Clinical Study Protocol

Drug Substance	Symbicort
Study Code	D589CL00003
Edition Number	3.0
Date	03 October 2016

A randomized clinical study to assess the impact of Symbicort® pMDI medication reminders on adherence in COPD patients

Sponsor: AstraZeneca Pharmaceuticals LP ██████████████████

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1	29 June 2016		
2	03 October 2016		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A randomized clinical study to assess the impact of Symbicort® pMDI medication reminders on adherence in COPD patients

Study site(s) and number of subjects planned

Approximately six study sites within the United States (US) will enroll approximately 487 subjects in order to randomize a total of 414 adult subjects with chronic obstructive pulmonary disease (COPD).

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2016	Phase IV
Estimated date of last subject completed	Q3 2017	Phase IV

Study design

This is a 26-week, 2-arm, randomized, multicenter, phase IV study to evaluate the impact of medication reminders on adherence to Symbicort pressurized metered-dose inhaler (pMDI), budesonide/formoterol, 160/4.5 µg x 2 actuations twice daily (bid) in subjects with COPD. This study will randomize approximately 414 subjects.

At the enrollment visit (Visit 1) entry criteria will be confirmed. Subjects who are already on Symbicort and have met all eligibility criteria will be randomized at Visit 1 and will directly enter a 26-week treatment period (no run-in period). Subjects who are taking another inhaled corticosteroid/long-acting β-agonist (ICS/LABA) combination at a dose approved for COPD at Visit 1 will be converted to Symbicort pMDI and will enter a 25-day run-in period after which they will attend Visit 2. Subjects who still meet the eligibility criteria will be randomized at Visit 2 to the 26-week treatment period. Subjects who entered the study on Symbicort will not participate in Visit 2.

Subjects will be randomized (1:1) to receive current care and a medication usage monitoring device (control group) or current care, a medication usage monitoring device and a supportive service (intervention group). The service known as 'BreatheMate' includes a BreatheMate bluetooth device that monitors daily Symbicort inhaler use and a cellular phone application that provides support for subjects in the intervention group who are using Symbicort as part of their COPD maintenance therapy. All subjects will receive a BreatheMate bluetooth monitoring device that will monitor daily Symbicort inhaler use, as well as a study-supplied cellular phone that is paired with the BreatheMate device and used to transmit data regarding

Symbicort usage. Subjects in the intervention group will also receive audio-visual daily reminders (beeps and flashes) on the BreatheMate bluetooth monitoring device to take their Symbicort, and medication reminders from the cellular phone application. Subjects in the control group will not receive any reminders.

Subjects will be provided with a helpline phone number should they have any questions regarding use of the BreatheMate device or application. All subjects will also receive a telephone call from the study site coordinator 4 days after randomization to help resolve any issues they may have using the BreatheMate device or using the application (intervention group only). In addition, 14 days after the randomization visit, all subjects' data will be checked by the study coordinator. If it appears that there is a technical issue (i.e., no data has been received from subjects following the enrollment visit), subjects will be contacted to assess if there are any potential technical issues, for example low signal (poor communication of phone signal) or issues due to removing the inhaler from the device. Subjects may be asked to return to the clinic to receive additional training as required. All subjects will receive a telephone call 90 days after randomization, to assess any adverse events (AEs) experienced, along with concomitant medication use. There will be a final clinic visit (Visit 3) for all subjects at the end of the 26-week/6-month treatment period, as well as a follow-up phone call 30 days thereafter. The follow-up phone call will assess any AEs experienced since Visit 3, along with concomitant medication use.

Objectives

Primary Objective:	Outcome Measure:
Demonstrate the impact of the BreatheMate medication reminders on adherence to Symbicort in COPD patients.	Adherence measured as mean number of sets of puffs/day for the entire 6 month study period. Example: Mean of 2.00 would be equal to 100% adherence (2 sets of 2 puffs). To constitute as a set, 2 puffs must be taken within 60 minutes.
Secondary Objectives:	Outcome Measure:
Demonstrate improved symptom control from baseline with use of medication reminders.	Mean Clinical COPD Questionnaire (CCQ) symptom score (total, symptom, mental, and function score) in the control vs. intervention group at baseline, end of study, and change over the 6 month period. Mean total and domain weekly CCQ scores for each 2 month study interval (intervention group only).

Demonstrate the impact of the BreatheMate medication reminders on additional adherence measures.	Mean number of sets of puffs/day for each 2-month study interval.
	Mean and total number of adherent days (2 sets of 2 puffs per day) per subject.
	Mean number of prescription refills at pharmacy

Target subject population

The target population includes patients (men or women) ≥40 years of age, who are current or past smokers with at least a 10 pack-year cigarette smoking history and a diagnosis of moderate to very severe COPD. COPD must be confirmed by a spirometry-verified post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio of <0.70 at any time in the last 3 years. Most recent post-bronchodilator FEV1 should be <80% of predicted. Patients must be on an ICS/LABA indicated for COPD, and are already being treated with or are willing to convert to Symbicort at a dose labelled for COPD. Patients are required to have been on a stable dose of ICS/LABA combination products approved for COPD for at least 3 months prior to Visit 1. Additional medications for the treatment of COPD are allowed, if usage has been stable for at least 3 months. Patients are not eligible for study enrollment if they have had an acute exacerbation of COPD that required hospitalization or urgent ER visit, or treatment with systemic steroids or antibiotics, or both during the 28 day period prior to Visit 1, or if they have a known malignancy, clinical disease, or disorder which in the Investigator's opinion may put them at risk because of their participation. At Visit 2, patients who convert to Symbicort will be asked if they have had a COPD exacerbation during the run-in period. Should a COPD exacerbation have occurred during run-in, these patients will be considered to have failed screening, and will not be randomized at this time, but are eligible for a re-screen 28 days after the exacerbation.

Patients who failed screening at Visit 1 or Visit 2 due to a COPD exacerbation may be re-screened once. Re-screening can occur no earlier than 28 days from the last dose of systemic steroid and/or antibiotics and/or hospitalization, whichever is later. For patients who fail screening at Visit 1, re-screening shall include completion of a new Visit 1, and if the patient meets all eligibility criteria at the time of the new Visit 1, the patient can then proceed to the treatment period (for those who were on Symbicort at study entry) or enter the run-in period (for those who were not on Symbicort at study entry). For patients who fail screening at Visit 2, re-screening shall include completion of a new Visit 1; patients would be required to go through the run-in period again, and patients would also be required to attend Visit 2 screening prior to being randomized.

Duration of treatment

Subjects who enter the study already on a stable dose of Symbicort will be enrolled and randomized at Visit 1 followed by a 26-week treatment period. Subjects who are converted to Symbicort will be enrolled at Visit 1 and enter a 25-day run-in period after which they will be randomized at Visit 2, followed by a 26 week treatment period. All subjects will receive a

phone call at 90 days after randomization to check on AEs and concomitant medications, will return to the clinic at week 26 for Visit 3 at the end of treatment, and will also participate in a follow-up telephone call 4 weeks after Visit 3.

The total planned study duration is 30 to 34 weeks (depending on whether the subject participates in a run-in period).

Investigational product, dosage and mode of administration

There is no pharmaceutical investigational product. Symbicort pMDI will be the ICS/LABA utilized in this study as the BreatheMate bluetooth monitoring device has been designed and built to fit onto this specific inhaler.

All subjects will be taking Symbicort pMDI, budesonide/formoterol, 160/4.5 µg x 2 actuations bid, for oral inhalation.

Outcome Measures:

Primary Outcome Measure:

- Adherence measured as mean number of sets of puffs/day for the entire 6 month study period

Secondary Outcome Measures:

- Mean Clinical COPD Questionnaire (CCQ) symptom score (total, symptom, mental, and function score) in the control vs. intervention group at baseline, end of study, and change over the 6 month period

- Mean total and domain weekly CCQ scores for each 2 month study interval (intervention group only)

- Mean number of sets of puffs/day for each 2 month study interval

- Mean and total number of adherent days (2 sets of 2 puffs per day) per subject

- Mean number of prescription refills at pharmacy

Statistical methods

- Analyses to address primary and secondary endpoints will be based on the full analysis set. The full analysis set will consist of all enrolled subjects who meet eligibility criteria and received at least 1 dose of Symbicort. This analysis set will be used for primary and secondary endpoints.

- In general, summaries of continuous variables will be provided using number, mean, median, standard deviation, minimum, and maximum values. Summaries of categorical variables will be provided using number and percentage of subjects. The comparison of mean values between the intervention and control groups will be performed using a t-test. An Analysis of Covariance (ANCOVA) model with the individual secondary continuous outcome measure as a dependent variable and potential covariates as independent variables will be used to estimate and compare means between the control and intervention groups. To select the best fit model, the backward elimination method will be used for the ANCOVA model. Details of the methodology will be explained in the statistical analysis plan (SAP).

- The possible covariates that may affect adherence include: age, gender, race, smoking status, severity of COPD (Moderate, Severe + Very Severe), number of COPD exacerbations during the past 12 months at baseline, prior exposure to Symbicort at baseline (Symbicort naïve, Symbicort pre-treated), time on ICS/LABA medications in months at baseline (<6 months, ≥6 months). New covariates and/or interactions may be added to the model if the real data exploration suggests that they are required.

- Demographics, baseline disease characteristics, and vital signs will be summarized by treatment arm, and overall. Baseline vital signs and physical examinations will be summarized descriptively or categorically as applicable.

- Safety analyses will include an analysis of concomitant medication use. Concomitant medications will be analyzed by preferred medication terms and Anatomical Therapeutic Chemical classification using number and percentage of subjects. AEs will be presented in data listings using standard Medical Dictionary for Regulatory Activities (MedDRA) terms.

- Subgroup analyses will be performed for the secondary outcome measures of interest. A 2-step approach will be followed for performing subgroup analyses. First, for a covariate to be qualified for the subgroup analyses a statistically significant association is to be established through a multivariable ANCOVA model for the continuous outcome variables. The backward elimination method will be used to select the best model and covariates. Second, a t-test comparison between the treatment arms for continuous secondary outcome measures stratified by individual covariates will be performed. The second step will be followed for all eligible covariates which have a statistically significant association with the outcome variable in step one.

- In general, missing data will not be imputed and the data will be analyzed as recorded on the study electronic case report forms (eCRFs).

Sample Size Determination

A total sample size of 352 subjects will be required for this study to achieve ~80% power to reject the null hypothesis of equal means of daily sets of Symbicort puffs per day when mean difference is $\mu 1 - \mu 2 = 0.18$, with a standard deviation for both groups of 0.6 and with a significance level (α) of 0.05 using a 2-sided 2 sample equal-variance t-test. A dropout rate of 15% will give rise to the total sample size of approximately 414 subjects. Therefore, the study will randomize approximately 207 subjects into each individual group.

TABLE OF CONTENTS   PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

Appendix A   Signatures

Appendix B   Additional Safety Information

Appendix C   Clinical COPD Questionnaire

Appendix D   User Satisfaction Survey

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event
ANCOVA	Analysis of Covariance
bid	Twice daily
CCQ	Clinical COPD Questionnaire
COPD	Chronic obstructive pulmonary disease
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
eCRF	electronic case report form
EOT	End of treatment
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonization
ICS/LABA	Inhaled corticosteroid/long acting β-agonist
IRB	Institutional Review Board
IVRS	Interactive voice response system
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
pMDI	Pressurized metered dose inhaler
SAE	Serious adverse event
SAP	Statistical analysis plan
US	United States

Abbreviation or special term	Explanation
WBDC	Web based data capture
WOCBP	Women of child-bearing potential

1.   INTRODUCTION

1.1   Background and rationale for conducting this study

Chronic obstructive pulmonary disease (COPD) is a common disease with substantial associated morbidity and mortality. COPD is the third-leading cause of death in the United States (US) and claimed 133,965 US lives in 2009 (Murphy et al 2013). In 2011, 12.7 million US adults were estimated to have COPD (NHLBI 2012). However, approximately 24 million US adults have evidence of impaired lung function, indicating an under diagnosis of COPD (Mannino et al 2002, van den Boom et al 1998). COPD also has a potentially harmful economic impact. In 2010, COPD resulted in over 10 million office visits, nearly 1.5 million emergency department visits, 700,000 hospitalizations, and 133,575 deaths in the US (Ford et al 2013). In 2010, US total medical treatment costs attributed solely to COPD (i.e., excluding comorbidities) were estimated to be $32.1 billion, with an additional $3.9 billion in COPD costs resulting from worker absenteeism (Ford et al 2015). Even in industrialized countries such as the US where anti-smoking initiatives have been relatively successful, the legacy of past smoking behavior in aging populations ensures that the COPD burden will—unavoidably—continue to climb over the next 20 to 30 years (Feenstra et al 2001).

Adherence rates for inhaled combination therapy is poor (average 3.9 refills per year) (Kern et al 2015). COPD patients with lower adherence tend to have higher overall healthcare costs, as demonstrated in a 24-month study of 33,816 patients in the US (Simoni-Wastila et al 2012), which found:

- Patients continuing therapy had lower costs of care by $3764 compared with patients who had ceased to take their maintenance therapy

- COPD patients with higher adherence to prescribed regimens experienced fewer hospitalizations and lower Medicare costs (-$2185) than those who exhibited lower adherence behaviors

Given the poor adherence with inhaled combination therapy seen in patients with COPD, and associated morbidity/mortality and economic costs, the present study is being conducted to see if medication reminders can be used to improve adherence in this population.

1.2   Rationale for study design, doses and control groups

Note: In this CSP, the term "intervention group" refers to subjects who receive the BreatheMate bluetooth device (including audio-visual medication reminders) and a supportive BreatheMate cellular phone application. The term "control group" refers to subjects who receive the BreatheMate bluetooth device with no audio-visual medication reminders, and a cellular phone but no supportive BreatheMate cellular phone application. The term "BreatheMate service" refers to the BreatheMate bluetooth device and the BreathMate cellular phone application.

The primary objective of this study is to determine the impact of medication reminders on adherence to Symbicort pressurized metered dose inhaler (pMDI) 160/4.5 µg x 2 actuations twice daily (bid) in patients with COPD, as measured by mean number of sets of puffs/day over the entire 6 month study period.

The BreatheMate bluetooth device is attached to subjects' Symbicort pMDI inhaler and automatically detects and logs their maintenance medication use. The bluetooth device transmits this data to a cellular phone that is provided to all subjects in the study.

In addition, for subjects in the intervention group only, BreatheMate also includes a cellular phone application that delivers: 1) daily reminder messages (pre-emptively) and alerts (following missed doses) to prompt subjects to take their medication as prescribed by their physician; 2) weekly reminders to fill out the Clinical COPD Questionnaire (CCQ); and 3) monthly reminders to obtain Symbicort refills and attach them to the BreatheMate device. Subjects in the intervention group will also be able to receive feedback regarding their medication compliance over the previous 7-day period and will receive a notification from the application if no record of Symbicort use has been received over a 7-day period.

Subjects will have access to the BreatheMate device and application for a 6-month period. The primary outcome under investigation is the adherence to Symbicort among subjects in the intervention group versus the control group throughout the treatment period. Secondary outcomes to be investigated include: 1) mean total and domain CCQ scores (total, symptom, mental, and function score) at baseline, end of study, and change over the 6 month study period in the intervention vs. control group, 2) change in total and domain CCQ scores for each 2-month study interval (intervention group only), 3) mean number of sets of puffs/day for each 2-month study interval, 4) mean and total number of adherent days and 5) mean number of prescription refills from the pharmacy.

A control group is included in this study in order to have a basis for comparison of adherence rates with and without the BreatheMate device audio-visual notifications and application messaging reminders. Subjects in the control group will receive treatment with the same medication and dose as subjects in the intervention group. Symbicort pMDI 160/4.5 µg x 2 actuations bid was chosen because it is Food and Drug Administration (FDA)-approved as standard-of-care treatment for COPD and because the BreatheMate device is specifically engineered to fit the Symbicort pMDI.

Allocation of subjects to the intervention or control groups will be unblinded. Sites will need to know how to instruct subjects in use of the device and cellular phone. To avoid potential unintended differences in how subjects are treated, interaction with site staff will be kept to a minimum following randomization (1 phone call 4 days after randomization to answer questions, 1 phone call 14 days after randomization to subjects whose Symbicort bluetooth data seen from the server are low [i.e., no data received since enrollment visit], 1 phone call 90 days after randomization to assess for adverse events [AEs] and concomitant medications, 1 visit at the end of the 26-week treatment period, and 1 follow-up phone call to assess for AEs and concomitant medications 30 days post-treatment period).

Subjects who had an exacerbation of COPD symptoms within 28 days before randomization are excluded so that an accurate symptom baseline may be captured.

1.3 Benefit/risk and ethical assessment

The efficacy and safety profiles of Symbicort pMDI 160/4.5 μg x 2 actuations bid is well established for the maintenance treatment of COPD. There are no known risks to general health or COPD symptoms associated with the BreatheMate service (device and application), and thus the service is considered to be of low risk to the subject. If the service malfunctions (no reminders are sent) the subjects' COPD treatment will be no different from standard medical practice. The risk/benefit profile is considered to be acceptable.

In addition, risks to study subjects have been minimized in the following ways:

- All subjects will be screened and those with any chronic condition that could, in the judgment of the Investigator, represent a risk to safe participation, will be excluded.

- Subjects will be routinely monitored for AEs during telephone contacts and clinic visits.

Each participating site will obtain Institutional Review Board (IRB) approval.

1.4 Study Design

Figure 1 presents the overall design of the study.

This is a 26-week, 2-arm, randomized, multicenter phase IV study to evaluate the impact of medication reminders on adherence to Symbicort pMDI 160/4.5 μg x 2 actuations bid in subjects with COPD. This study will randomize approximately 414 subjects.

At the enrollment visit (Visit 1), entry criteria will be confirmed. Subjects who are already on Symbicort and have met all eligibility criteria will be randomized at Visit 1 and will directly enter a 26-week treatment period (no run-in period). Subjects who are taking another inhaled corticosteroid/long-acting β-agonist (ICS/LABA) combination at a dose approved for COPD at Visit 1 will be converted to Symbicort pMDI and will enter a 25-day run-in period after which they will attend Visit 2. Subjects who still meet the eligibility criteria will be randomized at Visit 2 to the 26-week treatment period. Subjects who entered the study on Symbicort will not participate in Visit 2. At the point of randomization, subjects in the control group will fill out a paper-based CCQ and subjects in the intervention group will fill out the CCQ using the study-supplied cellular phone.

Subjects will be randomized (1:1) to receive current care and a medication usage monitoring device (control group) or current care and a supportive service (intervention group). All subjects will receive a BreatheMate bluetooth device that is attached to subjects' Symbicort pMDI inhaler and automatically detects and logs their maintenance medication use. All

subjects will also receive a study-supplied cellular phone that is paired with the BreatheMate device and used to transmit data regarding Symbicort usage. All subjects will be required to place the cellular phone near the BreatheMate device on a daily basis so that data regarding Symbicort usage can be transmitted to the study site through the cellular phone.

Subjects in the intervention group will receive audio-visual daily reminders (beeps and flashes) on the BreatheMate bluetooth device to take their medication. In addition, for subjects in the intervention group only, BreatheMate also includes a cellular phone application that delivers: 1) daily reminder messages (pre-emptively) and alerts (following missed doses) to prompt subjects to take their medication as prescribed by their physician; 2) weekly reminders to fill out the CCQ; and 3) monthly reminders to obtain Symbicort refills and attach them to the BreatheMate device. Subjects in the intervention group will also be able to receive feedback regarding their medication compliance over the previous 7-day period and will receive a notification from the application if no record of Symbicort use has been received over a 7-day period.

Subjects in the control group will receive treatment with the same medication and dose as subjects in the intervention group. Symbicort pMDI 160/4.5 µg x 2 actuations bid was chosen because it is FDA-approved as standard-of-care treatment for COPD and because the BreatheMate device is specifically engineered to fit the Symbicort pMDI.

Subjects will be provided with a helpline phone number should they have any questions regarding use of the BreatheMate device or application. All subjects will also receive a telephone call from the study site coordinator 4 days after randomization to help resolve any issues they may have using the BreatheMate device or using the application (intervention group only). In addition, 14 days after the randomization visit, all subjects' data will be checked by the study coordinator. If it appears that there is a technical issue (i.e., no data has been received from subjects following the enrollment visit), subjects will be contacted to assess if there are any potential technical issues, for example low signal (poor communication of phone signal) or issues due to removing the inhaler from the device. Subjects may be asked to return to the clinic to receive additional training as required. All subjects will receive a telephone call 90 days after randomization, to assess any AEs experienced, along with concomitant medication use. There will be a final clinic visit (Visit 3) for all subjects at the end of the 26-week treatment period, at which time all subjects will fill out a paper-based CCQ. All subjects will receive a follow-up phone call 30 days thereafter. The follow-up phone call will assess any AEs experienced since Visit 3, along with concomitant medication use.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
Demonstrate the impact of the BreatheMate medication reminders on adherence to Symbicort in COPD patients.	Adherence measured as mean number of sets of puffs/day for the entire 6 month study period. Example: Mean of 2.00 would be equal to 100% adherence (2 sets of 2 puffs). To constitute as a set, 2 puffs must be taken within 60 minutes.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
Demonstrate improved symptom control from baseline with use of medication reminders.	Mean CCQ symptom score (total, symptom, mental, and function score) in the control vs. intervention group at baseline, end of study, and change over the 6 month period. Mean total and domain weekly CCQ scores over each 2 month study interval (intervention group only).
Demonstrate the impact of the BreatheMate medication reminders on additional adherence measures.	Mean number of sets of puffs/day for each 2-month study interval Mean and total number of adherent days (2 sets of 2 puffs per day) per subject. Mean prescription refills at pharmacy

3. SUBJECT SELECTION, ENROLLMENT, 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 fulfill the following criteria:

1.   Signed informed consent at Visit 1 prior to any study specific procedures.

2.   Outpatient adults 40 years and older.

3.   A diagnosis of COPD confirmed by a post-bronchodilator Forced Expiratory Volume in 1 second/Forced Vital Capacity (FEV1/FVC) <0.70 at some point in the past 3 years.

4.   Moderate to Very Severe COPD as defined by a post-bronchodilator FEV1 <80% of predicted on most recent spirometry.

5.   Had been on an ICS/LABA combination therapy of a brand and dose approved for COPD, for at least 3 months prior to screening.

6.   Current or previous smoker with a smoking history equivalent to 10 or more pack years (1 pack year = 20 cigarettes smoked per day for 1 year).

7.   Willing to discontinue all medications containing both a LABA and an ICS and to begin Symbicort 160/4.5 μg, 2 inhalations bid.

8.   Must be willing to make a return visit, and complete all study assessments for the duration of study.

9.   Life expectancy >12 months.

10.   Must be willing to comply with all study procedures including being able to remove and attach device to the inhaler.

11.   Must be able and willing to read and write/respond using the electronic device provided.

3.2   Exclusion criteria

Patients 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 both AstraZeneca staff and/or staff at the study site).

2.   Previous randomization in the present study.

3.   Patients who have been randomized in a clinical study and received an investigational product within 30 days of Visit 1 (participation is defined as the completion of a treatment related visit).

4.   Current diagnosis of asthma.

5.   Known history of drug or alcohol abuse which, in the opinion of the Investigator, may interfere with subject's ability to participate or comply with the study.

6.   An acute exacerbation of COPD that required hospitalization or emergency room visit or treatment with systemic steroids and/or antibiotics during the 28 days before Visit 1.

Patients who had a COPD exacerbation within 28 days of Visit 1 can be re-screened once. Re-screening can occur no earlier than 28 days from the last dose of systemic steroids and/or antibiotics and/or hospitalization, whichever is later.

7.   Enrolled patients that have a COPD exacerbation during the run-in period, defined as worsening symptoms which in the judgment of the Investigator requires treatment with systemic steroids and/or antibiotics and/or hospitalization.

Patients who had a COPD exacerbation during the run-in period can be re-screened once. Re-screening can occur no earlier than 28 days from the last dose of systemic steroid and/or antibiotics and/or hospitalization, whichever is later.

8.   Any hospital admissions due to ischemic heart disease or heart failure within 3 months of study enrollment.

9.   Any significant disease or disorder (e.g., gastrointestinal, liver, renal, neurologic, musculoskeletal, endocrine, metabolic, infectious, psychiatric, major physical impairment) which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or may influence the results of the study, or the patient's ability to participate in the study.

10.   History of lung or upper airway cancer and any other malignancy not in remission for 5 years or more, except for patients who have had basal cell carcinoma, or in situ carcinoma of the cervix provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained.

11.   Use or planned use of systemic corticosteroids as a maintenance treatment (defined as daily or every other day treatment for 21 or more days) for inflammatory or immunologic conditions unrelated to their COPD.

12.   Planned hospitalization or surgical procedure requiring inpatient stay during the study.

13.   Pregnancy, breast-feeding or planned pregnancy during the study; fertile women not using acceptable contraceptive measures, as judged by the Investigator. Female subjects who are not post-menopausal or surgically sterile must have a negative urine pregnancy test (urine dipstick test only) prior to randomization and must comply with contraceptive methods.

14.   Any clinically relevant abnormal findings in physical examination or vital signs, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study.

15.   Known or suspected hypersensitivity to the study therapy (Symbicort).

16.   Patients who are unable or unwilling to use mobile communication devices, or patients who plan to be away from home for a significant part of the study without access to cellular connectivity are excluded because of the challenges of collecting data and providing information to these patients who are unable to use the service.

17.   Patients with thoracic surgery within 6 months of Visit 1.

18.   Patients who have received a lung transplant or are currently active on the lung transplant waiting list.

Procedures for withdrawal of incorrectly enrolled subjects are described in Section 3.4.

3.3   Subject enrollment 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 informed consent from the potential subject before any study specific procedures are performed.

2.   Assign potential subject a unique enrollment number, beginning with 'E#'.

3.   Determine subject eligibility. See Section 3.1 and 3.2.

4.   Assign eligible subject a unique randomization code via an interactive voice response system (IVRS)/interactive web response system (IWRS).

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

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

If any patient reports symptoms of a COPD exacerbation within 28 days before Visit 1 or during the run-in period between Visit 1 and Visit 2, the patient shall not proceed to the treatment period, but may be re-screened once. This is the only condition during which re-screening is permitted in the study (see Section 4.1.3).

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 at Visit 1 or enter the study treatment period. 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 or meets any of the exclusion criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Subjects who meet all inclusion criteria and none of the exclusion criteria for this study will be randomized at Visit 1 (if they enter the study already on Symbicort) or Visit 2 (if they require conversion to Symbicort).

After the subject eligibility (based on inclusion/exclusion criteria) is confirmed, the subject will be randomly assigned either to the intervention group or the control group. Enrollment and randomization will be implemented using an IVRS/IWRS, which will be built and managed by _____. Using the randomization schedule the system will assign the next randomization record including randomization number. Treatment assignment will be performed manually at the site.

The lead study statistician at _____ will be responsible for generating randomization schedules complying with the protocol and IVRS/IWRS specifications. The randomization schedules will be developed based on the specifications provided in the IVRS/IWRS requirements and design specification document. There will be no stratification by site or any other parameters. The list will be generated using SAS version 9.2 or higher in a permuted block design. The block size will be balanced within each block and will maintain a 1:1 ratio between the intervention group and the control group. Details of the format and generation of the randomization schedule will be provided in the statistical analysis plan (SAP).

3.6 Methods for ensuring blinding

Not applicable.

3.7 Methods for unblinding

Not applicable.

3.8 Restrictions

Refer to Exclusion Criteria in Section 3.2.

3.9 Discontinuation of use of the BreatheMate device

Subjects may be discontinued from using the BreatheMate device in the following situations:

- Subject decision. The subject is free to discontinue treatment at any time, without prejudice to further treatment;

- Safety reasons as judged by the Investigator and/or AstraZeneca.

Subjects who are discontinued will attend an end of treatment (EOT) visit.

3.9.1 Procedures for discontinuation of a subject

At any time, subjects are free to discontinue use of the BreatheMate device or withdraw from the study (i.e., BreatheMate device and assessments – see Section 3.10), without prejudice to further treatment. A subject that decides to discontinue use of the BreatheMate device will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (see Section 6); the BreatheMate device and cellular phone, as well as all study drugs and vouchers should be returned by the subject.

If a subject is withdrawn from the study, see Section 3.10.

3.10 Criteria for withdrawal

Subject participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.

2. Pregnancy.

3. Any serious adverse event (SAE), clinically significant AE, intercurrent illness, or other medical condition where the Investigator or the Sponsor determines that continued participation is not in the best interest of the subject.

4. Subject's decision to withdraw.

5. Subject failure to comply with protocol requirements or study related procedures per Principal Investigator (PI) discretion. Low adherence to BreatheMate is not a criteria for withdrawal.

6.   Termination of the study by the Investigator, Sponsor, FDA, or other regulatory authorities.

The clinical study report (CSR) will include reason(s) for subject withdrawals as well as details relevant to the subject withdrawal. If a subject is withdrawn from the trial prior to study completion, the subject will undergo all procedures scheduled for study completion (EOT evaluations) as the situation allows. Subjects who do not withdraw consent will receive a follow-up phone call 30 days after treatment ends. Any subject withdrawn due to an AE (whether serious or non-serious) will be evaluated by the Investigator and will be treated and/or followed up until the symptoms return to normal or acceptable levels, as judged by the Investigator.

3.10.1 Screen failures

Screening failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be randomized.

Patients who are screen failures due to an exacerbation of COPD during the 28 days prior to Visit 1, or during the run-in period between Visit 1 and Visit 2, may be re-screened once. This is the only provision for re-screening of screen failures in this study (see Section 4.1.3).

3.10.2 Withdrawal of the informed consent

Subjects are free to withdraw from the study at any time without prejudice to further treatment.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up AEs outside of the clinical study. The subject will return the BreatheMate device, the study-provided cellular phone and prescription vouchers.

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

If possible, subjects should complete the EOT visit at the time of withdrawal of consent.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that are not considered to be consistent with continuation of the study.

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 electronic Case Report Form (eCRF). All reasons for discontinuation of treatment must be documented.

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 1 Study Plan

Assessment	Screening		Treatment				Follow-up
Visit	**1**	**2[a]**	**Phone Calls[b]**			**3[c] (EOT)**	**Phone Call**
Days	**0**	**-25[a]**	**Day 4**	**Day 14**	**Day 90**	**Day 180**	**30 days after Visit 3**
Visit Window (days)		**±3**	**±1**	**±3**	**±7**	**±7**	**±3**
Informed consent	X						
Review of inclusion/exclusion criteria with documentation of post-bronchodilator FEV1/FVC ratio and FEV1% predicted	X	X					
Demography and review of prior medications/therapies	X						
Medical/surgical history	X						
COPD exacerbation history	X[d]						
COPD exacerbation assessment		X[d]				X	
Smoking history	X						
Height and weight	X						
Physical examination	X					X	
Randomization	X[e]	X[f]					
Vital signs (pulse rate, blood pressure, respiratory rate, body temperature)	X	X				X	
Pregnancy testing[g]	X	X				X	
Distribute Symbicort pMDI[h]	X						
Provide Symbicort pMDI training	X						
Distribute prescription voucher cards[i]	X	X					
BreatheMate device and phone training[j]	X[e]	X[f]					
BreatheMate device and phone dispensed[k]	X[e]	X[f]					
Check-in on use of BreatheMate device/cellular phone application			X[b]	X[b]			
Device and phone returned[l]						X	
Control only: paper-based CCQ[m]	X	X					
Intervention only: app-based CCQ[n]	X	X					
Both Intervention and Control: paper-based CCQ[o]						X	
User Satisfaction Survey[p]						X	
Concomitant medication/therapy review	X	X			X	X	X
Adverse event collection(AEs and SAEs)		X			X	X	X

CCQ: Clinical COPD Questionnaire, COPD: chronic obstructive pulmonary disease, EOT: end of treatment, pMDI: pressurized metered-dose inhaler, SAE: serious adverse event.

[a] Only subjects who are not already on Symbicort at study entry will be required to attend Visit 2.

[b] There will be up to 3 phone calls during the Treatment Phase. The first phone call will occur 4 days after start of the treatment intervention, to answer any questions the subject may have regarding use of the BreatheMate device or cellular phone application. Fourteen days after subjects start the treatment intervention, the study site coordinator will check the subject's Symbicort bluetooth data from the server. If it appears that there is a technical issue (i.e., no data has been received from subjects following the enrollment visit), subjects will be contacted to assess if there are any

potential technical issues. Subjects whose bluetooth data are being received by the server will not receive a phone call on Day 14. All subjects will receive a phone call 90 days after the start of the treatment intervention to collect information regarding AEs and concomitant medication use.

c Visit 3 will occur 180 days after the start of the treatment intervention.

d Subjects who had an exacerbation of COPD during the 28 days prior to Visit 1 or during the run-in period between Visit 1 and Visit 2 will be considered to have failed screening and will not be randomized. However, re-screening is permitted once.

e For subjects taking Symbicort at study entry and randomized at Visit 1.

f For subjects who are converted to Symbicort and are randomized at Visit 2.

g For women of child-bearing potential (WOCBP). Pregnancy testing will be performed using a urine dipstick.

h Subjects who agree to convert to Symbicort at Visit 1 will receive a Symbicort pMDI at Visit 1. Subjects who convert to Symbicort will be asked to bring the inhaler with them to Visit 2 to be collected

i Subjects who are randomized at Visit 1 will receive a 30-day prescription voucher that can be re-used each month at Visit 1. Subjects who are randomized at Visit 2 will receive prescription vouchers at Visit 2.

j Timing of reminders will be set at this visit for subjects in the intervention group.

k All subjects will receive a starter pack which will include the BreatheMate device, cellular phone, cellular phone charger, and patient information leaflet (instructions on how to use the BreatheMate device and for subjects in the intervention group, instructions on using the cellular phone application). The starter pack will also include contact information should subjects have questions on using the BreatheMate device or application.

l At Visit 3, the site should confirm that the BreatheMate device and the phone are paired and connecting to ensure that all possible data has been transferred from the device to the application.

m Completed on paper at Visit 1 for subjects randomized at Visit 1, and at Visit 2 for subjects randomized at Visit 2.

n Completed weekly throughout the trial using the BreatheMate app, starting at Visit 1 for subjects randomized at Visit 1, and Visit 2 for subjects randomized at Visit 2.

o Completed on paper at Visit 3 (EOT) for all subjects.

p Completed by subjects in the intervention group only.

4.1 Enrollment/screening period

4.1.1 Screening Visit (Visit 1)

Procedures will be performed according to the Study Plan (Table 1). Informed consent will be signed prior to performing any protocol-required procedures. Of note, the following will be performed during this visit:

- Subjects who are randomized at Visit 1 will be trained in the use of the Symbicort inhaler, including priming procedures. Subjects who agree to convert to Symbicort at Visit 1 will receive a Symbicort inhaler and training in use of the inhaler, including priming procedures at Visit 1.

- Subjects who are randomized at Visit 1 will be dispensed a 30-day prescription voucher card which must be used each month during the study to obtain their Symbicort.

- For subjects who are randomized at Visit 1: Device and cellular phone will be dispensed.

- For subjects who are randomized at Visit 1: Device and phone training will occur for all subjects. Subjects in the intervention group will also receive training on the BreatheMate supportive intervention application, and the timing of application reminders will be set at Visit 1 for these subjects.

- Subjects in the intervention group will complete the CCQ at randomization through the cellular phone application. Subjects randomized to the control group will complete the paper version of the CCQ.

- Subjects will also be provided with contact information should they have any questions during the study.

4.1.2 Run-in Period and Visit 2

Patients who require conversion to Symbicort (are receiving a different ICS/LABA combination approved for COPD at Visit 1) will receive Symbicort pMDI, budesonide/formoterol, 160/4.5 µg x 2 actuations bid during a run-in period, and will participate in a second screening visit (Visit 2) on Day 25 (± 3 days).

Procedures at Visit 2 will be performed according to the Study Plan (Table 1). Device and cellular phone training will be provided as described for Visit 1. Subjects will be asked to bring their Symbicort inhaler with them to Visit 2 to be collected. Reusable 30-day prescription vouchers will be dispensed to subjects who meet the inclusion and exclusion criteria and are randomized at Visit 2.

Subjects who require a run-in period and are randomized to the intervention group will complete the CCQ at Visit 2 through the cellular phone application. Subjects who require a run-in period and are randomized to the control group will complete the paper version of the CCQ at Visit 2.

4.1.3   Re-screen

If any patient reports symptoms of a COPD exacerbation (defined as worsening symptoms which in the judgment of the Investigator requires treatment with systemic steroids and/or antibiotics and/or hospitalization), within 28 days before Visit 1 or during the run-in period between Visit 1 and Visit 2, the patient shall not proceed to the treatment period, but may be re-screened. Re-screening can occur no earlier than 28 days from the last dose of systemic steroid and/or antibiotics and/or hospitalization, whichever is later.

For patients who fail screening at Visit 1, re-screening shall include completion of a new Visit 1 and if the patient meets all eligibility criteria at the time of the new Visit 1, the patient can then proceed to the treatment period (for those who were on Symbicort at study entry) or enter the run-in period (for those who were not on Symbicort at study entry). For patients who fail screening at Visit 2, re-screening shall include completion of a new Visit 1, going through the run-in period, and attending Visit 2 screening again prior to being randomized.

Patients who had a COPD exacerbation during screening can be re-screened only once.

4.2   Treatment period

Descriptions of the procedures for this period are included in the Study Plan with exceptions of the following specific requirements for the treatment period.

4.2.1   Telephone contacts during the treatment period

A member of the site staff will contact subjects by phone 4 days following randomization to offer support and help resolve any issues the subject may be having with the BreatheMate device (all subjects) or with the supportive BreatheMate application (intervention group only), or in completing the CCQ (intervention group only).

Fourteen days after the randomization visit, all subjects' data in the system will be checked by the study staff. If it appears that there is a technical issue (i.e., no data has been received from subjects following the enrollment visit), subjects will be contacted to resolve possible issues such as an area of low signal (poor communication of phone signal), or removal of the BreatheMate device from the inhaler, and may be asked to return to the clinic to receive additional training as required. No discussion regarding compliance should occur during this call.

All subjects will receive a telephone call 90 days after randomization. The purpose of this phone call will be to collect information regarding AEs and concomitant medication use since randomization.

At Week 26 of the treatment period, subjects will return to the study site for the Visit 3/EOT visit. Procedures at the EOT visit will be performed according to the Study Plan (Table 1). Of note, at Visit 3, the site should confirm that the BreatheMate device and the phone are paired and connecting, to ensure that all possible data has been transferred from the device to the application.

4.3   Follow-up period

All subjects will be contacted by phone 30 days after Visit 3 as a follow-up for safety. Adverse events and concomitant medications will be recorded.

5.   STUDY ASSESSMENTS

An Inform web based data capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs 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 eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1   Efficacy assessments

Efficacy data are collected using the BreatheMate service. The service collects medication use measured and reported by a paired bluetooth device on a daily basis.

Data reporting for BreatheMate includes the following components:

- The web portal provides secure user registration for each study coordinator and Investigator for the intervention and control groups.

- Linked mobile and web portal interfaces.

- In-application messaging on the importance of taking Symbicort including both pre-emptive reminders to take medication as well as reminders of missed doses (intervention group only).

- Reminders to obtain Symbicort refills and attach them to the BreatheMate device (intervention group only).

- Collection of weekly respiratory symptoms through the CCQ via the BreatheMate application (intervention group only).

- Collection of CCQ on paper forms at randomization (control group only) and EOT (both control and intervention groups).

31(56)

5.1.1 Primary efficacy endpoints

5.1.1.1 Adherence

Adherence will be quantified as mean sets of puffs per day over the 6 month study period. A mean of 2.00 sets would be equal to 100% adherence (2 sets of 2 puffs). The 2 puffs that constitute a set must be taken within 60 minutes to count as a set. A patient will not be given credit for taking more than 2 sets of 2 puffs a day, and any sets of puffs above 2 per day will not be included in calculations of the primary endpoint.

5.1.2 Secondary efficacy endpoints

5.1.2.1 Mean CCQ domain and total scores

The CCQ is a 10-item measure, divided into 3 domains (Symptoms: Items 1, 2, 5 and 6; Functional State: Items 7, 8, 9, and 10; and Mental State: Items 3 and 4) (Clinical COPD Questionnaire website; van der Molen et al 2003). Individual items within the CCQ are equally weighted. The total score is calculated by adding the scores of the 10 items and dividing that number by 10 (=number of items). In addition, individual domain scores can be calculated. The total CCQ score, and the score on each of the 3 domains, varies between 0 (very good health status) to 6 (extremely poor health status).

In the intervention group, the CCQ is completed at Visit 1 for subjects randomized at Visit 1, Visit 2 for subjects randomized at Visit 2 and on a weekly basis, via the BreatheMate app. At the EOT visit (Visit 3), the CCQ is completed on paper.

In the control group, the CCQ is completed on paper at Visit 1 for subjects randomized at Visit 1, Visit 2 for subjects randomized at Visit 2, and Visit 3/EOT visit for all subjects in the control group.

Mean CCQ domain and total scores will be estimated at baseline and at EOT and compared between intervention and control groups using Analysis of Covariance (ANCOVA). The change in mean CCQ domain and total scores from baseline to EOT will be estimated and compared between intervention and control groups using ANCOVA. Additionally, mean weekly CCQ domain and total scores over each 2 month study interval will be estimated in the intervention group only. The change in mean weekly CCQ domain and total scores between the 2 immediate intervals and the first and the last intervals within the intervention group will be estimated and compared using ANCOVA. Thus the change in mean weekly CCQ domain and total scores will be compared within the intervention group between the following 2-months intervals.

- ≤2 Months (Month 2 follow-up period) and >2 Months - ≤4 Months (Month 4 follow-up period)

- >2 Months - ≤4 Months (Month 4 follow-up period) and >4 Months - ≤6 Months (Month 6 follow-up period)

- ≤2 Months (Month 2 follow-up period) and >4 Months - ≤6 Months (Month 6 follow-up period)

5.1.2.2 Additional adherence measures

Additional adherence measures include:

- Mean number of sets of puffs/day for each 2-month study interval.

- Mean and total number of adherent days (2 sets of 2 puffs per day) per subject.

- Mean number of prescription refills at pharmacy

5.2 Safety assessments

5.2.1 Laboratory safety assessments

No laboratory safety assessments will be conducted during the study.

Urine pregnancy testing will be conducted on WOCBP at Screening (Visit 1 and Visit 2 [as applicable]) and at Visit 3. Urine dipsticks will be analyzed by study personnel at the study center.

5.2.2 Physical examination

A physical examination will be performed at Visit 1 and Visit 3/EOT and will include an assessment of the following: general appearance, abdomen, cardiovascular and respiratory systems, weight and height.

5.2.3 Vital signs

Vital sign measurements in this study will include sitting systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Vital sign measurements will be measured at Visit 1, Visit 2 [as applicable], and Visit 3.

5.2.3.1 Pulse and blood pressure

Pulse rate should be measured before the blood pressure measurement. An appropriate-sized cuff (cuff bladder encircling at least 80% of the group) should be used to ensure accuracy. This will be documented in the source documents at the investigative site.

Blood pressure and pulse rate measurements must be performed while the subject is in a seated position.

5.2.3.2 Respiratory rate

Respiratory rate (breaths/min) will be measured.

5.2.3.3   Body temperature

Body temperature will be recorded in Celsius in accordance with local standards.

5.2.4   Diagnosis of COPD

Clinic Site Investigator will document date of diagnosis and a confirmatory post-bronchodilator FEV1/FVC ratio <0.70.

5.2.4.1   Level of COPD severity by airflow limitation

Clinic Site Investigator will document most recent post-bronchodilator FEV1 % predicted.

5.2.5   COPD exacerbation assessment

Subjects will be queried at Visit 1, Visit 2 [as applicable], and Visit 3 as to whether they have experienced a COPD exacerbation, defined as an acute event characterized by a worsening of the subject's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in COPD medications. In addition, if the study physician responds to calls from the subject or elevated symptoms reported by the subject, they may determine that the subject is experiencing an exacerbation. In all cases where an exacerbation of COPD is reported, the following definitions will be used to grade the level of the exacerbation. A moderate exacerbation shall be defined as worsening of COPD symptoms which in the judgment of the Investigator requires treatment with systemic steroids with or without antibiotics or antibiotics alone. A severe exacerbation shall be defined as a worsening of COPD symptoms which in the judgment of the Investigator or other healthcare provider requires emergency room (ER) stay for ≥24 hours or hospital admission.

5.2.6   Other safety assessments

Adverse events and information regarding use of concomitant medications will be collected throughout the study (see Section 6). Device malfunctions that do not result in an AE will be tracked separately.

5.3   Other assessments

5.3.1   Patient reported outcomes

Subjects will complete the following self-administered patient-reported outcome measures at Visit 3 (EOT visit).

5.3.1.1   BreatheMate User Satisfaction Survey (Intervention group only)

Subjects in the intervention group will complete a paper-and-pencil user satisfaction survey regarding the BreatheMate device concerning ease of use, appearance and feel of the device. In addition, these subjects will complete questions regarding the cellular phone application including ease of use, design, and helpfulness of reminders in improving compliance.

Investigators and study coordinators will fill out similar surveys regarding ease of use, accessibility of the BreatheMate web portal, design, patient adherence with daily ICS/LABA

medication and medication re-fills, as well as overall usefulness of the BreatheMate device in clinical practice.

5.3.1.2 CCQ

Subjects in the intervention group will complete the CCQ using the BreatheMate app at randomization and weekly throughout the study. Subjects in the control group will complete a paper version of the CCQ according to the Study Plan (see Table 1). At Visit 3, all subjects will complete the CCQ on paper.

5.4 Pharmacokinetics

Not applicable.

5.5 Pharmacodynamics

Not applicable.

5.6 Pharmacogenetics

Not applicable.

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.

6.1 Definition of adverse events

An AE 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 SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death;

- Is immediately life-threatening;

- Requires in-patient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;

- Is a congenital abnormality or birth defect;

- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the CSP.

6.3   Recording of adverse events

6.3.1   Time period for collection of adverse events

Adverse events will be collected from time of signature of informed consent (Visit 1) throughout the treatment period, and including the 30-day follow-up period (last telephone contact).

SAEs will be recorded from the time of informed consent.

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 eCRF. 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)- specify if causally related to device or application;

- The date (and time) when the AE started and stopped;

- Maximum intensity of the AE;

- Whether the AE is serious or not;

- Investigator causality rating against Symbicort (yes or no);

- Action taken with regard to Symbicort;

- Whether or not AE caused subject's withdrawal from study (yes or no);

- Outcome.

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

- Date AE met criteria for SAE;

- Date Investigator became aware of SAE;

- Reasons AE is considered serious;

- Date of hospitalization;

- Date of discharge;

- Probable cause of death;

- Date of death;

- Autopsy performed;

- Causality assessment in relation to study procedure(s);

- Description of AE.

Maximum intensities will be reported for each AE. Maximum intensity refers to the complete course of the AE. The subjects will be asked to assess the maximum intensity of the reported AEs according to the following scale:

- Mild (awareness of sign or symptoms, but easily tolerated);

- Moderate (discomfort sufficient to cause interference with normal activities);

- Severe (incapacitating, with inability to perform normal activities).

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

6.3.4 Causality collection

The Investigator will assess causal relationship between Symbicort and each AE, 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 Symbicort?'.

A guide to the interpretation of the causality question can be found in Appendix B to the CSP.

The Investigator will also assess the causal relationship between the device (Bluetooth monitoring device or phone) and each AE using the same criteria outlined above. If the Investigator feels the AE is related to the device, this should be captured in the AE Verbatim term field.

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

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. 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 assessments and vital signs will be summarized in the CSR. Deterioration as compared with baseline in protocol-mandated vital signs or assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation from the study.

If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Malfunctions based on electronic devices used in the study

AEs that are related to the subjects' use of the devices being tested in the study (BreatheMate device or cellular phone) will be collected by AstraZeneca and reported to the companies that manufacture those devices. Malfunction means the failure of a device to perform as specified or otherwise perform as intended.

6.3.8 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to COPD. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events that are unequivocally due to disease progression, should not be reported as an AE during the study. Exacerbations of COPD that meet SAE criteria should be reported as SAEs.

6.3.9 Concomitant medications

All changes to a subject's concomitant medications must be reported on the concomitant medications page of the eCRF and reasons for a change in medication that reflects an AE must be recorded on the AE page of the eCRF.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to Symbicort, the device (Bluetooth monitoring device or phone), or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day 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 AEs 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.

Once the Investigators or other site personnel indicate an AE is serious in the Inform system (WBDC) an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by facsimile machine.

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

6.5 Overdose

For the purposes of this study, an accidental or deliberate intake of more than 10 inhalations of Symbicort (1600 µg budesonide/45 µg formoterol) during a 24 hour period is defined as an overdose. All overdoses with Symbicort should be reported to AstraZeneca.

Background

The risks associated with overdosage of Symbicort pMDI are considered to be small, as the safety margins for inhaled budesonide and formoterol are substantial. Administration of a Symbicort Turbuhaler dose of 1600/45 µg over 1 hour on top of maintenance treatment with daily doses of 640 µg budesonide and 18 µg formoterol in asthmatic patients raised no safety concerns, nor did a formoterol dose of 90 µg over 3 hours in adult patients with acute bronchoconstriction or a budesonide dose of 7200 µg in healthy volunteers.

Symptoms

Corticosteroids have a low toxicity and are virtually without harmful effects after a single or a few doses, even if the doses are very high. Thus, acute overdosage with budesonide – even in excessive doses – is not a clinical problem. As with all ICSs, systemic corticosteroid effects may appear if used chronically in excessive doses.

There is limited clinical experience regarding overdosage with inhaled formoterol. An overdose would likely lead to effects that are typical of β2-agonists such as tremor, headache, and palpitations. Symptoms and signs reported with formoterol from isolated cases are tachycardia, hyperglycemia, hypokalemia, prolonged QTc interval, arrhythmia, nausea, and vomiting.

Experience with other β2-agonists has shown that overdoses may also cause restlessness, irritability, excitation, somnolence, convulsions, and hyper- or hypotension. Metabolic effects may include acidosis and in serious cases, possibly rhabdomyolysis and renal failure.

Treatment suggestions

Normally, an overdose with Symbicort pMDI should not require any special treatment. However, if signs of adrenergic effects occur, these should be counteracted by supportive and symptomatic treatment, according to local routines.

Procedures for reporting an overdose

The following information should be provided:

- Details of the subject who was prescribed the medication allowed in the study protocol.

40(56)

- Details of the subject who took the overdose (demographic information, was subject a study participant?).

- Details of the drug overdose (total daily dose, route, formulation, overdose start and stop dates).

- Details of whether the recorded overdose was from actual inhalation of the Symbicort or discharge of the inhaler into the environment

- Was the overdose accidental or intentional?

- Was the overdose associated with an AE (serious or non-serious)?

- AE description: provide start and stop dates of the event, or indicate if the event is ongoing.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **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.

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

6.6　　Pregnancy

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

6.6.1　　Maternal exposure

Pregnancy in itself is not regarded as an AE or SAE. However, Investigator/site staff should report pregnancies and their outcomes to AstraZeneca. 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 1 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 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

The Investigator should also inform AstraZeneca of any paternal exposure pregnancies during the course of the study. The female partner of the subject will be asked to consent to allow collection of information and follow-up on the pregnancy. The outcome of the pregnancy should be reported to AstraZeneca.

6.7 Management of IP related toxicities

Not applicable.

6.8 Study governance and oversight

Not applicable.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
BreatheMate Device and Application	Not Applicable	Adherium

7.2 Dose and treatment regimens

There is no pharmaceutical investigational product. Symbicort pMDI will be the ICS/LABA utilized in this study because the BreatheMate bluetooth monitoring device has been designed and built to fit onto this specific inhaler. All subjects will use Symbicort pMDI, budesonide/formoterol, 160/4.5 µg x 2 actuations bid, for oral inhalation. Subjects who require a run-in period will be provided with a Symbicort inhaler at Visit 1. All subjects will obtain Symbicort inhalers, 160/4.5 µg x 2 actuations bid, needed for the treatment period through reusable prescription voucher cards provided at randomization.

The service known as 'BreatheMate' is a patient support tool that monitors daily Symbicort inhaler use. This service will also provide support for subjects in the intervention group who are using Symbicort as part of their COPD maintenance therapy.

BreatheMate service includes:

- A bluetooth monitoring device provided to subjects in both the intervention and the control groups. The bluetooth monitoring device is

attached to the COPD subjects' Symbicort pMDI inhaler which automatically detects and logs their maintenance medication use. Subjects in the intervention group will receive audio-visual daily reminders (beeps and flashes) on the BreatheMate bluetooth device. This functionality is deactivated for the control group.

- A cellular phone application, for subjects in the intervention group only, that delivers: 1) daily reminder messages (pre-emptively) and alerts (following missed doses) to prompt subjects to take their medication as prescribed by their physician; 2) weekly reminders to fill out the CCQ; and 3) monthly reminders to obtain Symbicort refills and attach them to the BreatheMate device. Subjects, in the intervention group only, will also be able to receive feedback regarding their medication compliance over the previous 7-day period and will receive a notification from the application if no record of Symbicort use has been received over a 7-day period.

Note: Subjects in the control group will receive study cellular phones but they will not be equipped with the supportive application. The cellular phone for the control group will display whether the bluetooth monitoring device is paired and communicating with the cellular phone. The bluetooth device will transmit data regarding medication usage to the cellular phones of all subjects, including those in the control group. These data will be available for access by the study sites, but subjects in the control group will not have access to the data. Subjects in the control group will receive treatment with the same medication and dose as subjects in the intervention group. Symbicort pMDI 160/4.5 µg x 2 actuations bid was chosen because it is FDA-approved as standard-of-care treatment for COPD and because the BreatheMate device is specifically engineered to fit the Symbicort pMDI.

7.3   Labelling

Drugs and devices are labelled according to local regulatory requirements.

7.4   Storage

All study drugs and devices should be kept in a secure place under appropriate storage conditions as stated on the labels and described in instructions provided together with the study drug/devices. The study devices (i.e. BreatheMate device, Symbicort inhaler, and cellular phone) will be stored at ambient temperature.

7.5   Compliance

Adherence with the BreatheMate device and with the Symbicort medication will be measured by the BreatheMate device.

7.6   Accountability

The study personnel will account for all items dispensed at the sites including: Symbicort pMDI used during run-in period, the training inhaler, the BreatheMate device, and cellular phone.

Study personnel will also account for prescription voucher cards dispensed to and returned from the subject.

7.7   Concomitant and other treatments

Not applicable. There is no disallowed medication in this study.

7.8   Post Study Access to Study Treatment

Not applicable.

8.   STATISTICAL ANALYSES

Adherence will be estimated as the mean number of sets of Symbicort puffs per day over the 6 month study period within the intervention and control groups and compared between the 2 groups using a t-test statistic.

The mean domain and total CCQ scores at baseline, EOT and the mean change in CCQ domain and total scores from baseline to EOT will be compared between intervention and control groups using ANCOVA. The mean change in CCQ domain and total scores between every immediate interval and first and last interval (as explained in Section 5.1.2.1) will be estimated and compared within intervention group using ANCOVA. Other additional adherence measures such as mean numbers of sets of puffs per day between every immediate interval and first and last interval, mean and total number of adherent days, and mean number of pharmacy refills will be estimated at a respective time points/interval and compared between intervention and control group using ANCOVA model.

Analyses may be stratified by potential confounding variables for the outcome measures of interest if the confounding variables are found to be significantly associated with adherence. Details of the specific subgroup analyses will be described in the SAP.

8.1   Statistical considerations

Statistical analyses will be performed by ███████. Details of the statistical analyses will be provided in the SAP.

Analyses to address primary and secondary endpoints will be based on the full analysis set. The full analysis set will consist of all randomized subjects who meet eligibility criteria and received at least 1 dose of Symbicort.

In general, summaries of continuous variables will be provided using number, mean, median, standard deviation, minimum, and maximum values. The comparison of mean values between the intervention and control groups will be performed using ANCOVA for the secondary continuous outcome measures. The comparison of mean number of sets of Symbicort puffs per day will be performed using a t-test for the primary endpoint. Summaries of categorical variables will be provided using the number and percentage of subjects. As applicable 2-sided binomial exact confidence intervals for proportions, and 95% confidence intervals for means of normally distributed variables will be provided. All significance tests will be conducted at the 0.05 significance level.

Demographic, baseline disease characteristics, and vital signs will be summarized by intervention group, control group, and overall. Baseline vital signs and physical examinations will be summarized descriptively or categorically as applicable.

Safety analyses will include an analysis of concomitant medications use.

In general, missing data will not be imputed and the data will be analyzed as recorded on the study eCRFs.

8.2   Sample size estimate

The sample size is based on the primary endpoint of an 18% absolute increase in mean number of daily sets of Symbicort puffs in COPD subjects receiving reminders compared with those who are not receiving reminders. The null hypothesis is that there is no difference in adherence to Symbicort as measured by sets of puffs/day in COPD subjects who receive reminders compared with those who do not receive reminders. The alternate hypothesis is that there is a difference in adherence to Symbicort as measured by sets of puffs/day in COPD subjects who receive reminders compared with those who do not receive reminders. A mean of 2 sets of 2 Symbicort puffs per day is defined as 100% adherence to Symbicort. Based on the information received from the Health Core Research Environment claims database, and the Simmons et al 1996 manuscript from the Lung Study, the mean Symbicort sets of puffs per day is assumed to be 1.0 (50% adherence) in COPD subjects. It is assumed that the mean Symbicort sets of puffs per day in subjects receiving reminders will be 1.18 which is an improvement in adherence of 18 percentage points compared with subjects not receiving reminders. Thus a total sample size of 352 achieve ~ 80% power to reject null hypothesis of equal means of daily sets of Symbicort puffs per day when mean difference is $\mu1 - \mu2 = 0.18$ with a standard deviation for both groups of 0.6 and with a significance level (α) of 0.05 using a two-sided two sample equal-variance t-test. A dropout rate of 15% will give rise to the total sample size of approximately 414 subjects. Therefore, the study will randomize approximately 207 subjects in each individual group. The sample size was calculated using PASS software.

8.3 Definitions of analysis sets

8.3.1 Full analysis set

The full analysis set will consist of all randomized subjects who meet eligibility criteria and received at least 1 dose of Symbicort. This analysis set will be used for both efficacy and safety analyses.

8.4 Outcome measures for analyses

8.4.1 Primary outcome measure:

- Adherence measured as mean number of sets of puffs/day for the entire 6 month study period

8.4.2 Secondary outcome measures:

- Mean CCQ symptom score (total, symptom, mental, and function score) in the control vs. intervention group at baseline, end of study, and change over the 6 month period

- Mean total and domain weekly CCQ scores over each 2 month study interval (intervention group only)

- Mean number of sets of puffs/day for each 2 month study interval

- Mean and total number of adherent days (2 sets of 2 puffs per day) per subject

- Mean number of pharmacy refills

8.5 Methods for statistical analyses

All computations and generation of tables, listings, and figures will be performed using SAS version 9.2 or higher.

The SAP will be generated to provide the details of the planned analysis.

8.5.1 Demographic and baseline characteristics

Demographic and baseline characteristics will be summarized by intervention group, control group, and overall. Baseline demographic and clinical characteristics of study subjects will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum values for continuous variables); and number and percentage of subjects for categorical variables. Baseline characteristics will be provided with respect to

- Age, sex, and race (in countries where legally allowed)

- Baseline vital signs such as height, weight, pulse rate, blood pressure, respiratory rate, and temperature

- Baseline physical examination

- COPD disease severity via airflow limitation

- COPD disease via exacerbation history

- COPD treatment history prior to start of Symbicort

The categorical variables will be compared using a chi-square test and the continuous variables will be compared between treatment arms using a t-test.

8.5.2   Analysis of the primary variable (s)

8.5.2.1   Mean number of sets of Symbicort puffs/day over an average of 6 months

The number of sets of Symbicort puffs per day will be estimated using means and compared using t-test between the intervention and control groups over an average of 6 months. The mean numbers of sets of Symbicort puffs/per day are calculated as explained in Section 8.4.1.

8.5.3   Analysis of the secondary variable(s)

8.5.3.1   Mean CCQ scores

The CCQ domain and total scores will be summarized descriptively. The mean domain and total CCQ scores at baseline and EOT will estimated and compared using ANCOVA between the intervention and control groups.

Adjusted (least square) CCQ means may be analyzed for the statistically significant confounders.

8.5.3.2   Change in weekly total and domain CCQ scores in the intervention group for each 2 month interval

The change in weekly CCQ domain and total scores will be summarized descriptively. The change in mean weekly CCQ domain and total scores from baseline to 6 months will be estimated and compared using ANCOVA between the intervention and control groups. Additionally, the mean change between 2 immediate intervals and the first and last intervals will be estimated within intervention group and compared using ANCOVA.

The change from baseline to 6 months is calculated as weekly CCQ domain/total scores at 6 months – weekly CCQ domain/total scores at the baseline

The change between every 2-month intervals is calculated in intervention group as follows

Weekly CCQ domain/total scores at the follow-up period 4 months – weekly CCQ domain/total scores at the follow-up period 2 months

Weekly CCQ domain/total scores at the follow-up period 6 months –weekly CCQ domain/total scores at the follow-up period 4 months

Weekly CCQ domain/total scores at the follow-up period 6 months – weekly CCQ domain/total scores at the follow-up period 2 months

Adjusted (least square) means for change in CCQ scores may be provided for the statistical significant confounders.

8.5.3.3   Mean number of sets of Symbicort puffs per day at every 2 month interval

Mean number of sets of Symbicort puffs per day are calculated as explained in Section 8.4.2. The number of sets of Symbicort puffs per day will be summarized descriptively between and within treatment arms for every 2 months intervals. The comparisons of mean number of sets of Symbicort puffs per day between treatment arms at each interval will be performed using ANCOVA. The comparisons between each interval within individual treatment arm will be performed using ANCOVA.

8.5.3.4   Mean and total number of adherent days

The number of adherent days will be calculated as explained in Section 8.4.2. The number of adherent days will be summarized descriptively. The mean adherent days will be compared between the intervention and control groups using ANCOVA. Adjusted (least square) means for adherent days may be provided for the statistically significant covariates.

8.5.3.5   Mean number of Symbicort prescription refills

The mean number of Symbicort prescription refills will be calculated as explained in Section 8.4.2. The number of prescription refills will be summarized descriptively. The mean number of refills will be compared between the intervention and control groups using ANCOVA. Adjusted (least square) means for prescription refills may be provided for the statistically significant covariates.

8.5.4   Potential Covariates

The following covariates will be evaluated to assess their association with the secondary outcome measures of

- Demographics (age [continuous], sex [male, female], race [white, non-white])

- Smoking status (yes, no)

- Severity of COPD disease at baseline via level of airflow limitation-moderate: post-bronchodilator FEV1 % predicted 50 to 79%, severe + very severe : post-bronchodilator FEV% predicted < 50%

- Number of COPD exacerbations during the past 12 months at baseline (continuous)

- COPD severe exacerbations during past 12 months at baseline (severe exacerbations, not severe exacerbations) where severe exacerbation of COPD is defined as the hospitalization for COPD during the past 12 months of the baseline.

- Prior Symbicort treatment at baseline (Symbicort naïve, Symbicort pre-treated)

- Time on ICS/LABA medications in months at baseline (<6, ≥6)

If the number of subjects in the subcategories is <5, categorical covariates may be dropped or merged.

8.5.5   Subgroup analysis (if applicable)

Subgroup analyses will be performed for the secondary outcome measures of interest. Details of specific subgroups will be provided in the SAP. A 2- step approach will be followed for performing subgroup analyses. The step 1 will be analogous to performing analyses using either an ANCOVA for the continuous outcome variable. A backward elimination method will be used to select the best model.

The second step will include a t-test comparison between the treatment arms for the continuous secondary outcome measures stratified by individual covariates. The second step will be followed for all eligible covariates which have demonstrated statistically significant association in the first step.

The following subgroups are deemed to be of interest

- Sex (male, female)

- Race (white, non-white)

- Smoking status (yes, no)

- Severity of COPD disease at baseline (moderate, severe + very severe)

- COPD severe exacerbations during past 12 months at baseline (severe exacerbations, not severe exacerbations) where severe exacerbation of COPD is defined as the hospitalization for COPD during the past 12 months of the baseline.

- Prior Symbicort treatment at baseline (Symbicort naïve, Symbicort pre-treated)

- Time on ICS/LABA medications in months at baseline ($<6, \geq 6$)

For the binary outcomes, the proportion of subjects, odds ratios, and associated 95% confidence intervals will be estimated by the subgroup for intervention group and control. For the continuous outcomes the descriptive statistics will be provided. The subgroup analysis will only be performed if the number of subjects within each subgroup is at least 5.

8.5.6   Safety analysis

Safety analyses will include an analysis of concomitant medications use. Concomitant medications will be analyzed using medication preferred name and Anatomical Therapeutic Chemical class. The number and percentage of subjects using concomitant medication will be summarized. Adverse events will be presented in data listings.

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 will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures, the BreatheMate service (device and application), and any study specific procedures and systems utilized.

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 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 eCRFs

- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other

records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center need information or 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 center 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 CSP and the CSA, the terms of CSP 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 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 end of the study definition is for the entire study, and not for a specific site.

The study is expected to start in Q3 2016 and to end by Q3 2017. The recruitment period is expected to last approximately 6 months.

The study may be terminated at individual centers 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 ICS/LABA medications.

9.4 Data management by ▮▮▮▮▮

Data management will be performed by ▮▮▮▮, according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology

of the latest version of the Medical Dictionary for Regulatory Activities. Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by ▮▮▮▮▮ .

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data Management of genotype data

Not applicable.

Management of external data

Not applicable.

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 Council for Harmonization (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2   Subject data protection

The informed consent form (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 IRB 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 IRB, and to the study site staff.

The opinion of the IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any subject into the study.

The IRB 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 IRB annually.

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

AstraZeneca will provide Regulatory Authorities, IRBs, and PIs with safety updates/reports according to local requirements.

10.4   Informed consent

The PI(s) at each center will:

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

- Ensure each subject is notified that they are free to discontinue from the study at any time.

- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided.

- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study.

- Ensure the original, signed ICF(s) is/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 IRB.

10.5   Changes to the protocol and informed consent form

Study procedures will not be changed without the agreement of 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 CSP).

The amendment is to be approved by the relevant IRB 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(s). For distribution to IRB see Section 10.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's IRB 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 IRB.

10.6   Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IRB may perform audits or inspections at the center, 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, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

11.   LIST OF REFERENCES

Clinical COPD Questionnaire website
Clinical COPD Questionnaire website. http://ccq.nl/?page_id=15. Accessed January 15, 2016.

Feenstra et al 2001
Feenstra TL, van Genugten ML, Hoogenveen RT, Wouters EF, Rutten-van Mölken MP. The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. Am J Respir Crit Care Med 2001;164(4):590-596.

Ford et al 2013

Ford ES, Croft JB, Mannino DM, Wheaton AG, Zhang X, Giles WH. COPD surveillance--United States, 1999-2011. Chest 2013;144(1):284-305.

Ford et al 2015

Ford ES, Murphy LB, Khavjou O, Giles WH, Holt JB, Croft JB. Total and state-specific medical and absenteeism costs of chronic obstructive pulmonary disease among adults aged ≥18 years in the United States for 2010 and projections through 2020. Chest 2015;147(1):31-45.

Kern et al 2015

Kern DM, Davis J, Williams SA, Tunceli O, Wu B, Hollis S, et al. Comparative effectiveness of budesonide/formoterol combination and fluticasone/salmeterol combination among chronic obstructive pulmonary disease patients new to controller treatment: a US administrative claims database study. Respir Res 2015;16:52.

Mannino et al 2002

Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. Respir Care 2002;47(10):1184-1199.

Murphy et al 2013

Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. Natl Vital Stat Rep 2013;61(4):1-117.

NHLBI 2012

National Institutes of Health National Heart, Lung, and Blood Institute Fact Book Prevalence of Common Cardiovascular and Lung Diseases, U.S., 2007-2011. *https://www nhlbi nih gov/about/documents/factbook/2012/chapter4 htm#4_5* ;2014.

Simmons et al 1996

Simmons MS, Nides MA, Rand CS, Wise RA, Tashkin DP Trends in compliance with bronchodilator inhaler use between follow-up visits in a clinical trial. Chest 1996: 109:963-968.

Simoni-Wastila et al 2012

Simoni-Wastila L, Wei YJ, Qian J, Zuckerman IH, Stuart B, Shaffer T, et al. Association of chronic obstructive pulmonary disease maintenance medication adherence with all-cause hospitalization and spending in a Medicare population. Am J Geriatr Pharmacother 2012;10(3):201-210.

van den Boom et al 1998

van den Boom G, van Schayck CP, van Mollen MP, Tirimanna PR, den Otter JJ, van Grunsven PM, et al. Active detection of chronic obstructive pulmonary disease and asthma in the general population. Results and economic consequences of the DIMCA program. Am J Respir Crit Care Med 1998;158(6):1730-1738.

van der Molen et al 2003

van der Molen T, Willemse BW, Schokker S, ten Hacken, NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health Qual Life Outcomes 2003;1:13. DOI: 10.1186/1477-7525-1-13.

Clinical Study Protocol Appendix A

Drug Substance   Symbicort

Study Code   D589CL00003

Edition Number   3.0

Date   03 October 2016

Protocol Dated   03 October 2016

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A randomized clinical study to assess the impact of Symbicort® pMDI medication reminders on adherence in COPD patients

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

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

ASTRAZENECA SIGNATURE(S)

A randomized clinical study to assess the impact of Symbicort® pMDI medication reminders on adherence in COPD patients

---

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

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development
site representative

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

ASTRAZENECA SIGNATURE(S)

A randomized clinical study to assess the impact of Symbicort® pMDI medication reminders on adherence in COPD patients

---

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

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representativ

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

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

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). 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, hospitalization, 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 intravenous 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 anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization

- Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

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

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

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

Appendix C
Clinical COPD Questionnaire

1. CLINICAL COPD QUESTIONNAIRE

CLINICAL COPD QUESTIONNAIRE

Please **circle** the number of the response that best describes how you have been feeling during the **past week**.
(Only **one** response for each question).

On average, **during the past week**, how often did you feel:	never	hardly ever	a few times	several times	Many Times	a great many times	almost all the time
1. Short of breath **at rest**?	0	1	2	3	4	5	6
2. Short of breath **doing physical Activities**?	0	1	2	3	4	5	6
3. **Concerned** about getting a cold or your breathing getting worse?	0	1	2	3	4	5	6
4. **Depressed (down)** because of your breathing problems?	0	1	2	3	4	5	6
In general, **during the past week**, how much of the time:							
5. Did you **cough**?	0	1	2	3	4	5	6
6. Did you **produce phlegm**?	0	1	2	3	4	5	6
On average, **during the past week**, how limited were you in these activities **because of your breathing problems**:	not limited at all	very slightly limited	slightly limited	moderately limited	very limited	extremely limited	totally limited /or unable to do
7. **Strenuous physical activities** (such as climbing stairs, hurrying, doing sports)?	0	1	2	3	4	5	6
8. **Moderate physical activities** (such as walking, housework, carrying things)?	0	1	2	3	4	5	6
9. **Daily activities at home** (such as dressing, washing yourself)?	0	1	2	3	4	5	6
10. **Social activities** (such as talking, being with children, visiting friends/ relatives)?	0	1	2	3	4	5	6

Clinical Study Protocol Appendix D

Drug Substance	Symbicort
Study Code	D589CL00003
Edition Number	3.0
Date	03 October 2016

Appendix D
User Satisfaction Survey

1. USER SATISFACTION SURVEY

BreatheMate User Satisfaction Survey - Patient

We would like your feedback on the product. We will assess and use your feedback to improve the product.

PART 1 – BreatheMate Mobile App

Have you used BreatheMate mobile app? YES/NO [if 'YES' selected, continues to questions below, 'NO' exits part 1]

	Statement	1 Strongly disagree	2 Disagree	3 Indifferent	4 Agree	5 Strongly agree
1	The BreatheMate app is easy to use					
2	I did not have any technical difficulties in using the app and phone					
3	The BreatheMate app has a suitable number of options to tailor how I would like to receive my reminders					
4	The BreatheMate app has a clean, uncluttered design					
5	The medication reminders were helpful to ensure I was talking my medication as prescribed.					

PART 2 – SmartTouch Symbicort Device

Have you used the SmartTouch Symbicort device? YES/NO [YES, continues to questions below, NO exits]

	Statement	1 Strongly disagree	2 Disagree	3 Indifferent	4 Agree	5 Strongly agree
1	SmartTouch Symbicort device is easy to use					
2	SmartTouch Symbicort device has all the features I expected it to have					
3	The visual and audio reminders on the device were helpful to ensure I was taking my medication as prescribed					
4	The SmartTouch Symbicort device was easy to take on and off of my Symbicort medication					
5	SmartTouch Symbicort device has a great look and feel					

BreatheMate User Satisfaction Survey – Investigator and Study Coordinator

[Note: Investigators and Study Coordinators will complete separate and identical User Satisfaction Surveys at the completion of the study]

Have you used the BreatheMate web portal? YES/NO [YES, continues to questions below, NO exits]

	Statement	1 Strongly disagree	2 Disagree	3 Indifferent	4 Agree	5 Strongly agree
1	The BreatheMate web portal is easy to use					
2	The BreatheMate web portal has all the features I expected it to have					
3	I could complete/view tasks in the BreatheMate web portal with a minimum number of clicks					
4	The BreatheMate web portal has a clean, uncluttered design					
5	The information provided by the BreatheMate web portal is easy to find and to understand (including graphs)					
6	The BreatheMate reminders improve patient compliance with their daily ICS/LABA medication					
7	The BreateMate service improves medication refills					
8	The BreatheMate service would be useful to me in helping patients to manage their condition					

Thank you very much for completing the survey, your support and feedback are appreciated