- **Protocol number:** D6571C00001
- **Document title:** A 24 week treatment, multicenter, randomized, double blinded, double dummy, parallel-group, clinical trial evaluating the efficacy and safety of aclidinium bromide 400 µg/formoterol fumarate 12 µg fixed-dose combination BID compared with each monotherapy (aclidinium bromide 400 µg BID and formoterol fumarate 12 µg BID) and tiotropium 18 µg QD when administered to patients with stable chronic obstructive pulmonary disease
- **Version number:** 3
- **Date of the document:** 21 March 2016
- **NCT number:** NCT02796677

Clinical Study Protocol

Drug Substance	Aclidinium Bromide/ Formoterol Fumarate
Study Code	D6571C00001
Version	3.0
Date	21 March 2016

A 24 week treatment, multicenter, randomized, double blinded, double dummy, parallel-group, clinical trial evaluating the efficacy and safety of aclidinium bromide 400 µg/formoterol fumarate 12 µg fixed-dose combination BID compared with each monotherapy (aclidinium bromide 400 µg BID and formoterol fumarate 12 µg BID) and tiotropium 18 µg QD when administered to patients with stable chronic obstructive pulmonary disease.

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

EudraCT number: 2015-005444-33

VERSION HISTORY

Version 3.0, 21 March 2016 Changes to the protocol are summarised below,
Synopsis (page 8), Section 1.4. Study Design (page 28), Section 4. Study Plan and Timing of Procedures (Table 2, page 45), Section 7.6. Compliance (page 84): The collection of IP intake has been included in the e-diary. Appendix C (page 111), 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 2.0, 01 March 2016 Changes to the protocol are summarised below,
Version History section included into this new version. Synopsis: International Co-ordinating Investigator (page 4): Name corrected. Defined primary objective for Market Access (page 5 and 12). Atrovent (page 7): specified brand name for US and rest of the word countries and dose corrected. Target population (page 10): "stable" has been added in the definition of COPD. List of abbreviations (page 22): Added abbreviation for MCV (Mean Corpuscular Volume). Section 1.1. Background and rationale for conducting this study (page 25): Included reference for Bretaris® Genuair® and Bretaris® Genuair® SmPC. Section 1.2. Rationale for study design, doses and control groups (page 25): Defined primary objective for Market Access. Section 1.3. Benefit/Risk and ethical assessment (page 27): Included reference for Bretaris® Genuair® and Bretaris® Genuair® SmPC. Section 1.4. Study Design (page 28): Corrected dose for Atrovent®. Section 2. Study Objectives (page 29 and page 30): Defined primary objective for Market Access.

Section 4. Study Plan and timing of procedures (pages 43 to 45): Replaced "Visit 8" from Table 2 by "follow-up call". Added clarifications on footnotes 1, 7 and 12 for EOT and EOS procedures.

Section 4.1.1. Visit 1 (Screening) (page 47): Corrected dose for Atrovent®.

Section 4.2.7. End of Treatment (EOT) (page 59) Section 4.2.9. End of Study (EOS) (page 62): Added 1h post-dose pulmonary function test after COPD prescribed treatment. Clarification on procedures.

Section 5.2.1. Laboratory Safety Assessments (page 71): Added red blood cells morphology, white blood cells differential and MCV in the laboratory assessments.

Section 7.2 Additional Drug (page 82) and 7.8. Concomitant and other treatments (page 87): Corrected dose for Atrovent®.

Section 8. Statistical Analyses by AstraZeneca (pages 88, 89, 93, 94 and 95): Defined Market Access analyses.

List of references (page 103): Added reference for Bretaris® Genuair® and Bretaris® Genuair® SmPC.

Version 1.0, 15 February 2016
Initial creation

PROTOCOL SYNOPSIS

A 24 week treatment, multicenter, randomized, double blinded, double dummy, parallel-group, clinical trial evaluating the efficacy and safety of aclidinium bromide 400 µg/formoterol fumarate 12 µg fixed-dose combination BID compared with each monotherapy (aclidinium bromide 400 µg BID and formoterol fumarate 12 µg BID) and tiotropium 18 µg QD when administered to patients with stable chronic obstructive pulmonary disease.

International Co-ordinating Investigator:

PPD ,
PPD
Tel: PPD
Fax: PPD

Study site(s) and number of subjects planned

Approximately 1500 patients: 300 patients for aclidinium bromide (AB) 400 µg/formoterol fumarate (FF) 12 µg fixed-dose combination and 300 patients for FF 12 µg arms; 450 patients for AB 400 µg and 400 patients for tiotropium (TIO) 18 µg arms will be randomized. Approximately 2200 patients will have to be screened in this study considering an estimated ineligibility rate of 30% prior to randomization

Approximately 200 sites will participate from US, Europe and rest of the world countries.

Study period		Phase of development
Estimated date of first subject enrolled	Q2 2016	III
Estimated date of last subject completed	Q1 2018	

Objectives and outcome variables

Primary Objectives for US	Outcome measure and comparison
To assess the bronchodilatory effect of AB/FF 400/12 µg compared to each individual component when administered twice daily via inhalation to COPD patients.	Co Primary endpoint and comparison: • Change from baseline in 1-hour morning post-dose dose FEV_1 of AB/FF 400/12 µg compared to AB 400 µg at week 24. • Change from baseline in morning pre-dose (trough) FEV_1 of AB/FF 400/12 µg compared to FF 12 µg at week 24.

Primary Objective for Market Access	Outcome measure and primary comparison
To assess the non-inferior bronchodilation of AB 400 µg BID as compared to TIO 18 µg QD in COPD patients.	• Change from baseline in morning pre-dose (trough) FEV_1 at week 24 comparing AB 400 µg versus TIO 18 µg.

Secondary Objectives	Outcome measure and primary comparison
To further characterize the effect of AB/FF 400/12 µg on bronchodilation and health related quality of life compared to individual components when administered twice daily via inhalation to COPD patients.	• Change from baseline in normalized $AUC_{0\text{-}3/3h}$ FEV_1 of AB/FF 400/12 µg at week 24 compared to AB 400 µg and FF 12 µg. • Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4 units from baseline) with AB/FF 400/12 µg in SGRQ total score at week 24 compared to AB 400 µg and FF 12 µg.

Safety objectives	Endpoints

To evaluate the safety and tolerability of AB/FF 400/12 µg as compared to individual components in COPD patients	• Adverse Events (AEs)/Serious Adverse Events (SAEs) • Clinical laboratory test (hematology and biochemistry) • Blood pressure • 12-lead ECG • Major Adverse Cardiac Events (MACE)

Additional efficacy variables to support the primary and secondary objectives including the following assessments:

- Pulmonary function variables (FEV_1, FVC) at each different time points, onset of action, peak and trough FEV_1 at each visit. Moreover, in the sub-set of patients with 24h serial pulmonary function tests the following variables will be assessed: FEV_1 and FVC at each time point and $AUC_{0\text{-}12h}$; $AUC_{12\text{-}24h}$, $AUC_{0\text{-}24h}$).

- Health related quality of life outcomes, St George Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT): change from baseline and responder analysis (percentage of patients reaching the minimally clinical important difference [MCID]) at each visit.

- Symptomatic outcomes, Evaluating Respiratory Symptoms in COPD (E-RS^{TM}: COPD), Night-time and Early morning symptoms of COPD (NiSCI & EMSCI): change from baseline and responder analysis (only E-RS) at each visit and over the treatment period

- COPD exacerbations, as defined by Health Care Research Utilization (HCRU) and Exacerbations of Chronic Pulmonary Disease Tool (EXACT): percentage of patients with at least one exacerbation, rate of exacerbations and time to first exacerbation.

- Use of relief medication: change from baseline at each visit and over the treatment period.

- Device preference.

Exploratory objectives

Treatment effects and comparisons in primary and secondary endpoints will be evaluated for the subgroup of patients which are more symptomatic at study entry based on different definitions.

Study design

This is a multiple dose, randomized, parallel, double blind, double dummy, active controlled, multicentre and multinational phase III study to determine the efficacy and safety of AB/FF

400/12 µg compared with its individual components 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.

After signature of the ICF, patients who require wash-out of prohibited medication will be provided Atrovent® (Atrovent® HFA inhalation aerosol 17 µg for US patients/Atrovent® Inhaler CFC-Free pressurised inhalation solution 20 µg for non-US patients) to be taken during the wash-out and run-in period (2 puffs four times per day). Atrovent® will be interrupted 6 hours before Visit 2 (randomization visit).

All patients will be provided with relief medication (albuterol/salbutamol) to be taken in case of need, since signature of the ICF through the study. 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 theophyllines) are permitted if the dose is stable for at least 4 weeks prior to entering the study (Visit 1).

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 guidelines 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.

Patients who meet entry criteria at Randomization Visit (Visit 2) will be randomized in a ratio 2:3:2:3 to one of the 4 treatment arms:

- AB/FF 400/12 µg BID
- AB 400 µg BID
- FF 12 µg BID
- TIO 18 µg QD

Smoking status (current smokers vs former smokers) and country will be the treatment allocation factors.

At Visit 2, after randomization, patient will receive investigational product (IP) 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. After treatment completion a follow-up contact will be performed approximately 2 weeks later.

From Screening Visit (Visit 1) to the end of the study, patients will use an electronic Patient Diary to capture their COPD symptoms, IP intake and the use of rescue medication, as well as 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.

Efficacy of treatments will be assessed by means of the following tests:

1. Bronchodilation:

- Morning pre-dose FEV_1, FVC: patients will perform two morning pre-dose spirometry separated by 15 to 30 min at all visits.
- Post-dose spirometry (FEV_1 and FVC) at 30 min, 1 hour, 2 hours, and 3 hours at Visits 2, 5 and 7. Additionally on Day 1 (Visit 2), post-dose spirometry will be assessed at 5 minutes (min) and 15 min to assess the onset of action. At Visits 4 and 6 post-dose spirometries will be performed at 1 hour.
- In a subset of patients (35%), post-dose spirometry (FEV_1 and FVC) will be additionally performed at +4h, +6h, +9h, +12h (pre-evening dose), +12.5h, +13h, +14h, (to characterize the evening peak effect) and +22h, +23.5h and +24h after the morning dose, at Visits 2 and 7.

2. Health related Quality of Life:

- SGRQ will be completed at visits: Visit 2 (baseline), 4, 5, 6 and 7.
- CAT questionnaire will be completed at visits: Visit 1 (Screening), Visit 2 (baseline), 4, 5, 6 and 7.

3. Exacerbations:

- Based on HCRU definition: At each visit the investigator will assess the occurrence of any COPD exacerbation defined as a worsening of symptoms for at least 2 consecutive days that requires a change in COPD treatment.
- Based on EXACT questionnaire: Patients will record electronically the 14-items of the EXACT questionnaire every evening, just before bed. Retrospectively, the sponsor will estimate the EXACT events based on a pre-defined algorithm.

4. COPD symptoms:

- Daily symptoms will be assessed from a subset of 11 out of the 14-items of the EXACT that conforms the E-RS^{TM};COPD, which captures the cardinal symptoms of COPD (dyspnea, cough and sputum production, chest symptoms).
- Patients will also complete the e-diary every morning to record NiSCI and EMSCI from Screening Visit (Visit 1) to the end of the study.

5. Others:

- Relief medication: the sponsor will provide the relief medication (albuterol/salbutamol) to be taken by the patients during the study. Patients will be requested to record the number of puffs of albuterol/salbutamol taken daily into the patient's electronic diary.
- Device preference: at the end of the treatment period (or upon early discontinuation) patients will be requested to assess their impression of the ease of use of the Pressair®/Genuair® and HandiHaler® inhalers (Device preference and willingness to continue questionnaire).

6. Safety and tolerability will be assessed by means of the following tests:

- Adverse events: patients will be instructed to record any untoward medical occurrence during the clinical trial after signing the ICF until the end of the trial (2 weeks after last study drug administration) into a paper diary.
- Clinical laboratory test (hematology, biochemistry and pregnancy test) at Screening Visit (Visit 1) and final visit (Visit 7).
- Blood pressure: to be measured at Screening Visit (Visit 1), pre-dose at all other visits, and 2h post-morning dose at Visits 2, 5 and 7.
- 12-lead ECG: to be taken at Screening Visit (Visit 1), pre-dose at all other visits, and 2h post-morning dose at Visits 2, 5 and 7.
- Major Adverse Cardiac Events (MACE): using an adjudication committee

Subjects who discontinue study treatment prior to week 24 (Visit 7) will be encouraged to remain in the study to complete all remaining study visits during the 24 week treatment period. Subjects who agree to continue to be followed post IP discontinuation will sign an ICF addendum. All subjects who agree to continue study participation beyond treatment discontinuation will complete an End of Treatment Visit (EOT) prior to transitioning back to regularly scheduled study visits which will include efficacy and safety assessments.

The IP and relief medication will be returned at the EOT visit but the paper diary and electronic diary will be re-dispensed to be used during the post-treatment follow-up. 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.

Subjects participating in the sub-study who choose to discontinue from treatment will only complete regular scheduled visits and not complete any remaining sub-study assessments.

Patients who prematurely discontinue from the study (withdrawal) will participate in an End of Study (EOS) Visit. The IP, paper diary and electronic diary will be returned at the EOS visit.

Treatment discontinuation subjects will return to appropriate maintenance COPD medications, per the investigators discretion.

All patients will perform a follow-up contact 14 days after last IP intake to assess new or ongoing adverse event (AE), COPD exacerbations, as well as any concomitant medication administered to treat the mentioned AE.

Target subject population

Current or former smokers, aged ≥ 40, symptomatic COPD patients (CAT score ≥10 at both, screening and randomization visit) with stable moderate to very severe airflow obstruction (post-bronchodilator test $FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ of the predicted normal value at Screening Visit).

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. AB/FF 400 µg/12µg, AB 400 µg, FF 12 µg and placebo to AB/FF will be administered via the Pressair®/Genuair®. Tiotropium 18 µg (TIO) and placebo to TIO will be administered via the Handihaler® device. Blinding will be ensured instructing the site staff that a third party administrator (not involved in other aspects of the study) will administer the IP at site. Patients will be instructed to take 1 dose of study drug from the Pressair®/Genuair® and 1 dose of study drug from the Handihaler® in the morning (09:00 ± 1 h) and one dose from the Pressair®/Genuair®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.

Note: The strengths are expressed as metered dose.

Substance and strength:	Aclidinium bromide 400 µg/Formoterol Fumarate 12 µg (AB/FF 400/12 µg)
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Pressair®/Genuair® Dry Powder Inhaler, DPI)
Substance and strength:	Aclidinium bromide 400 µg (AB 400 µg)
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Pressair®/Genuair® Dry Powder Inhaler, DPI)

Substance and strength:	Formoterol fumarate 12 µg (FF 12 µg)
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Pressair®/Genuair® ® Dry Powder Inhaler, DPI)
Substance and strength:	Placebo to AB/FF 400/12 µg, AB 400 µg and FF 12 µg
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Pressair®/Genuair® Dry Powder Inhaler, DPI)
Substance and strength:	Tiotropium 18 µg (TIO 18 µg)
Dosage form:	Powder in capsules for oral inhalation.
Administration route:	Oral Inhalation (by Handihaler® Dry Powder Inhaler, DPI)
Substance and strength:	Placebo to TIO 18 µg
Dosage form:	Powder in capsules for oral inhalation
Administration route:	Oral Inhalation (by Handihaler® Dry Powder Inhaler, DPI)

Statistical methods

Assumptions for the sample size:

Approximately, 2,200 patients will be screened in this trial (considering an estimated ineligibility rate of 30%) to have an overall sample size of 1,500 randomized patients to AB/FF 400/12 µg, AB 400 µg, FF 12 µg, and TIO 18 µg, based on a randomization ratio of 2:3:2:3, which corresponds to 300, 450, 300, and 450 patients per treatment arm, respectively.

Based on hypotheses derived from the evidence shown in our own previous clinical trials, this sample size will provide at least 90% power to detect a statistically significant treatment difference of 100 mL between AB/FF 400/12 µg and AB 400 µg in change from baseline in 1-hour morning post-dose FEV_1 at Week 24, and 65 mL between AB/FF 400/12 µg and FF 12 µg in change from baseline in morning pre-dose (trough) FEV_1 at Week 24, assuming a standard deviation (SD) of 230 mL, using two-sided tests, and adjusting for multiple tests at 5% overall significance level. The expected minimum statistically significant effect is 37 mL in trough FEV_1. The same sample size will have enough power to detect a statistically significant treatment difference between AB/FF 400/12 µg and both individual components in the change from baseline in normalized AUC_{0-3} FEV_1 at week 24.

The responder analysis of the SGRQ total score based on a decrease of at least 4-units from baseline will be tested, comparing AB/FF 400/12 µg versus both individual components.

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

This sample size will have 90% power to show that the lower bound of the two-sided 95% confidence interval for the difference between AB 400 µg and TIO 18 µg in change from

baseline in morning pre-dose (trough) FEV_1 at Week 24 is above -50 mL (non-inferiority limit), assuming that the expected difference is 0 mL, and a SD of 230 mL.

Multiplicity:

Separate multiplicity approaches will be considered for each region (US and Market Access). For US, sequential step-down closed testing procedure will be applied to control the overall type I error rate across the multiple comparisons of primary and secondary endpoints.

Statistical analyses:

All efficacy and analysis outcomes will be performed in the ITT population, except for the COPD exacerbations that will be analyzed under the safety population. The safety population is defined as all randomized patients who took at least one dose of IMP. The ITT population is defined as all randomized 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 randomized treatment.

For the non-inferiority objective the Per-Protocol (PP) population will be used. It is defined as a subset of the ITT population consisting of patients who met all inclusion/exclusion criteria liable to affect the efficacy assessment, have sufficient treatment compliance, and did not present serious deviations of the protocol that may affect efficacy.

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 including all data captured during the 24-week double-blind treatment period, and also under Missing-Not-At-Random (MNAR) assumptions.

The co-primary efficacy variables change from baseline in morning pre-dose (trough) FEV_1 and change from baseline in 1-hour morning post-dose FEV_1 at week 24 will be analyzed by means of mixed model for repeated measures (MMRM), adjusted for pre and post bronchodilator (albuterol/salbutamol) FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group, sex, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors, and country as random effect. The change from baseline in normalized AUC_{0-3} FEV_1 at week 24 will be analyzed based on the same MMRM model.

The number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4 units from baseline) compared to individual components in the SGRQ total score will be analyzed based on a logistic random-effect model using GLIMMIX that includes a random intercept to account the variability between subjects, and treatment, sex, smoking-status, country, visit, and treatment group-by-visit interaction as fixed factors, and with age and the corresponding baseline as covariates.

The objective of demonstrating non-inferiority between AB 400 µg and TIO 18 µg in change from baseline in morning pre-dose (trough) FEV_1 at week 24 will be analyzed by means of mixed model for repeated measures (MMRM). The model will adjust for pre and post

bronchodilator (albuterol/salbutamol) FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group, sex, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors, and country as random effect.

Each treatment effect and treatment differences between all treatments will be estimated by the Least Square means (LS Means) on the correspondent treatment-by-visit interaction, along with their standard errors (SE) and 95% confidence intervals (CI), and the p-value corresponding to the between-treatment group difference.

Health care questionnaires like SGRQ, CAT, COPD symptoms, and relief medication will be analysed by means of MMRM, adjusted by the corresponding baseline values and age as covariates, and treatment group, sex, smoking-status, country, visit, and treatment group-by-visit interaction as fixed effect factors.

In general, continuous variables defined as change from baseline or absolute values will be analysed by using MMRM models. Dichotomous variables will be analysed by means of Logistic Regression models (and taking into account the longitudinal nature of the data).

Rate of COPD exacerbations per patient/year will be modeled through negative binomial regression models. Time to first COPD exacerbation will be analyzed through Cox regression models. Number of patients with at least 1 COPD exacerbation will be analyzed through logistic regression models.

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

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Protocol Signatures

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
AB	Aclidinium bromide
AE	Adverse event
ALT	Alanine aminotransferase, also named GPT
AST	Aspartate aminotransferase, also named GOT
ATS	American Thoracic Society
AUC	Area under the curve
AUC_{0-3}	Area under curve from time 0 to 3 hours
AUC_{0-12}	Area under curve from time 0 to 12 hours
AUC_{12-24}	Area under curve from time 12 to 24 hours
AUC_{0-24}	Area under curve from time 0 to 24 hours
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
BDRM	Blind Data Review Meeting
BUN	Blood urea nitrogen
CAT	COPD assessment test
CDSIC	Clinical Data Interchange Standards Consortium
CI	Confidence intervals
COPD	Chronic obstructive pulmonary disease
CMA	Clinical Monitoring Associate
CRA	Clinical Research Associate
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CV	Cardiovascular
CVAC	Cardiovascular Adjudication Committee
DM	Data Management
DMP	Data Management Plan

Abbreviation or special term	Explanation
DPI	Dry Powder Inhaler
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMSCI	Early Morning Symptoms of COPD Instrument
EOS	End of Study
EOT	End of treatment
ePRO	Electronic Patient Reported Outcomes
ERS	European Respiratory Society
E-RS^{TM}: COPD	Evaluating Respiratory Symptoms in COPD
EU	European Union
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FAS	Full analysis set population
FEV_1	Forced expiratory volume in 1 second
FDA	U.S. Food and Drug Administration
FDC	Fixed-dose Combination
FF	Formoterol Fumarate
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
HBcAg	Hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HCRU	Healthcare resource utilization
HCV	Hepatitis C virus
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

Abbreviation or special term	Explanation
ICS	Inhaled corticosteroids
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
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting beta$_2$-adrenergic agonist
LAMA	Long-acting muscarinic antagonist/inhaled anticholinergic
LDH	Lactate dehydrogenase
LSMeans	Least Square means
MACE	Major Adverse Cardiac Events
MAR	Missing-at-random
MCV	Mean Corpuscular Volume
MNAR	Missing-Not-At-Random
MCID	Minimally clinical important difference
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
NiSCI	Nighttime Symptoms of COPD Instrument
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
PK	Pharmacokinetics
QD	Once daily

Abbreviation or special term	Explanation
QID	Four times a day
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
QTc	QT corrected
QTcB interval	QT interval corrected, Bazett formulae
QTcF interval	QT interval corrected, Fridericia formulae
QTc interval	QT interval corrected by heart rate
QTcF	QT corrected, Fridericia formulae
QT interval	Duration in milliseconds from the beginning of Q wave to the end of the T wave
RR interval	Duration in milliseconds between two R peaks of two consecutive QRS complexes
SMQ	Standard MedDRA Query
SmPC	Summary of Product Characteristics
SABA	Short-acting beta$_2$-adrenergic agonists
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonist/ inhaled anticholinergics
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard errors
SGRQ	St Georges Respiratory Questionnaire
ST segment	Part of an electrocardiogram between the QRS complex and the T wave
TEAE	Treatment-emergent adverse event
TIO	Tiotropium
US	United States
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. Dyspnoea, chronic cough and sputum production are the most common clinical symptoms. 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 (Buist et al, 2007, Buist et al, 2008).

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). Adrenergic and cholinergic pathways mediate bronchoconstriction in COPD.

Anticholinergic compounds such as ipratropium, 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 salbutamol/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 combined within the same inhalation device for the treatment of COPD. Administration of an inhaled fixed-dose combination of ipratropium (muscarinic antagonist) and salbutamol/albuterol (β_2-agonist) has been shown to produce a significantly greater improvement in pulmonary function than either ipratropium or salbutamol/albuterol monotherapies [Combivent® UDVs® United Kingdom (UK) Summary of Product Characteristics (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 long-acting β_2-adrenergic agonists (LABA) and long-acting muscarinic antagonists (LAMA) have been recently approved or the treatment of COPD, i.e. Ultibro®/Utibron® (indacaterol/glycopyrronium), Anoro® (vilanterol/umeclidinium) and Stiolto® (oladaterol/tiotropium). The clinical studies have shown that the combined use of a LABA and a LAMA provides greater bronchodilation and better symptoms control compared with the corresponding monotherapies (Pelaia et al 2014, Maltais et al 2014, Maleki-Yazdi et al 2014).

Duaklir® Genuair® is a fixed dose combination of AB 400 µg and FF 12 µg approved in Europe in November 2014 as a maintenance bronchodilator treatment to relieve symptoms in adult

patients with COPD. The approved posology is one inhalation twice daily (Duaklir® Genuair® SmPC 2015).

Eklira® Genuair®/Bretaris® Genuair®/Tudorza® Pressair® is a novel LAMA (AB 400 µg) approved in Europe and in the US in July 2012 as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The approved posology is one inhalation twice daily (Eklira® Genuair® SmPC Sep 2015; Bretaris® Genuair® SmPC 2015; Tudorza® Pressair® US Prescribing Information Apr 2015).

The current Phase III study is designed to investigate the long term bronchodilator efficacy of AB/FF 400/12 µg delivered by inhalation BID to support registration of the combination in US. The study will also assess the potential benefits of the Investigational Product (IP) on disease-related health status, COPD symptoms and other outcomes in patients with moderate to very severe COPD. In addition, the study will assess the non-inferior bronchodilation of AB 400 µg BID compared to TIO 18 µg QD, and evaluate the safety and tolerability of the 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 as well as the effect on health related quality of life of AB/FF 400/12 µg compared to the individual components (AB 400 µg and FF 12 µg). As a primary objective for Market Access, the study will assess the non-inferior bronchodilation of AB 400 µg BID as compared to TIO 18 µg QD in COPD patients.

FDA Code of Federal Regulations, Title 21, Section 300-50 and the Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 2009) 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 and benefits on health related quality of life of AB/FF 400/12 µg compared with AB 400 µg and FF 12 µg and an acceptable safety profile of the combination compared to the individual components.

An additional objective of the present study is to assess the non-inferior bronchodilation of inhaled AB 400 µg versus TIO 18 µg, at week 24. A previous phase IIIb trial of 6 weeks duration in moderate to severe COPD patients compared AB 400 µg to TIO 18 µg QD. The results of this study showed that at day 1 and after 6 weeks of treatment, AB 400 µg provided comparable results in bronchodilation over TIO 18 µg QD, with improvements being statistically superior favouring AB 400 µg on Day 1 for most of the spirometric variables, mainly due to differences during the night-time period (Beier et al, 2013).

The target study population of this study, symptomatic (CAT≥10) COPD patients with moderate to very severe airflow obstruction (Stage II to IV) according to the GOLD Guidelines classification, 2015: post-bronchodilator FEV_1 < 80% of the predicted normal and FEV_1/FVC < 70% has been commonly investigated in similar trials (Donohue JF et al, 2013; Bateman ED et al, 2013; Mahler DA et al, 2015).

The proposed trial duration of 24 weeks has been chosen as it will allow the assessment of the effect on symptoms improvement of the combined treatments versus individual components as well as the long term bronchodilation comparison between AB 400 µg and TIO 18 µg.

During the wash-out and run-in period, sponsor-provided ipratropium bromide (Atrovent® HFA inhalation aerosol for US patients/Atrovent® Inhaler CFC-Free pressurised inhalation solution for non-US patients) will be administered QID to the patients that require a wash-out of any prohibited medication.

In addition to the four active treatments in this study (AB/FF 400/12 µg, AB 400 µg, FF 12 µg and TIO 18 µg), relief medication (albuterol sulphate 108 µg/puff or salbutamol pMDI 100 µg/puff) as well as several background medications for the treatment of COPD (inhaled corticosteroids, oral or parenteral corticosteroids up to a maximum dose of 10 mg of prednisone per day or 20 mg every other day or lower doses, oxygen therapy, and oral sustained-release theophyllines) will be permitted throughout the study duration, if the dose is stable for at least 4 weeks prior to entering the study (Visit 1).

The above treatments will 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 randomization 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 randomization will be used as treatment allocation factor.

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 COPD Assessment Test (CAT), St. George Respiratory Questionnaire (SGRQ), Evaluating Respiratory Symptoms in COPD (E-RS™: COPD), Night-time and Early Morning Symptoms of COPD instrument (NiSCI and EMSCI), COPD exacerbations and use of relief 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.

In a subset of 35% of patients, 24 h spirometry assessments will be performed at Visits 2 and 7 to characterize the evening peak effect.

1.3. Benefit/risk and ethical assessment

The AB/FF 400/12 µg combination is approved in Europe as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. AB 400 µg and TIO 18 µg are both

approved in Europe and in the US also as a maintenance bronchodilator treatment in the same population. While FF 12 µg delivered by Pressair®/Genuair® is not an approved product, results from previously completed studies have demonstrated the efficacy and safety of FF 12 µg compared to placebo in 716 patients over a treatment period of 24 weeks (D'Urzo et al. 2014, Singh et al. 2014).

The clinical development programme for AB/FF 400/12 µg has shown to provide additional efficacy benefits compared to those associated with AB or FF monotherapies (as assessed by measures of lung function, COPD symptoms and disease-specific health status) with a safety profile comparable to the monotherapies (D'Urzo et al. 2014, Singh et al. 2014).

The safety profile of AB/FF 400/12 µg, AB 400 µg and TIO 18 µg are based on clinical and post-marketing experience.

As the IP contains AB and FF, the type and severity of adverse reactions associated with each of the components are the ones expected with AB/FF 400/12 µg.

Common adverse events (≥ 1%) to be expected for the different IPs are:

- AB 400 µg: sinusitis, nasopharyngitis, headache, cough, sinusitis, diarrhoea and nausea.
- FF 12 µg: palpitations, headache and tremor.
- AB/FF 400/12 µg: nasopharyngitis, urinary tract infection, sinusitis, tooth abscess, insomnia, anxiety, tremor, dry mouth, blood creatinine phosphokinase increased.
- TIO: dry mouth.

There is limited evidence on the management of overdose with Duaklir® Genuair®, Eklira®/Bretaris®/Tudorza® Genuair®/Pressair®. 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 SmPC (Eklira® Genuair® SmPC 2015, Bretaris® Genuair® SmPC 2015, Tudorza® Pressair® US Prescribing Information 2015, AB/FF Investigator's Brochure Edition 10 August 2015, Spiriva® SmPC 2015 and Spiriva® US Prescribing Information 2016).

Based on the study drug safety profile, no specific risks are 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, randomized, parallel, double blind, double dummy, multicentre and multinational Phase III study to determine the efficacy and safety of AB/FF 400/12 µg compared to individual components and TIO 18 µg when administered to patients with stable COPD.

The study will consist of a Screening Visit (Visit 1) conducted after signature of the ICF, where medical history, COPD history, physical examination, laboratory analysis, ECG and COPD severity stage (COPD assessment test and post-bronchodilator FEV_1 according to GOLD guidelines 2015) 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 require a wash-out of prohibited medication will be prescribed Atrovent® 2 puff QID to be taken during the wash-out and the run-in period. All patients will be provided with relief medication (salbutamol/albuterol) at the signature of the ICF, and will continue using only the allowed COPD medications through the study. At the Screening Visit (Visit 1) patients are provided with the e-diary to record the use of relief medication once daily and their COPD symptoms and IP intake every morning and night.

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 investigational product (IP) administration for patients that complete the study treatment and for patients that discontinue from the trial (withdrawals) to assess new or ongoing adverse events (AEs), COPD exacerbations, as well as any concomitant medication administered to treat the mentioned AE. Patients completing the trial will be the patients who performed the study procedures up to Visit 7 according to the protocol. Patients completing the treatment will be those patients who were on study drug during the 24 week treatment period, even if they do not complete the follow-up contact.

Patients who prematurely discontinue IP will perform an End of Treatment (EOT) Visit and will be encouraged to complete a post-IP discontinuation follow-up period including scheduled study visits. Patients participating in the sub-study who choose to discontinue from treatment will only complete scheduled visits and not complete any remaining sub-study assessments.

Patients who prematurely discontinue from the study (withdrawal) will participate in an End of Study (EOS).

Figure 1 Study flow chart

<table>
<tr><td>Visit 1</td><td>Visit 2</td><td>Visit 3</td><td>Visit 4</td><td>Visit 5</td><td>Visit 6</td><td>Visit 7</td><td>Follow Up Contact</td></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">AB/FF 400/12 µg (BID)</td></tr>
<tr><td colspan="6">AB 400 µg (BID)</td></tr>
<tr><td colspan="6">FF 12 µg (BID)</td></tr>
<tr><td colspan="6">TIO 18 µg</td></tr>
</table>

Refer to section 7.8 for the list of allowed and concomitant medication.

2. STUDY OBJECTIVES

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

2.1. Primary objective

Primary objective for US:

To assess the bronchodilatory effect of AB/FF 400/12 µg compared to each individual component when administered twice daily via inhalation to COPD patients.

Primary objective for Market Access:

To assess the non-inferior bronchodilation of AB 400 µg BID as compared to tiotropium (TIO) 18 µg QD in COPD patients.

2.2. Secondary objectives

To further characterize the effect of AB/FF 400/12 µg on bronchodilation and health related quality of life compared to individual components when administered twice daily via inhalation to COPD patients.

2.3. Safety objectives

To evaluate the safety and tolerability of AB/FF 400/12 µg as compared to individual components in COPD patients.

2.4. Exploratory objectives

Treatment effects and comparisons in primary and secondary endpoints will be evaluated for the subgroup of patients which are more symptomatic at study entry based on different definitions.

2.5. Outcome variables

The co-primary variables for US are the following:

- Change from baseline in 1-hour morning post-dose dose FEV_1 of AB/FF 400/12 µg compared to AB 400 µg at week 24.

- Change from baseline in morning pre-dose (trough) FEV_1 of AB/FF 400/12 µg compared to FF 12 µg at week 24.

The primary variable for Market Access is the following:

- Change from baseline in morning pre-dose (trough) FEV_1 at week 24 comparing AB 400 µg BID versus TIO 18 µg.

The secondary variables are the following:

- Change from baseline in normalized $AUC_{0\text{-}3/3h}$ FEV_1 of AB/FF 400/12 µg at week 24 compared to AB 400 µg and FF 12 µg.

- Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4 units from baseline) with AB/FF 400/12 µg in SGRQ total score at week 24 compared to AB 400 µg and FF 12 µg.

Additional efficacy variables:

- Pulmonary function variables (FEV_1, FVC) at each different time points, onset of action, peak and trough FEV_1 at each visit and average (i.e., Area Under the Curve over 3h post-dose [$AUC_{0\text{-}3/3h}$]). Moreover, in the sub-set of patients with 24h serial pulmonary function tests the following variables will be assessed: FEV_1 and FVC at each time point and $AUC_{0\text{-}12h}$; $AUC_{12\text{-}24h}$, $AUC_{0\text{-}24h}$.

- Health related quality of life outcomes, St George Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT): change from baseline and responder analysis (percentage of patients reaching the minimally clinical important difference [MCID]) at each visit.

- Symptomatic outcomes, Evaluating Respiratory Symptoms in COPD (E-RS^{TM}: COPD), Night-time and Early morning symptoms of COPD instrument (NiSCI & EMSCI): change from baseline and responder analysis (only E-RS) at each visit and over the treatment period.

- COPD exacerbations, as defined by Health Care Research Utilization (HCRU) and Exacerbations of Chronic Pulmonary Disease Tool (EXACT): percentage of patients with at least one exacerbation, rate of exacerbations and time to first exacerbation.

- Use of relief medication: change from baseline at each visit and over the treatment period.

- Device preference and willingness to continue.

Safety outcomes:

- Adverse Events (AEs)/Serious Adverse Events (SAEs)

- Clinical laboratory test (hematology and biochemistry)

- Blood pressure

- 12-lead ECG

- Major Adverse Cardiac Events (MACE)

3. SUBJECT SELECTION, ENROLMENT, RANDOMIZATION, 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 note: 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 (i.e 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 diagnosis of moderate to very severe stable COPD: post-bronchodilator FEV_1 < 80% of the predicted normal and post-bronchodilator FEV_1/FVC < 70% at Screening Visit.

   Explanatory note: Moderate to very severe COPD (Stage II or Stage IV, according to the GOLD guidelines classification 2015). Post-bronchodilation means FEV_1 and FVC between 10 to 15 minutes after inhalation of 4 puffs of albuterol/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 are based on the Global Lung Function Initiative predicted values (Quanjer et al. 2012).

3. Symptomatic patients with a CAT score ≥10 at Screening and Randomization visit (Visits 1 and 2).
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 x 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 acceptable and repeatable pulmonary function testing for FEV_1 according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 criteria at Visit 1.
6. Patients eligible and able to participate in the study and who had signed an Informed Consent Form prior to initiation of any study-related procedures.

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 randomization in the present study D6571C00001.
3. Patients with predominant asthma.

   Explanatory note: If the investigator in his or her medical judgement determines the prior asthma diagnosis is unrelated to subject current condition (e.g. misdiagnosis, premature diagnosis, or resolution of early onset disease), then the patient is eligible for the study.
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 a COPD exacerbation (an emergency room visit for longer than 24 hours is considered a hospitalization) within 3 months prior to Screening Visit.

6. Clinically significant respiratory conditions other than COPD,

   Explanatory note: Clinically significant respiratory conditions defined as:

   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 need thoracotomy or other lung surgery during the study.

   f. Bronchiectasis secondary to respiratory diseases other than COPD (e.g. cystic fibrosis, Kartagener's syndrome, etc.)

   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. Patients who do not maintain regular day/night, waking/sleeping cycles including night shift workers.

   Explanatory note: the use of continuous positive airway pressure (CPAP) is not an exclusion criteria.

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 6 months prior to screening.

    c. Unstable angina or unstable arrhythmia which had required changes in the pharmacological therapy or other intervention within 6 months prior to screening, or newly diagnosed arrhythmia within the 3 months prior to screening which required the pharmacological therapy or other intervention.

    d. Hospitalization within 6 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.

e. Presence of an implantable cardioverter-defibrillator (ICD) within the last year prior to Screening visit.

11. Patients with uncontrolled Type I or Type II diabetes, uncontrolled hypo-or hyperthyroidism, hypokalaemia, or hyperadrenergic state, uncontrolled hypertension.

12. Patients with history of long QT syndrome or whose QTc (calculated according to Fridericia's Formula $QTc=QT/RR^{1/3}$) > 470 ms as indicated in the centralised reading report assessed at Screening.

13. Patients with clinically significant abnormalities in the laboratory tests, ECG parameters (other than QTc) or in the physical examination at Screening Visit that might comprise patient safety.

14. Patient with known non-controlled history of infection with human immunodeficiency virus and/or active hepatitis.

    Explanatory note:

    a. *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.*
    b. *Active infection with human immunodeficiency virus is defined as a confirmed viral load >200 copies/mL and or CD4 Count < 500 cells/mm^3.*

15. Patient with a history of hypersensitivity reaction to inhaled medication or any component thereof, including paradoxical bronchospasm.

16. Patients with known narrow-angle glaucoma, symptomatic bladder neck obstruction, acute urinary retention or symptomatic non-stable prostate hypertrophy.

    Explanatory note: Patients with well-controlled, stable, benign prostatic hypertrophy are not excluded.

17. 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.

18. Patients with any other serious or uncontrolled physical or mental dysfunction.

    Explanatory note: As judged by the investigator, the dysfunction could place the patient at higher risk from his/her participation in the study, or could 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.

19. Patients with a history (within 2 years prior to screening) of drug and/or alcohol abuse that may prevent study compliance based on the Investigator judgment.

20. Patients unlikely to be cooperative or that cannot comply with the study procedures.

    Explanatory note: Patients who may have difficulties following the treatment, completing the patient diary, attending the clinic at the required times, or unable to properly use a DPI or pMDI inhaler device or performing spirometry measurements.

21. Patients treated with any investigational drug within 30 days (or 6 half-lives, whichever is longer) prior to Screening.

22. 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.

    Explanatory note: refer to section 7.8 for washout periods of prohibited medication.

23. Patients unable to give consent, or patients of consenting age but under guardianship, or vulnerable patients.

24. Patients who demonstrate < 80% compliance with the electronic diary during the run-in period.

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 randomization

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

The Investigator(s) will:

1. Obtain signed ICF from the potential subject before any study specific procedures are performed.

For patients participating in the 24h spirometry sub-study, an additional ICF will be required.

2. Call/access the Interactive Voice/Web Response System (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 Randomization 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 randomization code and first medication kit number.

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

Randomization codes will be assigned strictly sequentially as subjects become eligible for randomization.

3.4. Procedures for handling incorrectly enrolled or randomized 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 randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform PAREXEL immediately, and a discussion should occur between the PAREXEL Medical responsible 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 2:3:2:3 ratio:

- AB/FF 400/12 µg administered via Pressair®/Genuair® inhaler
- AB 400 µg administered via Pressair®/Genuair® inhaler
- FF 12 µg administered via Pressair®/Genuair® inhaler
- TIO 18 µg via Handihaler®

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

In the spirometry sub-study the randomization scheme will also ensure allocation of patients to the four treatment groups in a 2:3:2:3 ratio.

The randomization will be performed using the centralized IVRS/IWRS at Visit 2 (Day 1). Specific information concerning the use of the IVRS/IWRS will be provided in a separate manual. Randomized subjects who discontinue from the treatment will not be replaced.

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

3.6. Methods for ensuring blinding

All double-blind medication kits will have similar appearance regardless of the investigational product contained and will be labeled 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).

This is a double-dummy study because AB/FF 400/12 µg, AB 400 µg and FF 12 µg will be administered via Pressair®/Genuair® inhaler and TIO 18 µg will be administered via Handihaler® inhaler. Therefore, in order to ensure the double blind nature of the trial, patients will have to inhale from the Pressair®/Genuair® twice daily (in the morning and in the evening) and from the Handihaler® once daily (in the morning) following the schema below. Patients will be instructed to use the Genuair® device right before the Handihaler® device.

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

Treatment arm	Morning administration	Evening administration
AB 400 µg/FF 12 µg	AB/FF 400/12 µg (Pressair®/Genuair®) + placebo to TIO 18 µg (Handihaler®)	AB/FF 400/12 µg (Pressair®/Genuair®)
AB 400 µg BID	AB 400 µg (Pressair®/Genuair®) + placebo to TIO 18 µg (Handihaler®)	AB 400 µg (Pressair®/Genuair®)
FF 12 µg BID	FF 12 µg (Pressair®/Genuair) + placebo to TIO 18 µg (Handihaler®)	FF 12 µg (Pressair®/Genuair®)

TIO 18 µg QD µg	placebo to AB/FF 400/12 µg, AB 400 µg and FF 12 µg (Pressair®/Genuair®) + TIO 18 µg (Handihaler®)	Placebo to AB/FF 400/12 µg, AB 400 µg and FF 12 µg (Pressair®/Genuair®)

Although TIO and placebo to TIO capsules have a similar appearance, they are not an exact match, and therefore the preparation and administration of the IP will be performed by a third party (person independent to the study activities). The third party administrator should check that the patient has correctly used the inhaler.

3.7. Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) or Pharmacist(s) from the IVRS/IWRS. Only authorized 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 randomization. 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 7.8).

- 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. Any subject who suffers a severe exacerbation (requiring hospitalization) or more than two moderate exacerbations will be discontinued from the investigational product.
- Protocol deviation: This will include patients that have been wrongly randomized: not fulfilling inclusion/exclusion criteria but detected after randomization. After randomization, 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 randomization.
- 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. 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 and date for premature discontinuation of IP will be documented in the source documentation and in the eCRF.

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-IP discontinuation follow-up period according to the planned visit schedule including efficacy and safety assessments. Treatment discontinuation subjects will return to appropriate maintenance COPD medications, per the investigators discretion.

The IP and relief medication will be returned at the EOT visit but the paper diary and electronic diary will be re-dispensed. 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.

Subjects participating in the sub-study who choose to discontinue from treatment will only complete scheduled visits and not complete any remaining sub-study assessments.

If a subject chooses not to continue with study assessments, at a minimum the subject will complete the EOT visit. These subjects will return to appropriate maintenance COPD medications, per the investigators discretion. A follow-up telephone call will be performed at least 14 days after the last study drug dose. In the event the EOT visit is performed >14 days post last study drug dosing, a follow-up contact will not be required.

3.10. Patient discontinuation from the study (withdrawal)

Patients 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 randomized. These patients should have the reason for study withdrawal recorded as ‘Screen Failure (Non-fulfilment of inclusion/exclusion criteria)’ (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).
- 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.

- 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 Procedures for discontinuation of a subject from the study

Patients who prematurely discontinue from the study (withdrawal) will participate in an End of Study (EOS) Visit. A review of the e-diary and an assessment of AEs and COPD exacerbations will also be performed at the EOS visit. The IP, paper diary and electronic diary will be returned at the EOS visit.

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

1. Ask the patient to undergo the EOS 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/randomization 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 randomized in the trial perform the last contact (either Visit 7 or Follow-up contact) and will be communicated to Regulatory Authorities and Ethics Committees (EC) on due time according to local regulations.

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

- The principal investigator (PI) and the sponsor feel that the type, number and/or severity of AEs justify discontinuation of the trial.
- Data not known before become available and raise concern about the safety of the study drugs so that continuation would pose potential risks to the patient
- The sponsor decides to discontinue the study for reason not related to the safety of study drugs.

If the study is terminated, 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	**Washout Period**	**Screening Period**	**Treatment**							**Follow-up call**
Visit	**Visit 0 Registration[1]**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**EOT/EOS Visit[1]**	
Week	**Up to 6**	**2**	**0**	**1**	**4**	**12**	**18**	**24**		**26**
Day	**Up to 42**	**14**	**1**	**8**	**29**	**85**	**127**	**169**		**183**
Visit Window		**± 3 days**		**± 2 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**		**+ 3 days**
ICF	X									
Medical, Smoking, COPD and Medication History	X	X								
Physical examination[2]		X[2]						X	X	
Blood pressure and 12-lead ECG [3]		X	X	X	X	X	X	X	X	
Pre and post bronchodilator test[4]		X								
Dispense wash-out medication	X	X								
Inclusion/exclusion criteria	X	X	X							
Clinical laboratory testing[5]		X						X	X	
Randomization			X							

Period	**Washout Period**	**Screening Period**	**Treatment**							**Follow-up call**
Visit	**Visit 0 Registration[1]**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**EOT/EOS Visit[1]**	
Week	**Up to 6**	**2**	**0**	**1**	**4**	**12**	**18**	**24**		**26**
Day	**Up to 42**	**14**	**1**	**8**	**29**	**85**	**127**	**169**		**183**
Visit Window		**± 3 days**		**± 2 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**		**+ 3 days**
SGRQ, CAT[6]		X	X		X	X	X	X	X	
Device preference								X	X	
e-diary completion[7]		Daily since Screening Visit (Visit 1): EXACT in the evening and NiSCI and EMSCI in the morning							X	
Pre-dose Pulmonary Function Tet (PFT)[8]			X	X	X	X	X	X	X	
Post-dose PFT			X[9]		X[10]	X[11]	X[10]	X[11]	X[12]	
Training on inhalers			X	As needed						
Dispense relief medication	X	*As needed*								
Assess study drug compliance				X	X	X	X	X		
Dispense study drug via IWRS			X			X				
Paper Diary[13]		X	X	X	X	X	X	X	X	X
Adverse Events/COPD exacerbations		X	X	X	X	X	X	X	X	X
Prohibited/concomitant medications	X	X	X	X	X	X	X	X	X	X[14]
SERIAL SPIROMETRY SUBSTUDY: Additional Assessments										
24-hour PFT[15]			X					X		

Period	Washout Period	Screening Period	Treatment							Follow-up call
Visit	**Visit 0 Registration[1]**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**EOT/EOS Visit[1]**	
Week	**Up to 6**	**2**	**0**	**1**	**4**	**12**	**18**	**24**		**26**
Day	**Up to 42**	**14**	**1**	**8**	**29**	**85**	**127**	**169**		**183**
Visit Window		**± 3 days**		**± 2 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**		**+ 3 days**

Time windows for all visits are related to visit 2.
[1] Patients requiring a washout of prohibited COPD medications will sign the ICF, be assigned a Patient Identification number (enrolment code) by the IWRS system, and receive Atrovent® and relief medication (albuterol/salbutamol) at Visit 0. Visit 0 may occur the same day as Visit 1 if the patient does not require a washout. In this case, only relief medication will be provided to the patient.
EOT = End of Treatment; EOS = End of Study for patients who discontinue from the treatment and from the study at the same time. Patients who discontinue from the treatment post follow-up period should undergo a reduce EOS visit to collect the diaries.
[2] Height and weight only at Screening Visit
[3] Blood Pressure (after being seated for 5-10 minutes and before the ECG assessment) and ECG will be performed once at Screening Visit to determine patient eligibility and once at EOT/EOS visit. At other visits, ECG and Blood Pressure will be performed pre-morning dose (before the patient exerts any effort, including PFTs) and 2 hours post-morning dose only at visits 2, 5 and 7.
[4] One pre-bronchodilator PFT, followed by one post-bronchodilator PFT 10-15 minutes after the inhalation of 4 puffs of albuterol/salbutamol through a spacer device.
[5] Hematology and biochemistry. Serum pregnancy test only in female patients of child bearing potential.
[6] At Screening visit only the CAT questionnaire will be administered to assess the fulfillment of the inclusion criteria. At other visits, SGRQ and CAT questionnaires will be administered prior to study drug administration. SGRQ will be the first questionnaire to be administered.
[7] Patient will record number of doses taken of relief medication once daily (in the evening); IP intake will be recorded in the morning and evening; EXACT questionnaire will be completed every evening; and Night-time and Early Morning COPD symptoms questionnaire will be completed every morning. Following EOT visit patients will be asked to complete the e-diary only in the evening for the EXACT questionnaire.
[8] Two pre-PFTs (approximately 15 to 30 minutes apart) both to be completed within 60 minutes prior to the morning dose of study drug.
[9] At Visit 2: 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours post study drug administration.
[10] At Visits 4 and 6: 1 hour post study drug administration.
[11] At Visits 5 and 7: 30 minutes, 1 hour, 2 hours, and 3 hours post study drug administration.
[12] At EOT/EOS visit: 1 hour post COPD treatment administration.
[13] Patient will record in the paper diary the AEs and new concomitant medication during the study.
[14] Only concomitant medication related to AEs must be recorded at follow-up contact.
[15] Additional PFTs at Visit 2 and 7 only for 35% of patients who will participate in the 24-hour serial spirometry sub-study: +4h, +6h, +9h, +12h (pre-evening dose), +12.5h, +13h, +14h, +22, +23.5h and +24h after the morning dose. Subjects participating in the sub-study who choose to discontinue from treatment will not complete the 24h spirometry assessments at the EOT visit.

4.1. Enrolment/screening period

This period will start with the signature of the ICF, will follow with Visit 1 (Screening) and will end at the randomization visit (Visit 2).

Patients requiring a washout of prohibited COPD medications will sign the ICF, be assigned a Patient Identification number (enrolment code) by the IWRS system, and receive Atrovent® and relief medication (albuterol/salbutamol) at Visit 0 (registration visit). Visit 0 may occur the same day as Visit 1 if the patient does not require a washout. In this case, only relief medication will be provided to the patient.

Prior to signing the ICF, 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.

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.

Any patient signing the ICF should be recorded in IVRS/IWRS and should be assigned a patient ID number.

A separate ICF will be obtained for those patients who agree to participate in the 24-h spirometry sub-study.

4.1.1 Visit 1 (screening)

Screening Visit will be scheduled in the morning, at a similar start time than future study visits. 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, if required. Record in the eCRF all medications the patient is currently taking and has taken during the previous 15 days before signature of the ICF.

- Review of any Adverse Event and COPD exacerbations since signature of the ICF.

- Register patient in IVRS/IWRS (if not done yet).

- Review medical history, demographic, COPD history (date of COPD diagnosis, diagnosis of chronic bronchitis or emphysema, number of COPD exacerbations during last year and date of last COPD exacerbation and if hospitalization) and smoking information (i.e., date of smoking initiation, current smoker or former smoker, date of smoking cessation and total-pack years).

- CAT questionnaire.
- 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; and when appropriate, pregnancy test.
- Spirometry Forced manoeuvre test (FEV_1 and FVC measurement): 1 set of tests will be performed.
- Bronchodilator test (Reversibility test): administer inhaled albuterol/salbutamol (4 puffs) through a spacer device at least 10 minutes after previous spirometry test. Afterwards, 10 to 15 minutes after albuterol/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 or EDC. When patient fulfilled inclusion/exclusion criteria, the following will occur:

- Patient will be dispensed the relief medication inhaler and trained on its use (if required).
- Patients who required a wash-out of any prohibited medication will be dispensed with Atrovent® to be taken 2 puffs QID during the run-in period.
- 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 record new AEs and changes in the concomitant medication (if any).
- Next protocol visit will be scheduled. Patient will be reminded to avoid the intake of relief and wash-out medication for at least 6 hours before attending the next visit, and to bring back the relief and wash-out medications, the electronic and the paper Patient Diary.

FOR 24h-SPIROMETRY SUB-STUDY PATIENTS ONLY:

- Patients who participate in the 24-h spirometry sub-study will sign a specific ICF. They will be reminded that if they are randomized at next visit, they will be required to stay on-site to perform spirometries for approximately 25 hours.

4.2. Treatment period

4.2.1 Visit 2 (Randomization Visit)

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

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

- Electronic Patient Diary review. Check if patient has completed the morning questionnaire on the e-diary. If no, patient should complete the e-diary at the site before any study procedure. In case of low compliance with the e-diary (less than 80 % 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.

- Retrieval of wash-out medication (Atrovent®), for those patients who required wash-out of prohibited medication.

A. Pre-dose assessments (baseline)

- SGRQ: this should be the first questionnaire to be completed.

- CAT questionnaire.

- 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 or EDC.

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

- Blood pressure.

- 12-lead ECG.

- Spirometry forced manoeuvre tests (FEV_1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning IP dose, allowing approximately 30 min between them.

B. Randomization

- Randomize the patient via IWRS/IVRS, and obtain kit number assignment. Document the randomization date on the medical notes.

C. Morning IP administration

- Dispense the kit numbers assigned by IWRS/IVRS and record the kit numbers dispensed on the Drug Accountability Log.

- Train the patient on the use of Pressair/Genuair® and Handihaler® with the empty training inhalers and empty capsules provided.

- **Administration of the IPs should be performed by a third party administrator (person independent to the study activities).** Administer the first dose of IP at approximately 09:00±1h by inhalation of 1 puff from the Pressair/Genuair® inhaler and 1 puff from the Handihaler® inhaler. The third party administrator should check that the patient has correctly used the inhalers.

- Instruct the patient to inhale from the Pressair/Genuair® every morning and evening and from the Handihaler® every morning until the last evening before next visit. Remind the patient to use the Genuair® device right before the Handihaler® device, and to come to next visit with the medication kits to assess the drug accountability.

- Record the date and time of the first IP administration in the medical notes and in the spirometry equipment, Masterscope CT.

D. Post-dose assessments

- Post-dose PFT (FEV_1 and FVC): at +5 min, +15 min, +30 min, +1h, +2h, and +3h.

- Blood pressure: at +2h.

- 12-lead ECG: at +2h.

Note: for T+2h 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 kits will be given to the patient and reminded about the correct dose regimen and timing.

- Relief medication will be dispensed, as needed.

- Patient will be provided with a new 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 relief medication for at least 6 hours before attending the next visit, and to bring the IP kits, the relief medication inhaler, the electronic and the paper Patient Diary to the clinic.

FOR 24h-SPIROMETRY SUB-STUDY PATIENTS ONLY:

- Post-dose PFT (FEV_1 and FVC): at +4h, +6h, +9h and +12h (pre-evening dose)
- Administer the evening dose with the Pressair/Genuair® inhaler 12 hours apart from the morning dose.
- Post-dose PFTs at +12.5h, 13h, +14h, +22h, +23.5h and +24h after the morning dose.

4.2.2 Visit 3: Week 1

A. Pre-dose assessments

- Paper Patient Diary review: Adverse events, COPD exacerbation, and concomitant medication review since last visit.
- Electronic Patient Diary review.
- Check appropriate medication wash-outs before visit (at least 6h since last relief medication intake).
- **Third party administrator should check study drug compliance and re-train patient if required.**
- Blood pressure.
- 12-lead ECG.
- Spirometry forced manoeuvre tests (FEV_1 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 Pressair/Genuair® and Handihaler® with the empty training inhalers and capsules. The third party administrator will evaluate proper use of the devices by the patient and provide additional training if needed.

- **Administration of the IPs should be performed by the third party administrator.** Administer the first dose of IP at approximately 09:00±1h by inhalation of 1 puff from the Pressair/Genuair® inhaler and 1 puff from the Handihaler® inhaler. The third party administrator should check that the patient has correctly used the inhalers.

- Remind the patient to inhale from the Pressair/Genuair® every morning and evening and from the Handihaler® every morning until the last evening before next visit. Remind the patient to use the Genuair® device right before the Handihaler® device, and to come to next visit with the medication kits to assess the drug accountability.

- Record the date and time of the IP administration in the medical notes and in the spirometry equipment, Masterscope CT.

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

- **Third party administrator should collect empty TIO capsules.**

- IP kits will be redispensed to the patient and reminded about the correct dose regimen and timing.

- Relief medication will be dispensed, as needed.

- Patient will be provided with a new 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 relief medication for at least 6 hours before attending the next visit, and to bring the IP kits, the relief medication inhaler, the electronic and the paper Patient Diary to the clinic.

4.2.3 Visit 4: Week 4

A. <u>Pre-dose assessments</u>

- Paper Patient Diary review: Adverse events, COPD exacerbation, and concomitant medication review since last visit.

- Electronic Patient Diary review.

- Check appropriate medication wash-outs before visit (at least 6h since last relief medication intake).

- Third party administrator should check study drug compliance and re-train patient if required.

- SGRQ: this should be the first questionnaire to be completed.

- CAT questionnaire.

- Blood pressure.

- 12-lead ECG.

- Spirometry forced manoeuvre tests (FEV_1 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 Pressair/Genuair® and Handihaler® with the empty training inhalers and capsules. **The third party administrator will evaluate proper use of the devices by the patient and provide additional training if needed.**

- **Administration of the IPs should be performed by the third party administrator.** Administer the first dose of IP at approximately 09:00±1h by inhalation of 1 puff from the Pressair/Genuair® inhaler and 1 puff from the Handihaler® inhaler. The third party administrator should check that the patient has correctly used the inhalers.

- Remind the patient to inhale from the Pressair/Genuair® every morning and evening and from the Handihaler® every morning until the last evening before next visit. Remind the patient to use the Genuair® device right before the Handihaler® device, and to come to next visit with the medication kits to assess the drug accountability.

- Record the date and time of the IP administration in the medical notes and in the spirometry equipment, Masterscope CT.

C. Post-dose assessments

- Post-dose PFT (FEV_1 and FVC): at +1h.

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

- **Third party administrator should collect empty/locked Pressair/Genuair® and empty TIO capsules.**

- IP kits will be redispensed to the patient and reminded about the correct dose regimen and timing.
- Relief medication will be dispensed, as needed.
- Patient will be provided with a new 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 relief medication for at least 6 hours before attending the next visit, and to bring the IP kit, the relief medication inhaler, the electronic and the paper Patient Diary to the clinic.

4.2.4 Visit 5: Week 12

A. Pre-dose assessments

- Paper Patient Diary review: Adverse events, COPD exacerbation, and concomitant medication review.
- Electronic Patient Diary review.
- Check appropriate medication wash-outs before visit (at least 6h since last relief medication intake).
- **Third party administrator should collect ALL Pressair/Genuair® and Handihaler® capsules and check them in order to assess study drug compliance and perform drug accountability.**
- SGRQ: this should be the first questionnaire to be completed.
- CAT questionnaire
- Blood pressure.
- 12-lead ECG.
- Spirometry forced manoeuvre tests (FEV_1 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 Pressair/Genuair® and Handihaler® with the empty training inhalers and empty capsules.

- Call IVRS/access IWRS to assign a new medication kit and record the kit number in the drug accountability log.

- **Administration of the IPs should be performed by a third party administrator (person independent to the study activities).** Administer the first dose of IP at approximately 09:00±1h by inhalation of 1 puff from the Pressair/Genuair® inhaler and 1 puff from the Handihaler® inhaler. The third party administrator should check that the patient has correctly used the inhalers.

- Instruct the patient to inhale from the Pressair/Genuair® every morning and evening and from the Handihaler® every morning until the last evening before next visit. Remind the patient to use the Genuair® device right before the Handihaler® device, and to come to next visit with the medication kits to assess the drug accountability.

- Record the date and time of the first IP administration in the medical notes and in the spirometry equipment, Masterscope CT.

C. Post-dose assessments

- Post-dose PFT (FEV_1 and FVC): at +30 min, +1h, +2h and +3h.

- Blood pressure: at +2h

- 12-lead ECG: at +2h

Note: for T+2h 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 kits will be dispensed to the patient and reminded about the correct dose regimen and timing.

- Relief 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 relief medication for at least 6 hours before attending the next visit, and to bring the IP kit, the relief medication inhaler, the electronic and the paper Patient Diary to the clinic.

4.2.5 Visit 6: Week 18

A. Pre-dose assessments

- Paper Patient Diary review: Adverse events, COPD exacerbation, and concomitant medication review since last visit.
- Electronic Patient Diary review.
- Check appropriate medication wash-outs before visit (at least 6h since last relief medication intake).
- **Third party administrator should check study drug compliance and re-train patient if required.**
- SGRQ: this should be the first questionnaire to be completed.
- CAT questionnaire.
- Blood pressure.
- 12-lead ECG.
- Spirometry forced manoeuvre tests (FEV_1 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 Pressair/Genuair® and Handihaler® with the empty training inhalers and empty capsules.
- **Administration of the IPs should be performed by a third party administrator (person independent to the study activities).** Administer the first dose of IP at approximately 09:00±1h by inhalation of 1 puff from the Pressair/Genuair® inhaler and 1 puff from the Handihaler® inhaler. The third party administrator should check that the patient has correctly used the inhalers.
- Remind the patient to inhale from the Pressair/Genuair® every morning and evening and from the Handihaler® every morning until the last evening before next visit. Remind the patient to use the Genuair® device right before the Handihaler® device, and to come to next visit with the medication kits to assess the drug accountability.
- Record the date and time of the first IP administration in the medical notes and in the spirometry equipment, Masterscope CT.

C. Post-dose assessments

- Post-dose PFT (FEV_1 and FVC): at +1h.

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

- **Third party administrator should collect empty/locked Pressair/Genuair® and empty TIO capsules.**
- Same IP kits will be redispensed to the patient and reminded about the correct dose regimen and timing.
- Relief 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 relief medication for at least 6 hours before attending the next visit, and to bring the IP kit, the relief 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 medication wash-outs before visit (at least 6h since last relief medication intake).
- SGRQ: this should be the first questionnaire to be completed.
- CAT.
- Device Preference Questionnaire.
- Blood sampling for haematology and biochemistry; when appropriate, pregnancy test.
- Physical examination (any new or worsened finding will be recorded in the AE form of the EDC).

- Blood pressure.
- 12-lead ECG.
- Spirometry forced manoeuvre tests (FEV_1 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

- **Administration of the IPs should be performed by a third party administrator (person independent to the study activities).** Administer the first dose of IP at approximately 09:00±1h by inhalation of 1 puff from the Pressair/Genuair® inhaler and 1 puff from the Handihaler® inhaler. The third party administrator should check that the patient has correctly used the inhalers.
- Record the date and time of the IP administration in the medical notes and in the spirometry equipment, Masterscope CT.

C. Post-dose assessments

- Post-dose PFT (FEV_1 and FVC): at +30 min, +1h, +2h, and +3h.
- Blood pressure: at +2h
- 12-lead ECG: at +2h

Note: for T+2h 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:

- **Third party administrator should collect ALL Pressair/Genuair® and Handihaler® capsules and check them in order to assess study drug compliance and perform drug accountability.**
- Review and retrieve paper and electronic Patient Diary.
- Retrieval of relief medication.
- Research personnel will register patient´s completion of the treatment in IVRS/IWRS or EDC.
- 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.

FOR 24h-SPIROMETRY SUB-STUDY PATIENTS ONLY:

- Post-dose PFT (FEV_1 and FVC): at +4h, +6h, +9h and +12h (pre-evening dose)
- Administer the evening dose with the Pressair/Genuair® inhaler 12 hours apart from the morning dose.
- Post-dose PFTs at +12.5h, +13h, +14h, +22h, +23.5h and +24h after the morning administration.

4.2.7 End of Treatment (EOT)

The following procedures will be performed for patients that discontinue from the IP (EOT):

- Paper Patient Diary review: Adverse events, COPD exacerbation and concomitant medication review.
- Electronic Patient Diary review.
- SGRQ: this should be the first questionnaire to be completed.
- CAT.
- Device Preference Questionnaire.
- **Third party administrator should collect ALL Pressair/Genuair® and Handihaler® capsules and check them in order to assess study drug compliance and perform drug accountability**
- Retrieval of relief medication.
- Blood sampling for haematology and biochemistry; when appropriate, pregnancy test.
- Physical examination (any new or worsened finding will be recorded in the AE form of the EDC).
- 12-lead ECG.
- Blood pressure.
- Spirometry forced manoeuvre tests (FEV_1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning dose, allowing approximately

30 min between them. If the patient has taken the COPD treatment before the visit, the pulmonary function test should not be performed.

- 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.

- **Administration of the COPD treatment at the EOT visit.**

- Post-dose PFT (FEV_1 and FVC) at +1h. In case the COPD prescribed treatment is not administered during the EOT visit, the post dose PFT will be skipped.

- Record the date and time of the administration in the medical notes and in the spirometry equipment, Masterscope CT.

- Research personnel will register patient´s discontinuation of the treatment in IVRS/IWRS or EDC and will complete the corresponding visit in the EDC.

Patients who discontinue from IP will be encouraged to enter in a follow-up period. The following additional procedures will be performed at the EOT visit:

- Obtain signed ICF for patients who discontinue from IP.

- Re-dispense the paper diary and electronic diary. The electronic diary will need to be set-up to allow patient to complete only the SGRQ and E-RS^{TM}: COPD during the post-IP discontinuation follow-up period.

- Inform the patient that he/she should attend the clinic per the planned study visits until the 24 weeks of treatment are completed. If the EOT occurs within two weeks of the next scheduled visit, the next visit can be skipped.

- Schedule the next visit according to the protocol.

If any patient accepting the participation in the post-treatment follow-up period decides to discontinue from the study later on (withdrawal), an EOS visit should be scheduled in order to return the paper and electronic diaries as well as the relief medication. See section 4.2.8.1.

4.2.8 Follow-up period after IP discontinuation

Subjects who discontinue study treatment will be encouraged to remain in the study to complete all remaining study visits during the 24 week treatment period. Patients who agree to participate in the follow-up period after IP discontinuation (EOT) will attend to the clinic on the scheduled protocol visits.

They will perform the following procedures:

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

- Electronic Patient Diary review: evening diary completion (EXACT).

- SGRQ completion (except for follow up visit replacing regular Visit 3).

- Spirometry forced manoeuvre tests (FEV_1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning dose, allowing approximately 30 min between them. If the patient has taken the COPD treatment before the visit, the pulmonary function test should not be performed.

- **Administration of the COPD treatment prescribed at the EOT visit.**

- Record the date and time of the administration in the medical notes and in the spirometry equipment, Masterscope CT.

- Post-dose PFT (FEV_1): at +1h (except for visits replacing regular Visit 3)

- Research personnel will register patient´s discontinuation of the treatment in IVRS/IWRS or EDC and will complete the corresponding EOT visit in the EDC.

At the end of the visit the investigator will:

- Redispense the paper diary and electronic diary.

- Inform the patient that he/she should attend the clinic per the planned study visits until the 24 weeks of treatment are completed.

- Schedule the remaining on-site visits.

4.2.8.1 End of Study (EOS) visit for patients that discontinue from the treatment follow-up period

Patients who discontinue from the post-treatment follow-up period for any reason (i.e. withdrawal of consent) an EOS visit should be performed as soon as possible in order to retrieve the study material (paper diary, electronic diary).

No additional tests are required in this visit unless the investigator considers them necessary to ensure the patient's 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 of the study in IVRS/IWRS or EDC and will complete the corresponding EOS visit in the EDC respectively.

- Retrieve paper and electronic Patient Diary.

4.2.9 End of Study (EOS)

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

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

- Electronic Patient Diary review.

- SGRQ: this should be the first questionnaire to be completed.

- CAT.

- Device Preference Questionnaire.

- **Third party administrator should collect ALL Pressair/Genuair® and Handihaler® capsules and check them in order to assess study drug compliance and perform drug accountability**

- Retrieval of relief medication.

- Blood sampling for haematology and biochemistry; when appropriate, pregnancy test.

- Physical examination (any new or worsened finding will be recorded in the AE form of the EDC).

- 12-lead ECG.

- Blood pressure.

- Spirometry forced manoeuvre tests (FEV_1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning dose, allowing approximately 30 min between them. If the patient has taken the COPD treatment before the visit, the pulmonary function test should not be performed.

- 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.

- **Administration of the COPD treatment at the EOS visit.**

- Post-dose PFT (FEV_1 and FVC) at +1h. In case the COPD prescribed treatment is not administered during the EOS visit, the post dose PFT will be skipped.

- Record the date and time of the administration in the medical notes and in the spirometry equipment, Masterscope CT.

- Research personnel will register patient´s discontinuation of the study in IVRS/IWRS or EDC and will complete the corresponding visit in the EDC.

4.3. Follow-up period

A follow-up should be performed for patients completing the treatment or discontinued from the IP/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 randomization 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 time points) as well as SGRQ and CAT 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 for albuterol/salbutamol before any visit, and 6 hours for Atrovent® before screening and randomization visit: the randomization 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 Monitoring Associate (CMA).

- 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 albuterol/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 for SGRQ and CAT) 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 albuterol/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.

- For patients participating in the 24h spirometry sub-study: In case of intake of albuterol/salbutamol during the course of the visit after morning IP dose, spirometry tests will be skipped for 5 hours from the rescue medication intake. The number of puffs of albuterol/salbutamol will be recorded in the spirometer equipment.

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 (CSA). The investigator will sign the completed electronic Case Report Forms electronically. 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 PI (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).

- FEV_1 (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.

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 were 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 randomization.

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, so that they can be quickly and easily moved into a sitting position if they become lightheaded during the manoeuvre.

Each manoeuvre at each time point 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 time point will be skipped until patient recovers. Albuterol/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.

5.1.1.3 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 randomization, 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 (i.e., 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 (i.e., 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 (i.e., 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 at least 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 decrease in SGRQ total score of at least 4 units from baseline.

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

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 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 to ERT 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 Exacerbations of Chronic Pulmonary Disease Tool (EXACT) and Evaluating Respiratory Symptoms in COPD (E-RS^{TM}: COPD)

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 2010a, Leidy et al 2010b, 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 F) 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 Evaluating Respiratory Symptoms in COPD (E-RS^{TM}: COPD) questionnaire 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^{TM}: COPD is based on the 11 respiratory symptom items from the 14-item EXACT. The E-RS^{TM}: COPD 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.

5.1.4 Night-time and Early morning symptoms of COPD instrument (NiSCI and EMSCI)

The questionnaire is made up of two parts. The first part covering "last night" symptoms (time elapsed from the time patient went to bed until woke up and got out of bed to start his/her day) and the second part covering "this morning" symptoms (time elapsed since patient got out of bed to start the day).

The EMSCI was developed to collect data about the frequency and severity of early morning symptoms and the impact of COPD symptoms on early morning activity in patients with COPD. The EMSCI refers patients to think about the "time since when you got out of bed to start your day".

The NiSCI was developed to collect data about the frequency and severity of night-time symptoms and the impact of COPD symptoms on night-time awakenings in patients with COPD.

The data collected can be used to generate the following scores:

1. The six-Item Symptom Severity score is derived by averaging the responses from a patient on the six item-level symptom scores and can be used to quantify the severity of early morning and night-time symptoms.

2. The Overall COPD Symptom Severity score is comprised of a single item asking about overall COPD symptom severity in the early morning and at night.

3. The Early Morning Activity score obtains information on the reduction in early morning activity limitation due to COPD symptoms. The Night-time Awakenings score can be used to obtain information on the number (or proportion) of days without night-time awakening due to COPD symptoms.

The NiSCI and EMSCI (see Appendix G) will be recorded by the patient in the electronic Patient Diary, provided by ERT in relevant local language, every morning between 7 and 11 am from the day after Visit 1 (Screening) and up to Visit 7 morning entry (included).

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

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

5.1.5 Device Preference and Willingness to Continue Questionnaire

At the end of the treatment period (at Visit 7 or EOT/EOS), patients will be requested to evaluate the convenience of the device by means of the questionnaires included in Appendix H.

The questionnaire will be provided to the patients in local language. Data will be recorded by the patient in the e-diary (logpad) provided by ERT. Data will be transferred to ERT after completion. During the study data will be accessible to investigators on an online website.

The electronic entries on the 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 using the Health Care Resource Utilisation definition 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 not be recorded in the AE form of the EDC, but in a devoted COPD Exacerbation form of the EDC.

Any subject who suffers a severe exacerbation (requiring hospitalization) or more than two moderate exacerbations will be discontinued from the study.

Information to be recorded in the COPD Exacerbation includes start and stop date, treatment received (antibiotics, systemic corticosteroids, increase in relief 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 randomization:

- The next study visit (Va, other than Visit 7) must be postponed until 4 weeks after the resolution of a moderate 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 (i.e., with respect to Randomization 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: End of Treatment Visit will be performed.

COPD exacerbations will be analysed in this study on the basis of EXACT questionnaire (section 5.1.3) as well as on the basis of health care utilisation definition.

5.1.7 Other concomitant medication

Patients will record once daily in the electronic Patient Diary (logpad) the number of inhalations (puffs) of relief medication (albuterol/salbutamol) taken during the last 24h. The question displayed on the device will be: "How many puffs of relief medication (albuterol/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.

At pre-screening visit patients who require a wash-out of prohibited medication will be provided with Atrovent® to be taken during the wash-out and run-in period. Atrovent® administration will be recorded in the EDC.

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 Covance laboratory services which will provide the report to sites. A specific manual will be distributed by Covance.

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), red blood cells morphology, white blood cells differential and MCV.

- 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 C 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) which 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.

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. At following visits, 12-lead ECG will be recorded pre-dose, and 2h post-dose at Visits 2, 5 and 7.

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 of 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.

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

Not applicable.

5.4. Pharmacokinetics

Pharmacokinetics 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.

5.7. Biomarker analysis

Not applicable.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The PI 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 (i.e., 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
- 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 A 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 the ICF throughout the treatment period and including the follow-up period (i.e. 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, except when the AE started before first IP administration, persisted after it and worsened in intensity any time after first IP. In this latter case, the AE will be collected with each respective intensity. AE term recorded must be exactly the same in the different intensities collected

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. 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.

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 A 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, ECGs, physical examination and vital signs will be summarised in the clinical study report (CSR).

Medical disorders present at the time of signing the ICF 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 are the reason for discontinuation of treatment with the investigational product 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 ICF throughout the treatment period and including the follow-up period (i.e., 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. 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 any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., 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 i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

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.

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, ECs and/or investigators when applicable according to local regulations.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug and the EU Summary of Product Characteristics (SPC) for the active comparator.

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.

If an overdose with associated AE 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, and **no later than 24 hours** of when he or she becomes aware of it following the same process described in section 6.3.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to AstraZeneca Safety Database.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4.

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 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 i.e., 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.

6.6.2 Paternal exposure

Provided that nonclinical data with AB and FF 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)

Substance and strength:	Aclidinium bromide 400µg/Formoterol Fumarate 12 µg (AB/FF 400/12 µg)
Dosage form:	Inhalation powder.

Administration route:	Oral Inhalation (by Pressair®/Genuair® Dry Powder Inhaler, DPI)
Substance and strength:	Aclidinium bromide 400 µg (AB 400 µg)
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Pressair®/Genuair® Dry Powder Inhaler, DPI)
Substance and strength:	Formoterol fumarate 12 µg (FF 12 µg)
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Pressair®/Genuair® ® Dry Powder Inhaler, DPI)
Substance and strength:	Placebo to AB/FF 400/12 µg, placebo to AB 400 µg and placebo to FF 12 µg
Dosage form:	Inhalation powder.
Administration route:	Oral Inhalation (by Pressair®/Genuair® Dry Powder Inhaler, DPI)
Substance and strength:	Tiotropium 18 µg (TIO 18 µg)
Dosage form:	Powder in capsules for oral inhalation.
Administration route:	Oral Inhalation (by Handihaler® Dry Powder Inhaler, DPI)
Substance and strength:	Placebo to TIO 18 µg
Dosage form:	Powder in capsules for oral inhalation
Administration route:	Oral Inhalation (by Handihaler® Dry Powder Inhaler, DPI)

Note: The strengths are expressed as metered dose.

7.2. Additional Drug

Relief medication albuterol sulphate 108 µg/puff (in US) and salbutamol pMDI 100 µg/puff (in European countries), is considered as additional study drug and the accepted standard brand available in the country will be sourced.

Atrovent® will be provided by the sponsor during the wash-out period to those patients that require wash-out of any prohibited medication. Patients will be required to use Atrovent® 2 puffs QID during the wash-out and run-in period.

The CRO/AstraZeneca will provide the relief and wash-out medication.

7.3. Dose and treatment regimens

7.3.1 Wash-out and Run-in period

Patients that are required to wash-out any medication will be dispensed with Atrovent® HFA inhalation aerosol for US patients and Atrovent® Inhaler CFC-Free pressurised inhalation solution for non-US patients to be administered QID during the wash-out and run-in period. Atrovent® will be withheld 6 hours before Visit 1 and Visit 2.

At the moment of the ICF signature or Visit 1 (screening) all subjects will receive relief medication (see Section 7.7.1) to be administered as needed until Visit 2 (randomization).

Instructions will be given to the subject on how to use the inhalers (inhalation technique and priming instructions).

7.3.2 Double-blind treatment period

A double-dummy design will be adopted in the study to achieve blinding. AB/FF 400/12 µg, AB 400 µg, FF 12 µg and placebo to AB/FF 400/12 µg and its monocomponents will be administered via the Pressair®/Genuair®. TIO 18 µg and placebo to TIO 18 µg will be administered via the Handihaler® device. Additionally, blinding will be ensured instructing the site staff that a third party administrator (not involved in other aspects of the study) will administer the IP at site. Patients will be instructed to take 1 dose of study drug from the Pressair®/Genuair® and 1 dose of study drug from the Handihaler® in the morning (09:00 ± 1 h) and one dose from the Pressair®/Genuair® 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.

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, except for the empty training inhalers and capsules that will have an English label only.

At Visit 2 patients will be provided with 3 different kits:

- For (4) Genuair® inhalers (60 doses per inhaler), each inserted in a bag, in one box.
- Ten (10) TIO or placebo to TIO blister cards (10 capsules per blister), in one box.
- One (1) Handihaler® inhaler, in one box.

At Visit 5 patients will be provided with 2 different kits:

- For (4) Genuair® inhalers (60 doses per inhaler), each inserted in a bag, in one box.
- Ten (10) TIO or placebo to TIO blister cards (10 capsules per blister), in one box.

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 (once the inhalers are returned).

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, empty training Pressair®/Genuair® devices and empty TIO capsules will be available at each study site for instructional purposes as well as for subjects to practice the correct inhalation technique. Handihaler® device provided at randomization visit (Visit 2) will be used to perform the training with the empty TIO capsules. Instruction and practice should occur prior to dispensing study medication. The empty training Pressair®/Genuair® devices and empty TIO capsules will be used in the clinic only and will not be dispensed to subjects for use at home.

The total number of IP inhalations from Pressair®/Genuair® device will be recorded twice daily (morning and evening) and the inhalations from the HandiHaler® will be recorded once daily (evening). At each visit, the investigator will review the e-diary data to assess the treatment compliance.

Additionally, the third party administrator will check the returned Pressair®/Genuair® inhalers and tiotropium capsules to ensure that they were used properly and to double-check the number of doses taken against the information recorded on the e-diary. In case of discrepancies or suspected protocol deviations, the investigator will ask the patient to explain such findings, and the discrepancy or deviation will be documented in the medical notes.

The treatment compliance will be calculated for each IP as number of doses/capsules taken respect to the number of doses/capsules 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, Pressair®/Genuair® and Handihaler®. 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 third party administrator will account for all study drugs dispensed to and returned from the subject.

Subjects will be asked to bring all used and unused inhalers/capsules to the site at each on-site visit. The third party administrator will review the inhalers/capsules and will record the doses/capsules taken 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 and documented.

Third party administration 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, relief and wash-out medication), both used and 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

Allowed Medication/Class of drug:	Restrictions	Stabilization period
Inhaled corticosteroids*	Patients who were following a stable regimen of a LABA/ICS combination for at least 4 weeks can be switched to the same inhaled corticosteroid (at the same dose and dose regimen) as monotherapy. In this case no stabilisation period is needed. 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 Screening (Visit 1). 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	4 weeks
Continuous oral or parenteral corticosteroids*	Dose equivalent of 10 mg of prednisone per day or 20 mg every other day or lower than this.	4 weeks

Selective β-blocking agents (eg. Atenolol, metoprolol, nebivolol)	-	2 weeks
Oxygen therapy*	< 15 hours a day	4 weeks
Oral sustained-release theophyllines *	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
Twice daily long-acting inhaled anticholinergics, LAMAs (e.g. aclidinium bromide)	72h
Once daily long-acting inhaled anticholinergics, LAMAs (e.g. umeclidinium, tiotropium bromide, glycopyrrolate)[a]	7 days
Short-acting inhaled anticholinergics, SAMAs (except for ipratropium which is to be administered during the wash-out and run-in period)	6h
Inhaled and short acting β2-agonists, SABAs (eg, fenoterol or albuterol, except for albuterol/salbutamol)	6h
Once daily long-acting β2- agonists (LABAs) (eg, indacaterol, oladaterol) and once daily combination of LABAs+ICS (eg vilanterol/fluticasone)	7 days
Oral (terbutaline) and twice daily LABAs (eg, formoterol, salmeterol) and twice daily combination of LABAs+ICS (eg fluticasone/salmeterol, budesonide/formoterol) *Note: Patients can be switched to the same or a different inhaled corticosteroid as monotherapy (see restricted medication section for stabilization period)*	48 h
Combination of SABAs+SAMA (eg ipratropium/salbutamol)	12h
Combination of LABA+LAMA (eg indacaterol/glycopyrronium, umeclidinium/vilanterol, tiotropium/olodaterol)	7 days
Methyl-xanthines (eg. Theophylline, theobromine tablets)	72h
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

Relief/Wash-out and Run-in Medication/Class of drug:	**Usage:**
Albuterol sulphate 108 µg/puff / Salbutamol pMDI (100 µg/puff) *Note: marketed albuterol/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 and 5h during 24h serial spirometry.
Atrovent® HFA inhalation aerosol for US patients 17 µg /Atrovent® Inhaler CFC-Free pressurised inhalation solution 20 µg for non-US patients	• Administered as a maintenance treatment QID only during the wash-out and run-in period • 6h of wash-out is needed before screening and randomization visit • It should be interrupted before randomization visit

7.8.1 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.

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 randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

8.2. Sample size estimate

Approximately, 2,200 patients will be screened in this trial (considering an estimated ineligibility rate of 30%) to have an overall sample size of 1,500 randomized patients to AB/FF 400/12 µg, AB 400 µg, FF 12 µg, and TIO 18 µg, based on a randomization ratio of 2:3:2:3, which corresponds to 300, 450, 300, and 450 patients per treatment arm, respectively.

Based on hypotheses derived from the evidence shown in our own previous clinical trials, this sample size will provide at least 90% power to detect a statistically significant treatment difference of 100 mL between AB/FF 400/12 µg and AB 400 µg in change from baseline in 1-hour morning post-dose FEV_1 at Week 24, and 65 mL between AB/FF 400/12 µg and FF 12 µg in change from baseline in morning pre-dose (trough) FEV_1 at Week 24, assuming a standard deviation (SD) of 230 mL, using two-sided tests, and adjusting for multiple tests at 5% overall significance level. The expected minimum statistically significant effect is 37 mL in trough FEV_1. This sample size will provide enough power to detect a statistically significant treatment difference of 100 mL between AB/FF 400/12 µg and AB 400 µg and FF 12 µg in change from baseline in normalized AUC_{0-3} FEV_1 at week 24, assuming a SD of 220 mL.

The responder analysis of the SGRQ total score based on a decrease of at least 4-units from baseline will be tested, comparing AB/FF 400/12 µg versus both individual components.

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

Primary and secondary efficacy variables for US and Market Access are as follow:

	Step	Endpoint	Treatment Comparison
US Primary Endpoints	1	1-hour postdose FEV_1	AB/FF 400/12 µg vs. AB 400 µg
	2	Morning predose FEV_1	AB/FF 400/12 µg vs. FF 12 µg
Market Access Primary Endpoint	1	Morning predose FEV_1 at Week 24 is above -50 mL (non-inferiority limit)	AB 400 µg vs. TIO 18 µg
Secondary Endpoints	3	$nAUC_{0-3}$ FEV_1	AB/FF 400/12 µg vs. AB 400 µg
	4	$nAUC_{0-3}$ FEV_1	AB/FF 400/12 µg vs. FF 12 µg
	5	Responder analysis of SGRQ total score	AB/FF 400/12 µg vs. AB 400 µg
	6	Responder analysis of SGRQ total score	AB/FF 400/12 µg vs. FF 12 µg

The order of the hierarchy of endpoints and treatment comparisons is detailed in section 8.5.5.

This sample size will have 90% power to show that the lower bound of the two-sided 95% confidence interval for the difference between AB 400 µg and TIO 18 µg in change from baseline in morning pre-dose (trough) FEV_1 at Week 24 is above -50 mL (non-inferiority limit), assuming that the expected difference is 0 mL, and a SD of 230 mL.

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 (except for exacerbations) will be performed on the Intention-to Treat (ITT) population. The analysis of exacerbations will be performed on the Safety population. The analysis for Market Access will be performed on the Per Protocol (PP) population. All safety outcomes and other variables will be analysed using the Safety population.

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 Randomized analysis set

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

8.3.3 Safety analysis set

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

8.3.4 Efficacy analysis

The ITT population is defined as all randomized 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 randomized treatment.

The 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).

8.3.5 PK analysis set

Not applicable

8.3.6 PRO analysis set

Not applicable

8.4. Outcome measures for analyses

8.4.1 Primary efficacy variable for US

The co-primary variables are the following:

- Change from baseline in 1-hour morning post-dose dose FEV_1 of AB/FF 400/12 µg compared to AB 400 µg at week 24.

- Change from baseline in morning pre-dose (trough) FEV_1 of AB/FF 400/12 µg compared to FF 12 µg at week 24.

Morning pre-dose (trough) FEV_1 is defined as the average of the corresponding -30 and 0 minute time points 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 for US

The secondary variables are the following:

- Change from baseline in normalized $AUC_{0\text{-}3/3h}$ FEV_1 of AB/FF 400/12 µg compared to AB 400 µg at week 24.

- Change from baseline in normalized $AUC_{0\text{-}3/3h}$ FEV_1 of AB/FF 400/12 µg compared to FF 12 µg at week 24.

- Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4 units from baseline) of AB/FF 400/12 µg compared to AB 400 µg at week 24.

- Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4 units from baseline) of AB/FF 400/12 µg compared to FF 12 µg at week 24.

8.4.3 Primary efficacy variable

- Change from baseline in morning pre-dose (trough) FEV_1 at week 24 comparing AB 400 µg BID versus TIO 18 µg to demonstrate non-inferiority

8.4.4 Additional efficacy variables

Pulmonary Function Tests:

- Change from baseline in FEV_1 5 minutes after the first dose of AB/FF 400/12 µg on Day 1 (onset of action).

- Change from baseline in morning pre-dose FEV_1 and FVC at all visits, except for primary variables at week 24.

- Morning pre-dose FEV_1 and FVC at all visits.
- Change from baseline in FEV_1 and FVC by time point at all visits, except for the primary variable.
- FEV_1 and FVC by time point at all visits.
- Change from baseline in normalized area under curve from time 0 to 3 hours ($AUC_{0-3/3h}$) FEV_1 and FVC at Day 1 and at week 24 (except for $AUC_{0-3/3h}$ FEV_1 at week 24).
- Change from baseline in peak FEV_1 and FVC at Day 1 and at week 24.

Signs and Symptoms and Health-related Quality of Life:

- Change from baseline in SGRQ total score and three dimension scores at weeks 4, 12, 18 and 24.
- Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4 units from baseline) compared with baseline in SGRQ total score at Weeks 4, 12, 18 and 24.
- Change from baseline in the CAT score at weeks 4, 12, 18 and 24
- Number (%) of patients achieving a clinically meaningful improvement (≥2 units) in CAT total score at weeks 4, 12, 18 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, mild, moderate, severe, 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 relief 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).
- Change from baseline in the use of relief medication at all visits and over 24 weeks.

8.4.5 Safety outcomes

- Adverse Events (AEs)/Serious Adverse Events (SAEs)
- Clinical laboratory test (hematology and biochemistry)
- Blood pressure
- 12-lead ECG
- Major Adverse Cardiac Events (MACE)

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. 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 including all data captured during the 24-week double-blind treatment period, and under Missing-Not-At-Random (MNAR) assumptions.

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

For all patients with 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.

8.5.1 Demographic and patient characteristics

All variables in this section will be analyzed using the FAS.

Demographics and patient characteristics will be summarized by treatment group using frequency and percentages (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median, Q1, Q3 and maximum (for continuous variables).

8.5.2 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. In addition, frequency and percentages of withdrawal from the study together with reasons will be presented.

8.5.3 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.

8.5.4 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.

8.5.5 Analysis of the primary variable (s)

Co-primary endpoints:

The analyses of the co-primary variables will be performed on ITT. Safety outcomes and exacerbations will be analysed on the Safety population. The analysis for Market Access comparing AB 400 µg BID versus TIO 18 µg to demonstrate non-inferiority will be performed on the Per Protocol population. Moreover, smoking-status and country will be used as a treatment allocation factor during the randomization process.

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

An unstructured covariance pattern will be used to estimate the variance-covariance of the within-subject repeated measures. Parameters will be estimated using REML with Newton-Raphson algorithm and using the Kenward-Roger method for calculating the denominator degrees of freedom. In case of not convergence, the compound symmetry covariance pattern will be used.

Each treatment effect and treatment differences between all treatments will be estimated by the Least Square means (LS Means) on the correspondent treatment-by-visit interaction, along with their standard errors (SE) and 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.

For non-inferiority comparison between AB 400 µg and TIO 18 µg in change from baseline in morning pre-dose (trough) FEV_1 at Week 24 the lower bound of the tow-sided 95% confidence interval should be above -50 mL (non-inferiority limit). The comparison between AB 400 µg and TIO 18 µg in change from baseline in morning pre-dose (trough) FEV_1 at week 24 will be analyzed by means of mixed model for repeated measures (MMRM). The model will adjust for pre and post bronchodilator (albuterol/salbutamol) FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group, sex, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors, and country as random effect.

8.5.6 Analysis of the secondary variable(s)

The same MMRM model used for the co-primary endpoints will be used for the change from baseline in normalized AUC_{0-3} FEV_1 at week 24.

The number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4 units from baseline) compared to both individual components in the SGRQ total score will be analyzed based on a logistic random-effect model using GLIMMIX that includes a random intercept to account the variability between subjects, and treatment, sex, smoking-status, country, visit, and treatment group-by-visit interaction as fixed factors, and with age and the corresponding baseline as covariates

8.5.7 Multiplicity control

Different multiplicity approaches will be considered for each region for the US and for Market Access. Two different SAPs will be developed so that the same trial data separately will address the different standards of each region.

For the US filing, primary and secondary endpoints will be adjusted for controlling the family-wise type I error and carried out at 5% significance level according to a pre-specified fixed order in the sequence specified in the Table 3. Each endpoint in the hierarchy must be rejected at the 5% level in order to test the next one in the sequence at the 5% level. This strategy of sequential testing procedure controls the overall type I error at the 0.05 significance level.

Table 3 Pre-specified Sequence of Testing for Multiplicity Adjustment

Testing Order in Hierarchy	Endpoint (at week 24)	Treatment Comparison
1	1-hour postdose FEV1	AB/FF 400/12 µg vs. AB 400 µg
2	Morning predose FEV_1	AB/FF 400/12 µg vs. FF 12 µg
3	$nAUC_{0-3}$ FEV_1	AB/FF 400/12 µg vs. AB 400 µg
4	$nAUC_{0-3}$ FEV_1	AB/FF 400/12 µg vs. FF 12 µg
5	Responder analysis of SGRQ total score	AB/FF 400/12 µg vs. AB 400 µg
6	Responder analysis of SGRQ total score	AB/FF 400/12 µg vs. FF 12 µg

Note: Both co-primary endpoints (the first two testing hypothesis) should overcome the statistical hierarchy to meet the primary bronchodilator objective

For Market Access, the non-inferiority between AB 400 µg and TIO 18 µg in change from baseline in morning pre-dose (trough) FEV_1 at week 24 will be tested at a significance level of 0.05.

8.5.8 Subgroup analysis (if applicable)

Subgroup analyses (if applicable) will be described in the SAP.

8.5.9 Interim analysis

Not applicable

8.5.10 Sensitivity analysis

All data captured during the 24-week double-blind treatment period, defined as the period after administration of randomized investigational product at Visit 2 (Week 0). This includes data regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence, unless the patient withdraws consent to study participation.

Sensitivity analysis will be carried out for the co-primary and secondary endpoints including all data captured during the 24-week double-blind period and based on the direct likelihood approach, and adjusting the same statistical models described in sections 8.5.3 and 8.5.4. 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 is not available.

In addition, sensitivity analyses based on imputation using drop out reasons (IUDR) will be explored and added to the SAP if deem appropriate. To assess the robustness to variations of the missing data assumptions on the co-primary efficacy endpoints, sensitivity analyses will be conducted such as copy reference approach.

A sensitivity analysis will be carried out for all patients with exacerbations, SAE, and concomitant medication, including data captured during the 24-week double-blind period.

Further details will be provided in the SAP.

8.5.11 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. For example, the same MMRM model used for the co-primary endpoint will be used for the analysis of the change from baseline in FEV_1 5 minutes after the first dose of AB/FF 400/12 µg on Day 1 (onset of action). Dichotomous variables will be analysed by means of logistic regression models.

The rate of moderate to severe COPD exacerbations (HCRU) of AB 400 µg/FF 12 µg compared to AB 400 µg and FF 12 µg over 24 weeks of treatment will be modelled through negative binomial regression models including age as a covariate, and sex, baseline ICS use (yes/no), baseline COPD severity, smoking status, country, and treatment group as factors (the log exposure in years will be included as an offset).

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 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 analyzed will be provided in the SAP.

8.5.12 Analyses of safety and tolerability outcomes

Subjects will be analyzed according to the randomized treatment assignment and based on IP intake treatment period. Any major deviations from the randomized treatment assignment will be listed and considered when interpreting the safety data.

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 or if it started before treatment but its severity worsened afterwards. Adverse event 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), Major Adverse Cardiac Events (MACE), and 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, high level term, preferred term as well as SMQs for AEs of interest, 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 Fridericia's formula. The incidence of clinically notable ECG abnormalities will be summarized.

8.5.13 Exploratory Analysis

Not applicable.

8.5.14 Deviations from the planned analyses

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

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 PI 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 PI 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 [Clinical Research Associate (CRA) and CMA] 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 ICF of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)

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 CSA for location of source data.

9.2.2 Study agreements

The PI at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, 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 CSA shall prevail.

Agreements between AstraZeneca/CRO and the PI 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 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 Q2 2016 and to end by Q1 2018.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (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 AB or FF.

9.4. Data management

Data Management (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 Clinical Data Interchange Standards Consortium (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 Enhanced. 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 DMP. 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, 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 International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2. Subject data protection

The ICF 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 EC should approve the final study protocol, including the final version of the ICF 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 EC, and to the study site staff.

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

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

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

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

Before enrolment of any subject into the study, the final study protocol, including the final version of the ICF, 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, ECs and PIs with safety updates/reports according to local requirements.

10.4. Informed consent

The PI 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 ICF before conducting any procedure specifically for the study
- Ensure the original, signed ICFs are stored in the Investigator's Study File

- Ensure a copy of the signed ICF 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 ICF that is approved by an EC.

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 EC 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 PI. For distribution to EC see Section10.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's EC are to approve the revised ICF before the revised form is used.

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

10.6. Audits and inspections

Authorised representatives of AstraZeneca/CRO, a regulatory authority, or an EC 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, GCP, ICH guidelines 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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Tudorza® Pressair® US Prescribing Information Apr 2015
Tudorza® Pressair® US Prescribing Information Apr 2015

Appendix A 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 (eg, 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 (eg, 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 B International Airline Transportation Association (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 C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

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.

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 IMP, 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 (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

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

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

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits

Follow-up

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.

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

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 IMP. 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

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 D Saint George Respiratory Questionnaire (SGRQ)

Screen Title	Question Text	Response Values
SGRQ	**The St. George's Respiratory Questionnaire** This questionnaire is designed to help us learn 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 the most problems, rather than what the doctors and nurses think your problems are.	-
SGRQ	Please read the instructions carefully and ask if you do not understand anything. Do not spend a long time deciding on your answers.	
SGRQ	Please select response to show how you describe your current health:	4 = Very good 3 = Good 2 = Fair 1 = Poor 0 = Very poor
SGRQ	**The St. George's Respiratory Questionnaire** **PART 1** Please describe how often your respiratory problems have affected you over the past 4 weeks.	-
SGRQ	Over the past 4 weeks, I have coughed:	4 = almost every day 3 = several days a week 2 = a few days a month 1 = only with respiratory infections 0 = not at all
SGRQ	Over the past 4 weeks, I have brought up phlegm (sputum):	4 = almost every day 3 = several days a week 2 = a few days a month 1 = only with respiratory infections 0 = not at all
SGRQ	Over the past 4 weeks, I have had shortness of breath:	4 = almost every day 3 = several days a week 2 = a few days a month 1 = only with respiratory infections 0 = not at all

Screen Title	Question Text	Response Values
SGRQ	Over the past 4 weeks, I have had wheezing attacks:	4 = almost every day 3 = several days a week 2 = a few days a month 1 = only with respiratory infections 0 = not at all
SGRQ	How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?	4 = more than 3 times 3 = 3 times 2 = 2 times 1 = 1 time 0 = none of the time
SGRQ	How long did the worst respiratory attack last?	3 = a week or more 2 = 3 or more days 1 = 1 or 2 days 0 = less than a day
SGRQ	Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?	0 = No good days 1 = 1 or 2 good days 2 = 3 or 4 good days 3 = nearly every day was good 4 = every day was good
SGRQ	If you wheeze, is it worse when you get up in the morning?	0 = No 1 = Yes
SGRQ	**The St. George's Respiratory Questionnaire** **Part 2**	-
SGRQ	**Section 1** How would you describe your respiratory condition?	3 = The most important problem I have 2 = Causes me quite a lot of problems 1 = Causes me a few problems 0 = Causes no problem

Screen Title	Question Text	Response Values
SGRQ	If you have ever held a job, please select only one.	3 = My respiratory problems made me stop working altogether 2 = My respiratory problems interfere with my job or made me change my job 1 = My respiratory problems do not affect my job
SGRQ	**Section 2:** **These are questions about what activities usually make you feel short of breath these days.**	–
SGRQ	These are questions about what activities usually make you feel short of breath these days. Please select the response that applies to you **these days**: Sitting or lying still	1 = True 0 = False
SGRQ	These are questions about what activities usually make you feel short of breath these days. Please select the response that applies to you **these days**: Washing or dressing yourself	1 = True 0 = False
SGRQ	These are questions about what activities usually make you feel short of breath these days. Please select the response that applies to you **these days**: Walking around the house	1 = True 0 = False
SGRQ	These are questions about what activities usually make you feel short of breath these days. Please select the response that applies to you t**hese days**: Walking outside on level ground	1 = True 0 = False
SGRQ	These are questions about what activities usually make you feel short of breath these days. Please select the response that applies to you **these days**: Walking up a flight of stairs	1 = True 0 = False

Screen Title	Question Text	Response Values
SGRQ	These are questions about what activities usually make you feel short of breath these days. Please select the response that applies to you **these days**: Walking up hills	1 = True 0 = False
SGRQ	These are questions about what activities usually make you feel short of breath these days. Please select the response that applies to you **these days**: Playing sports or other physical activities	1 = True 0 = False
SGRQ	**Section 3:** **These are more questions about your cough and shortness of breath these days.**	-
SGRQ	These are more questions about your cough and shortness of breath these days. Please select the response that applies to you **these days**: Coughing hurts	1 = True 0 = False
SGRQ	These are more questions about your cough and shortness of breath these days. Please select the response that applies to you **these days**: Coughing makes me tired	1 = True 0 = False
SGRQ	These are more questions about your cough and shortness of breath these days. Please select the response that applies to you **these days**: I am short of breath when I talk	1 = True 0 = False
SGRQ	These are more questions about your cough and shortness of breath these days. Please select the response that applies to you **these days**: I am short of breath when I bend over	1 = True 0 = False

Screen Title	Question Text	Response Values
SGRQ	These are more questions about your cough and shortness of breath these days. Please select the response that applies to you **these days**: My coughing or breathing disturbs my sleep	1 = True 0 = False
SGRQ	These are more questions about your cough and shortness of breath these days. Please select the response that applies to you **these days**: I get exhausted easily	1 = True 0 = False
SGRQ	**Section 4:** **These are questions about other effects that your respiratory problems may have on you <u>these days.</u>**	–
SGRQ	These are questions about other effects that your respiratory problems may have on you these days. Please select the response that applies to you **these days**: My cough or breathing is embarrassing in public	1 = True 0 = False
SGRQ	These are questions about other effects that your respiratory problems may have on you these days. Please select the response that applies to you **these days**: My respiratory problems are a nuisance to my family, friends or neighbors	1 = True 0 = False
SGRQ	These are questions about other effects that your respiratory problems may have on you these days. Please select the response that applies to you **these days**: I get afraid or panic when I cannot catch my breath	1 = True 0 = False
SGRQ	These are questions about other effects that your respiratory problems may have on you these days. Please select the response that applies to you **these days**: I feel that I am not in control of my respiratory problems	1 = True 0 = False

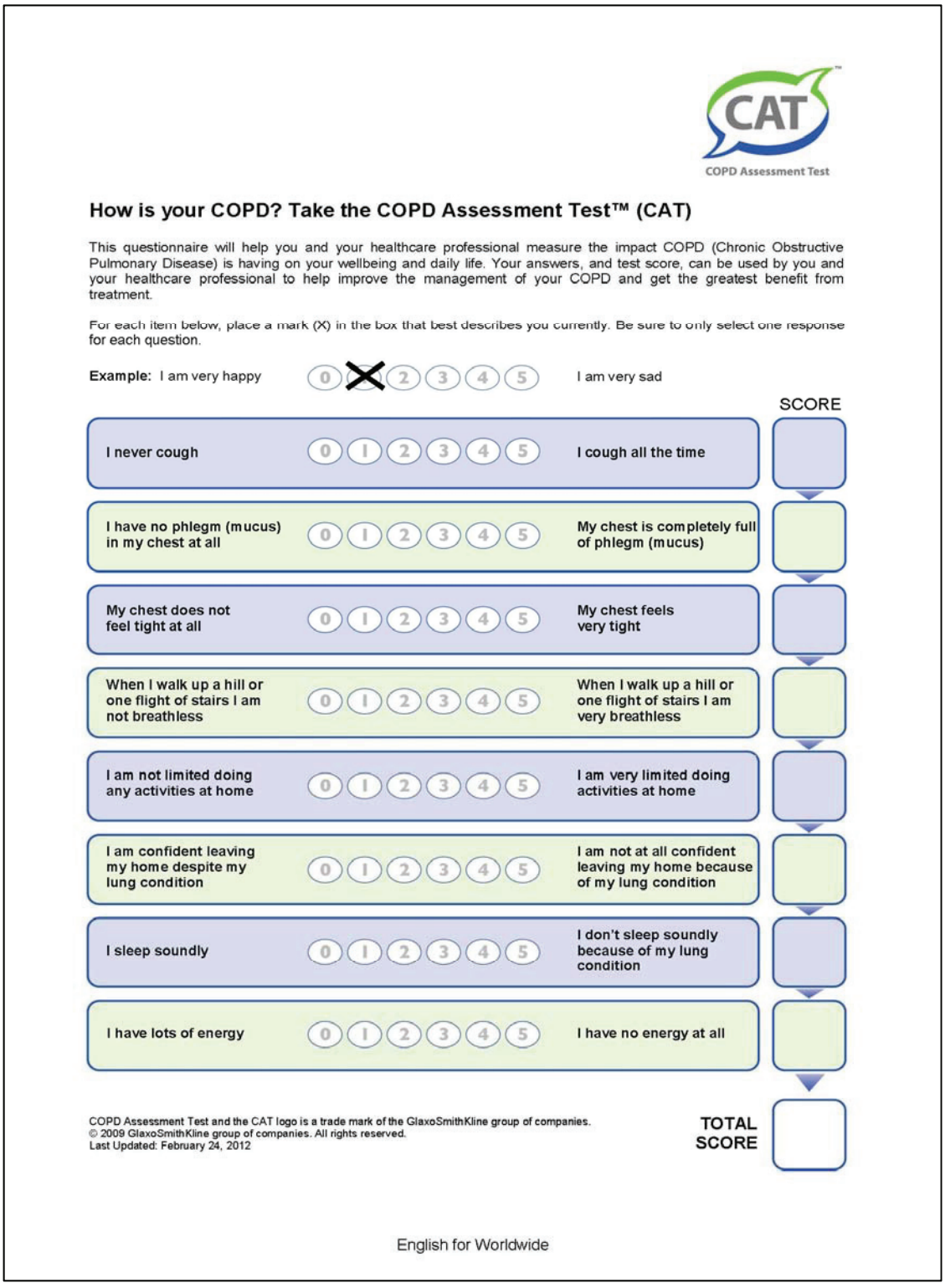
Screen Title	Question Text	Response Values
SGRQ	These are questions about other effects that your respiratory problems may have on you these days. Please select the response that applies to you **these days**: I do not expect my respiratory problems to get any better	1 = True 0 = False
SGRQ	These are questions about other effects that your respiratory problems may have on you these days. Please select the response that applies to you **these days**: I have become frail or an invalid because of my respiratory problems	1 = True 0 = False
SGRQ	These are questions about other effects that your respiratory problems may have on you these days. Please select the response that applies to you **these days**: Exercise is not safe for me	1 = True 0 = False
SGRQ	These are questions about other effects that your respiratory problems may have on you these days. Please select the response that applies to you **these days**: Everything seems too much of an effort	1 = True 0 = False
SGRQ	**Section 5:** **These are questions about your respiratory treatment.**	–
SGRQ	These are questions about your respiratory treatment. Please select the response that applies to you **these days**: My treatment does not help me very much	1 = True 0 = False
SGRQ	These are questions about your respiratory treatment. Please select the response that applies to you **these days**: I get embarrassed using my medication in public	1 = True 0 = False
SGRQ	These are questions about your respiratory treatment. Please select the response that applies to you **these days**: I have unpleasant side effects from my medication	1 = True 0 = False

Screen Title	Question Text	Response Values
SGRQ	These are questions about your respiratory treatment. Please select the response that applies to you **these days**: My medication interferes with my life a lot.	1 = True 0 = False
SGRQ	**Section 6:** **These are questions about how your activities might be affected by your respiratory problems.**	-
SGRQ	Please select the response that applies to you **because of your respiratory problems:** I take a long time to get washed or dressed	1 = True 0 = False
SGRQ	Please select the response that applies to you **because of your respiratory problems:** I cannot take a bath or shower, or I take a long time to do it	1 = True 0 = False
SGRQ	Please select the response that applies to you **because of your respiratory problems:** I walk slower than other people my age, or I stop to rest	1 = True 0 = False
SGRQ	Please select the response that applies to you **because of your respiratory problems:** Jobs such as household chores take a long time, or I have to stop to rest	1 = True 0 = False
SGRQ	Please select the response that applies to you **because of your respiratory problems:**. If I walk up one flight of stairs, I have to go slowly or stop	1 = True 0 = False
SGRQ	Please select the response that applies to you **because of your respiratory problems:** If I hurry or walk fast, I have to stop or slow down	1 = True 0 = False
SGRQ	Please select the response that applies to you **because of your respiratory problems:** My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, bowl or play golf	1 = True 0 = False
SGRQ	Please select the response that applies to you **because of your respiratory problems:** My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	1 = True 0 = False

Screen Title	Question Text	Response Values
SGRQ	Please select the response that applies to you **because of your respiratory problems:** My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	1 = True 0 = False
SGRQ	**Section 7:** **We would like to know how your respiratory problems <u>usually</u> affect your daily life.**	-
SGRQ	Please select the response that usually applies to you **because of your respiratory problems:** I cannot play sports or do other physical activities	1 = True 0 = False
SGRQ	Please select the response that usually applies to you **because of your respiratory problems:** I cannot go out for entertainment or recreation	1 = True 0 = False
SGRQ	Please select the response that usually applies to you **because of your respiratory problems:** I cannot go out of the house to do the shopping	1 = True 0 = False
SGRQ	Please select the response that usually applies to you **because of your respiratory problems:** I cannot do household chores	1 = True 0 = False
SGRQ	Please select the response that usually applies to you **because of your respiratory problems:** I cannot move far from my bed or chair	1 = True 0 = False
SGRQ	**There is a list on the following screen of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):**	–
SGRQ	Going for walks or walking the dog Doing activities or chores at home or in the garden Sexual intercourse Going to a place of worship, or a place of entertainment Going out in bad weather or into smoky rooms Visiting family or friends or playing with children	–

Screen Title	Question Text	Response Values
SGRQ	Please select the response that you think best describes how your respiratory problems affect you:	1 = It does not stop me from doing anything I would like to do 2 = It stops me from doing one or two things I would like to do 3 = It stops me from doing most of the things I would like to do 4 = It stops me from doing everything I would like to do
SGRQ	**Thank you for completing this questionnaire**	–
SGRQ	Copyright reserved P.W. Jones, PhD FRCP Professor of Respiratory Medicine, St. George's University of London, Jenner Wing, Cranmer Terrace, London SW17 ORE, UK.	–
SGRQ	Site: Participant Code: Thank you. You have provided all required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.	N/A

Appendix E COPD ASSESSMENT TEST (CAT)



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 1 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

English for Worldwide

Appendix F EXACT and E-RS™: COPD

Description	Required Text	Translation
Title	EXACT Daily Diary	EXACT Daily Diary
DD	Daily Diary	Daily Diary
Q 1 of 14	Question 1 {1} of 14	Question 1 {1} of 14
Instructions	As you answer the following questions, please select the option that best describes your experience.	As you answer the following questions, please select the option that best describes your experience.
1		
	Did your chest feel congested today?	Did your chest feel congested today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
2		
	How often did you cough today?	How often did you cough today?
	Not at all	Not at all
	Rarely	Rarely
	Occasionally	Occasionally
	Frequently	Frequently
	Almost constantly	Almost constantly
3		
	How much mucus (phlegm) did you bring up when coughing today?	How much mucus (phlegm) did you bring up when coughing today?
	None at all	None at all
	A little	A little
	Some	Some
	A great deal	A great deal
	A very great deal	A very great deal

4		
	How difficult was it to bring up mucus (phlegm) today?	How difficult was it to bring up mucus (phlegm) today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Quite a bit	Quite a bit
	Extremely	Extremely
5		
	Did you have chest discomfort today?	Did you have chest discomfort today?
	Not at all	Not at all
	Slight	Slight
	Moderate	Moderate
	Severe	Severe
	Extreme	Extreme
6		
	Did your chest feel tight today?	Did your chest feel tight today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
7		
	Were you breathless today?	Were you breathless today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely

8		
	Describe how breathless you were today:	Describe how breathless you were today:
	Unaware of breathlessness	Unaware of breathlessness
	Breathless during strenuous activity	Breathless during strenuous activity
	Breathless during light activity	Breathless during light activity
	Breathless when washing or dressing	Breathless when washing or dressing
	Present when resting	Present when resting
9		
	Were you short of breath today when performing your usual personal care activities like washing or dressing?	Were you short of breath today when performing your usual personal care activities like washing or dressing?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
10		
	Were you short of breath today when performing your usual indoor activities like cleaning or household work?	Were you short of breath today when performing your usual indoor activities like cleaning or household work?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	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?	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
12		
	Were you tired or weak today?	Were you tired or weak today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
13		
	Last night, was your sleep disturbed?	Last night, was your sleep disturbed?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely

14		
	How scared or worried were you about your lung problems today?	How scared or worried were you about your lung problems today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
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Training Material	Recommended Text	Translation (if available)
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.	Please complete your diary every evening, just before you go to bed.

Appendix G Night-time and Early Morning Symptoms (NiSCI and EMSCI)

Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI): Post psychometric validation version :
-Universal English Version: 15 May 2014-

Instructions

- We would like you to complete this diary every day, in the morning, anytime between 7 AM and 11 AM.
- The diary asks you questions about the symptoms of your chronic obstructive pulmonary disease, also called COPD.
- COPD is a lung disease that makes breathing difficult.

The diary is made up of two parts:

1. The first part of the diary asks you a few questions about your COPD symptoms LAST NIGHT.
   - » When you think about LAST NIGHT, we would like you to think about the time from when you went to bed last night until you woke up and got out of bed this morning to start your day.
2. The second part of the diary asks you a few questions about your COPD symptoms after you woke up this morning.
   - » When you think about THIS MORNING, please think about the time since you got out of bed to start your day.

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Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI): Post psychometric validation version :
-Universal English Version: 15 May 2014-

NiSCI

This is the first part of the diary that asks you about your COPD symptoms LAST NIGHT.

When you think about LAST NIGHT, we would like you to think about the time from when you went to bed last night until you woke up and got out of bed this morning to start your day.

Please complete the NIGHTTIME SYMPTOM diary now.

---

1. Last night, did you wake up because of your COPD symptoms?
☐ No
☐ Yes

1a. How many times did you wake up because of your COPD symptoms?
_____times

---

2. Did you experience any of the following last night?

2a. Cough	☐ No	☐ Yes
2b. Wheezing	☐ No	☐ Yes
2c. Shortness of breath	☐ No	☐ Yes
2d. Tightness in your chest	☐ No	☐ Yes
2e. Chest congestion	☐ No	☐ Yes
2f. Difficulty bringing up phlegm	☐ No	☐ Yes

You indicated that you experienced a cough last night…

2a.i. How severe was your cough?
☐ Mild
☐ Moderate
☐ Severe
☐ Very Severe

You indicated that you experienced wheezing last night…

2b.i. How severe was your wheezing?
☐ Mild
☐ Moderate
☐ Severe
☐ Very Severe

You indicated that you experienced shortness of breath last night…

2c.i. How severe was your shortness of breath?
☐ Mild
☐ Moderate
☐ Severe
☐ Very Severe

Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI): Post psychometric validation version :
-Universal English Version: 15 May 2014-

You indicated that you experienced tightness in your chest last night…

2d.i. How severe was the tightness in your chest?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced chest congestion last night…

2e.i. How severe was your chest congestion?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced difficulty bringing up phlegm last night…

2f.i. How severe was the difficulty with bringing up phlegm?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

---

3. Overall, how severe were your COPD symptoms last night?
- ☐ I did not experience any symptoms
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

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Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI): Post psychometric validation version :
-Universal English Version: 15 May 2014-

EMSCI

This is the second part of the diary.

This part asks you about your COPD symptoms THIS MORNING.

When you think about THIS MORNING, please think about the time since you got out of bed to start your day.

---

1. Did you experience any of the following this morning?

1a. Cough	☐ No	☐ Yes
1b. Wheezing	☐ No	☐ Yes
1c. Shortness of breath	☐ No	☐ Yes
1d. Tightness in your chest	☐ No	☐ Yes
1e. Chest congestion	☐ No	☐ Yes
1f. Difficulty bringing up phlegm	☐ No	☐ Yes

You indicated that you experienced a cough this morning…

1a.i. How severe was your cough?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced wheezing this morning…

1b.i. How severe was your wheezing?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced shortness of breath this morning…

1c.i. How severe was your shortness of breath?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced tightness in your chest this morning…

1d.i. How severe was the tightness in your chest?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced chest congestion this morning…

Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI): Post psychometric validation version :
-Universal English Version: 15 May 2014-

1e.i. How severe was your chest congestion?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced difficulty bringing up phlegm this morning…

1f.i. How severe was the difficulty with bringing up phlegm?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

---

2. Overall, how severe were your COPD symptoms this morning?
- ☐ I did not experience any symptoms
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

---

3. How much have you limited your activities this morning because of your COPD symptoms?
- ☐ Not at all
- ☐ A little
- ☐ Moderately
- ☐ A good deal
- ☐ A very great deal

CCI

Appendix H Device Preference and willingness to continue questionnaire

Device Preference

Which device do you prefer?:
(Please, tick one box only)

☐ Genuair/Pressair®

☐ HandiHaler®

☐ No preference

Which device do you prefer in term of the following attributes?
(Please, tick one box only)

Attribute	Which do you prefer ... ?
Ease of use	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Convenience	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Ease of learning to use	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Ease of holding	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Ease of operating	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Ease of preparation of the dose	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Feedback to indicate correct inhalation	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference

Willingness to continue

Please rate the extend to which you would be willing to continue using each of the devices:
(Please, write a number between "0 = not willing" and "100 = definitely willing" in the space provided below)

- Genuair/Pressair® ☐☐☐
- HandiHaler® ☐☐☐

Clinical Study Protocol - Addendum

Drug Substance	Aclidinium bromide/ Formoterol Fumarate
Study Code	D6571C00001
Addendum Version	3.0
Date	21 March 2016

Addendum

A 24 week treatment, multicenter, randomized, double blinded, double dummy, parallel-group, clinical trial evaluating the efficacy and safety of aclidinium bromide 400 µg/formoterol fumarate 12 µg fixed-dose combination BID compared with each monotherapy (aclidinium bromide 400 µg BID and formoterol fumarate 12 µg BID) and tiotropium 18 µg QD when administered to patients with stable chronic obstructive pulmonary disease

Sponsor: *AstraZeneca AB, 151 85 Södertälje, Sweden*

ASTRAZENECA SIGNATURE(S)

A 24 week treatment, multicenter, randomized, double blinded, double dummy, parallel-group, clinical trial evaluating the efficacy and safety of aclidinium bromide 400 µg/formoterol fumarate 12 µg fixed-dose combination BID compared with each monotherapy (aclidinium bromide 400 µg BID and formoterol fumarate 12 µg BID) and tiotropium 18 µg QD when administered to patients with stable chronic obstructive pulmonary disease.

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representatives

PPD

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21/MAR/16
Date
(Day Month Year)

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