grade 3	*Major*	Becomes short of breath only with such major activities as walking up a steep hill, climbing more than three flights of stairs, or carrying a moderate load on the level.
_____Grade 2	*Moderate*	Becomes short of breath with moderate or average tasks such as walking up a gradual hill, climbing fewer than three flights of stairs, or carrying a light load on the level.
_____Grade 1	*Light*	Becomes short of breath with light activities such as walking on the level, washing, or standing.
_____Grade 0	*No Task*	Becomes short of breath at rest, while sitting, or lying down.
_____W	*Amount Uncertain*	Subject's ability to perform tasks is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorised.
_____X	*Unknown*	Information unavailable regarding limitation of magnitude of task.
_____Y	*Impaired for Reasons Other than Shortness of Breath*	For example, musculoskeletal problem or chest pain.

Baseline Magnitude of Effort

_____Grade 4	*Extraordinary*	Becomes short of breath only with the greatest imaginable effort. No shortness of breath with ordinary effort.
_____Grade 3	*Major*	Becomes short of breath with effort distinctly submaximal, but of major proportion. Tasks performed without pause unless the task requires extraordinary effort that may be performed with pauses.
_____Grade 2	*Moderate*	Becomes short of breath with moderate effort. Tasks performed with occasional pauses and requiring longer to complete than the average person.
_____Grade 1	*Light*	Becomes short of breath with little effort. Tasks performed with little effort or more difficult tasks performed with frequent pauses and requiring 50-100% longer to complete than the average person might require.
_____Grade 0	*No Effort*	Becomes short of breath at rest, while sitting, or lying down.
_____W	*Amount Uncertain*	Subject's exertional ability is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorised.
_____X	*Unknown*	Information unavailable regarding limitation of effort.
_____Y	*Impaired for Reasons Other than Shortness of Breath.*	For example, musculoskeletal problems, or chest pain.

TRANSITION DYSPNEA INDEX

Change in Functional Impairment

_____-3	*Major Deterioration*	Formerly working and has had to stop working and has completely abandoned some of usual activities due to shortness of breath.
_____-2	*Moderate Deterioration*	Formerly working and has had to stop working or has completely abandoned some of usual activities due to shortness of breath.
_____-1	*Minor Deterioration*	Has changed to a lighter job and/or has reduced activities in number or duration due to shortness of breath. Any deterioration less than preceding categories.
_____ 0	*No Change*	No change in functional status due to shortness of breath.
_____+1	*Minor Improvement*	Able to return to work at reduced pace or has resumed some customary activities with more vigour than previously due to improvement in shortness of breath.
_____+2	*Moderate Improvement*	Able to return to work at nearly usual pace and/or able to return to most activities with moderate restriction only.
_____+3	*Major Improvement*	Able to return to work at former pace and able to return to full activities with only mild restriction due to improvement of shortness of breath.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has stopped working, reduced work, or has given up or reduced other activities for other reasons. For example, other medical problems, being "laid off" from work, etc.

Change in Magnitude of Task

_____-3	*Major Deterioration*	Has deteriorated two grades or greater from baseline status.
_____-2	*Moderate Deterioration*	Has deteriorated at least one grade but fewer than two grades from baseline status.
_____-1	*Minor Deterioration*	Has deteriorated less than one grade from baseline. Subject with distinct deterioration within grade, but has not changed grades.
_____0	*No Change*	No change from baseline.
_____+1	*Minor Improvement*	Has improved less than one grade from baseline. Subject with distinct improvement within grade, but has not changed grades.
_____+2	*Moderate Improvement*	Has improved at least one grade but fewer than two grades from baseline.
_____+3	*Major Improvement*	Has improved two grades or greater from baseline.
_____Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has reduced exertion capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

Change in Magnitude of Effort

_____-3	*Major Deterioration*	Severe decrease in effort from baseline to avoid shortness of breath. Activities now take 50-100% longer to complete than required at baseline.
_____-2	*Moderate Deterioration*	Some decrease in effort to avoid shortness of breath, although not as great as preceding category. There is greater pausing with some activities.
_____-1	*Minor Deterioration*	Does not require more pauses to avoid shortness of breath, but does things with distinctly less effort than previously to avoid breathlessness.
_____ 0	*No Change*	No change in effort to avoid shortness of breath.
_____+1	*Minor Improvement*	Able to do things with distinctly greater effort without shortness of breath. For example, may be able to carry out tasks somewhat more rapidly than previously.
_____+2	*Moderate Improvement*	Able to do things with fewer pauses and distinctly greater effort without shortness of breath. Improvement is greater than preceding category, but not of major proportion.
_____+3	*Major Improvement*	Able to do things with much greater effort than previously with few, if any, pauses. For example, activities may be performed 50-100% more rapidly than at baseline.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

Appendix G Saint George Respiratory Questionnaire (SGRQ)

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued…

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 4 weeks.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:
- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one*:
- No ☐
- Yes ☐

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✔) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✔) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✔) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

	Please tick (✓) in ***each box*** that applies to you ***because of your breathing***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

	Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***: True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog
Doing things at home or in the garden
Sexual intercourse
Going out to church, pub, club or place of entertainment
Going out in bad weather or into smoky rooms
Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

. . . . . .
. . . . . .
. . . . . .
. . . . . .

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐
It stops me doing one or two things I would like to do ☐
It stops me doing most of the things I would like to do ☐
It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

UK/ English (original) version 6

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Appendix H EXACT-RESPIRATORY SYMPTOMS (E-RS)

Description	Required Text
Title	EXACT Daily Diary
DD	Daily Diary
Q 1 of 14	Question 1 {1} of 14
Instructions	As you answer the following questions, please select the option that best describes your experience.
1	
	Did your chest feel congested today?
	Not at all
	Slightly
	Moderately
	Severely
	Extremely
2	
	How often did you cough today?
	Not at all
	Rarely
	Occasionally
	Frequently
	Almost constantly
3	
	How much mucus (phlegm) did you bring up when coughing today?

Description	Required Text
	None at all
	A little
	Some
	A great deal
	A very great deal
4	
	How difficult was it to bring up mucus (phlegm) today?
	Not at all
	Slightly
	Moderately
	Quite a bit
	Extremely
5	
	Did you have chest discomfort today?
	Not at all
	Slight
	Moderate
	Severe
	Extreme
6	
	Did your chest feel tight today?
	Not at all

Description	Required Text
	Slightly
	Moderately
	Severely
	Extremely
7	
	Were you breathless today?
	Not at all
	Slightly
	Moderately
	Severely
	Extremely
8	
	Describe how breathless you were today:
	Unaware of breathlessness
	Breathless during strenuous activity
	Breathless during light activity
	Breathless when washing or dressing
	Present when resting
9	
	Were you short of breath today when performing your usual personal care activities like washing or dressing?
	Not at all
	Slightly

Description	Required Text
	Moderately
	Severely
	Extremely
	Too breathless to do these
10	
	Were you short of breath today when performing your usual indoor activities like cleaning or household work?
	Not at all
	Slightly
	Moderately
	Severely
	Extremely
	Too breathless to do these
11	
	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?
	Not at all
	Slightly
	Moderately
	Severely
	Extremely
	Too breathless to do these
12	

Description	Required Text
	Were you tired or weak today?
	Not at all
	Slightly
	Moderately
	Severely
	Extremely
13	
	Last night, was your sleep disturbed?
	Not at all
	Slightly
	Moderately
	Severely
	Extremely
14	
	How scared or worried were you about your lung problems today?
	Not at all
	Slightly
	Moderately
	Severely
	Extremely
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Training Material	**Recommended Text**
Standardized instruction given to patients with PDA training and with take-home instruction manual	Please complete your diary every evening, just before you go to bed.

Appendix I CHANGES RELATED TO MITIGATION OF STUDY DISRUPTIONS DUE TO CASES OF CIVIL CRISIS, NATUARAL DISASTER, OR PUBLIC HEALTH CRISIS

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

I 1 Pausing recruitment and screening of new patients

During a civil crisis, natural disaster, or public health crisis, AstraZeneca will approve the continuation of the enrolment and randomization or if those activities will need to be temporarily placed on hold until the disruption stabilizes in the area.

I 2 Re-scheduling of visits

If, for reasons related to a civil crisis, natural disaster, or public health crisis, a patient is not able to attend their scheduled visit within CSP visit window (± 3 days), they can have their visit rescheduled within 14 days of the original scheduled visit; however, visits that cannot be rescheduled within a 14 day window must be skipped and patient should continue at the next scheduled visit. All assessments that cannot be performed should be marked as not done. If a patient is not able to attend their scheduled visit due to reasons related to and is running out of IP, IP maybe delivered to the patient depending on where allowable as described in Section I5.

I 3 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections I 4 to I 5. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

I4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events and concomitant medication to be reported and documented.

1 5 At-home delivery of Investigational Product

If a site visit is not possible, IP maybe delivered to the patients address subject to local laws. The option of home delivery of investigational product ensures patients safety in cases of a pandemic where patients may be at increased risk by traveling to the site/clinic.

SIGNATURE PAGE

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