2.0 SYNOPSIS

Name of Sponsor/Company: AstraZeneca	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Aclidinium bromide/formoterol fumarate fixed-dose combination (FDC)	**Volume:**	
Name of Active Ingredient: 3(R)-(2-hydroxy-2,2-dithiophen-2-yl-acetoxy)-1-(3 phenoxypropyl)-1-azoniabicyclo [2.2.2] octane bromide and (±)-N-[2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4 methoxyphenyl) 1 methylethyl]amino]ethyl]phenyl] formamide, (E)-2-butenedioate (2:1 salt) dihydrate	**Page:**	

Study Number: LAC-MD-32

Title of Study: A Long-Term, Randomized Study of the Safety and Tolerability of a Fixed-Dose Combination of Aclidinium Bromide/Formoterol Fumarate Compared With Formoterol Fumarate in Patients With Moderate to Severe, Stable Chronic Obstructive Pulmonary Disease (COPD)

Investigators: [redacted]

Study Centers: [redacted]

Publication (reference): Not applicable

Study Period (years): First Patient First Visit: 19 Sep 2011 Last Patient Last Visit/Early Termination Date of Study: 13 Mar 2013	**Development Phase:** 3

Objectives: To assess the long-term safety and tolerability of inhaled aclidinium bromide/formoterol fixed-dose combination (FDC) 400 µg/12 µg administered twice daily (BID), once in the morning and once in the evening, via a multidose dry-powder inhaler in patients with moderate to severe, stable COPD

Study Design: This was a randomized, double-blind, active-controlled, parallel group, long-term clinical study. Patients meeting entry criteria were randomized (2:1) to either the aclidinium bromide/formoterol FDC 400 µg/12 µg arm or the formoterol 12 µg arm, both administered BID via the dry-powder inhaler. The study consisted of a 2- to 3-week run-in period designed to assess the stability of patients' disease and establish each patient's baseline characteristics. The run-in period was followed by a 52-week double-blind treatment period.

Diagnosis and Main Criteria for Inclusion: Male or female outpatients, of at least 40 years of age, who had a diagnosis of moderate to severe, stable COPD as defined by guidelines of the Global Initiative for Chronic Obstructive Lung Disease, stable airway obstruction (specifically, a postbronchodilator forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] < 70% at Visit 1), postalbuterol FEV_1 values ≥ 30% to < 80% of predicted value, and a smoking history of 10 pack-years or more. Patients who had been hospitalized for an acute COPD exacerbation within 3 months before Visit 1 or who had any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation in the 6 weeks before Visit 1 could not participate in the study.

Investigational Product, Dose and Mode of Administration, Lot Number:
Aclidinium bromide/formoterol FDC 400 /12 µg administered BID, once in the morning and once in the evening, via a multidose dry-powder inhaler
Lot number: L0004629
Expiration/retest date: 02 Dec 2013

Reference Therapy, Dose and Mode of Administration, Batch Number: Formoterol 12 µg administered BID, once in the morning and once in the evening, via a multidose dry-powder inhaler
Lot number: L0004569
Expiration/retest date: 19 Oct 2013

Duration of Treatment: 52-week treatment period

Criteria for Evaluation:
Efficacy
There were no primary and secondary efficacy assessments. Additional efficacy assessments were evaluated and included morning predose (trough) FEV_1 and FVC, COPD exacerbations, and rescue medication use.
Health Economics and Outcomes Research
Health Economics and Outcomes Research assessments were self-administered by the patient each day beginning at Visit 1 (Screening Visit). The assessments included a night-time symptoms questionnaire, and early morning symptoms questionnaire.

Safety
Adverse event (AE) recording, physical examinations, clinical laboratory evaluations (hematology, chemistry, urinalysis, theophylline), electrocardiograms (ECGs), and vital signs (including blood pressure, pulse rate, respiratory rate, and body mass index). In addition, Holter monitoring was performed in a subset of patients.

Statistical Methods: All safety parameters were analyzed descriptively. Safety analyses were based on the Safety Population, defined as all randomized patients who took at least 1 dose of double-blind investigational product.

Rate of moderate-severe and any (mild-moderate-severe) COPD exacerbations per patient per year were analyzed by means of a negative binomial model. Time to first COPD exacerbation was analyzed by means of a Cox proportional hazard model. Statistical comparisons and corresponding p-values were reported. All COPD exacerbation efficacy analyses were based on an intent to treat (ITT)-exacerbation population, defined as all randomized patients who took at least 1 dose of double-blind investigational product.

All spirometric efficacy parameters were analyzed by means of a mixed model for repeated measures with corresponding baseline FEV_1, pre- and postbronchodilator (albuterol) FEV_1 (or FVC), and age as covariates, and sex, treatment group, visit, smoking-status, and treatment group-by-visit interaction as fixed-effect factors with the unstructured covariance matrix for the within-patient correlation. All efficacy analyses except COPD exacerbation efficacy parameters were based on the ITT Population using the observed-case approach, unless otherwise specified. The ITT Population was defined as all patients in the Safety Population who had a baseline and at least 1 postbaseline assessment of FEV_1.

Disposition: The number and percentage of patients completing and prematurely discontinuing the double-blind treatment period are listed for each treatment group and pooled across treatment groups for the Randomized Population.

Demographics and Other Baseline Characteristics: Demographic parameters and other baseline characteristics were summarized by treatment group for the Safety and ITT populations. For continuous variables, the number of nonmissing observations, mean, SD, median, minimum, and maximum is presented. No statistical tests were performed.

Health Economics and Outcomes Research: The analyses of all health economics and outcomes research (HEOR) parameters were based on the ITT Population using observed data.

SUMMARY OF RESULTS:

Disposition: A total of 590 patients were randomized to receive double-blind treatment; 392 received FDC 400/12 µg and 198 received formoterol 12 µg. Approximately 33% of all patients were discontinued from the study: 32.4% in the FDC 400/12 µg treatment group and 32.8% in the formoterol 12 µg treatment group. The most frequent reasons for discontinuation were withdrawal of consent (7.8% overall), adverse event (6.6% overall), protocol violation (6.1% overall), and insufficient therapeutic response (5.8% overall). In general, the percentage of patients who discontinued for these reasons was comparable between the treatment groups.

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Number of Patients in Populations

Population	***Number of Patients***		
	FDC 400/12 µg	***Formoterol 12 µg***	***Total***
Randomized	392	198	590
Safety	392	198	590
Holter substudy	107	54	161
ITT	385	196	581
ITT-Exacerbation	392	198	590

FDC = fixed-dose combination; ITT = intent to treat.

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

The Safety Population consisted of all patients in the Randomized Population who took at least 1 dose of double-blind treatment.

The Intent-to-Treat (ITT) Population consisted of all patients in the Safety Population who had a baseline and at least 1 postbaseline assessment of FEV_1.

The ITT-Exacerbation Population consisted of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product.

Demographics and Other Baseline Characteristics: Both treatment groups were generally comparable with respect to the demographic and physical characteristics. The mean age was 63.9 and 64.7 years in the FDC 400/12 µg and formoterol 12 µg treatment groups, respectively. The majority of patients enrolled in each treatment group were male (55.1% each). Most patients in each treatment group were white (92.9% and 91.4% in the FDC 400/12 µg and formoterol 12 µg treatment groups, respectively) followed by black (5.4% and 8.1% in the FDC 400/12 µg and formoterol 12 µg treatment groups, respectively). The mean body mass index was similar among the groups and ranged from 27.5 to 27.8 kg/m^2.

At Screening (Visit 1), both treatment groups were comparable with respect to FEV_1 prebronchodilator values (1.332 L and 1.259 L in the FDC 400/12 µg and formoterol 12 µg treatment groups, respectively). The mean postbronchodilator FEV_1/FVC ratios for each group were below the 70% threshold used to define COPD (52.7% and 50.6% in the FDC 400/12 µg and formoterol 12 µg treatment groups, respectively). The mean postbronchodilator FEV_1 was 51.8% and 50.5% of the predicted value in the FDC 400/12 µg and formoterol 12 µg treatment groups, respectively). Mean bronchodilator reversibility (calculated as a percentage change of the postbronchodilator FEV_1 from the prebronchodilator value after the administration of 400 µg of albuterol) was 17.7% in the FDC 400/12 µg treatment group and 15.9% in the formoterol 12 µg treatment group.

Efficacy Results:

Bronchodilation Results: The results of spirometric testing demonstrate that the FDC 400/12 µg treatment group had significantly greater lung function improvement as evidenced by the adjusted mean change from baseline in morning predose (trough) FEV_1 over patients in the formoterol 12 µg treatment group (Week 1: difference = 0.087 L, $p < 0.0001$ and Week 52: difference = 0.082 L, $p = 0.0207$). Lung function improvement was sustained over 52 weeks for FDC 400/12 µg compared with formoterol 12 µg. Similarly, greater improvements in trough FVC were observed with FDC 400/12 µg compared with formoterol 12 µg throughout the treatment period (Week 1: difference = 0.158 L, $p < 0.0001$ and Week 52: difference = 0.146 L, $p = 0.0023$).

COPD Exacerbation Results: There was no difference in the rate of COPD exacerbations or time to first exacerbation between the 2 treatment groups. It is important to note that the study had a randomization ratio of 2:1 and lacked sufficient power to detect statistical reductions in COPD exacerbations in the FDC 400/12 µg group relative to the formoterol 12 µg group.

Rescue Medication Use Results: Both treatment groups used fewer puffs of daily rescue medication compared with baseline throughout the double-blind treatment period, and the FDC 400/12 µg treatment group used numerically less rescue medication than the formoterol 12 µg treatment group at most time points.

Health Economics and Outcomes Research: At Week 52, the FDC 400/12 µg treatment group had numerically greater decreases in adjusted means than formoterol 12 µg for most of the COPD nighttime and morning symptom variables.

Safety Results:

When interpreting the safety data in this long-term study, it is important to take into consideration the 2:1 randomization ratio between the FDC 400/12 µg and formoterol 12 µg treatment groups.

The percentage of patients having treatment-emergent adverse events (TEAEs) was numerically higher in the FDC 400/12 µg treatment group (71.4%) compared with the formoterol 12 µg treatment group (65.7%). The most commonly reported TEAEs (reported in ≥ 5% of patients in both treatment groups) were sinusitis and urinary tract infection (UTI). Both of these TEAEs were reported in similar proportions of patients in each treatment group (5.1% and 5.6% for sinusitis, and 6.6% and 5.6% for UTI, in the FDC 400/12 µg and formoterol 12 µg groups, respectively).

Other commonly occurring TEAEs that were reported in ≥ 2% of the patients in either treatment group and that occurred more frequently for FDC 400/12 µg than formoterol 12 µg included nasopharyngitis (6.4% and 4.5%, respectively), anxiety (5.9% and 2.5%, respectively), muscle spasms (3.8% and 2.0%, respectively), back pain (4.8% and 2.5%, respectively), and headache (2.8% and 2.5%, respectively).

The majority of TEAEs were mild and moderate in intensity. The percentage of patients having 1 or more TEAEs reported as severe was 12.2% and 15.7% in the FDC 400/12 µg and formoterol 12 µg treatment groups, respectively. The most commonly reported severe TEAEs were pneumonia (3 patients) in the FDC 400/12 µg treatment group and coronary artery disease, intervertebral disc protrusion, and nausea (2 patients each) in the formoterol 12 µg treatment group.

The percentage of patients having 1 or more TEAEs considered by the Investigator to be related to the investigational product was 13.8% and 13.1% for FDC 400/12 µg and formoterol 12 µg, respectively. The most commonly reported of the related TEAEs were cough and muscle spasms (4 patients each [1.0%]) in the FDC 400/12 µg treatment group and dyspnea (5 patients [2.5%]) in the formoterol 12 µg treatment group.

The percentage of patients who had an on-therapy serious adverse event (SAE) was similar between treatment groups (9.7% and 10.6% for FDC 400/12 µg and formoterol 12 µg, respectively). The most commonly reported SAE was pneumonia in 4 patients (1.0%) in the FDC 400/12 µg treatment group and 1 patient (0.5%) in the formoterol 12 µg treatment group. All cases of pneumonia were moderate to severe in intensity and patients recovered from pneumonia. Only 1 patient experienced a temporary dose interruption due to pneumonia. All other on-therapy SAEs were reported by no more than 3 patients overall. Only 1 patient (FDC 400/12 µg group) had an SAE (severe ventricular tachycardia) that was considered by the Investigator to be related to the investigational product. The patient was discontinued from the study due to the SAE.

A total of 6 deaths occurred during the treatment period, and 2 deaths occurred more than 30 days after the last dose of investigational product; none of the deaths was judged to be related to the investigational product by the Investigator. Of the 6 deaths that occurred during the treatment period, 5 occurred in the FDC 400/12 µg group and 1 occurred in the formoterol 12 µg group. The causes of death were variable, did not suggest any specific pattern, and were consistent with those that are found in the general COPD population. There was no specific cause or pattern observed in the overall causes of death or temporal relationship to investigational product administration. Specific causes of death included completed suicide, metastatic lung cancer, cardio-respiratory arrest, death [cause unknown but adjudicated to cardiovascular death], and death [death unexplained but adjudicated to cardiovascular death]) in the FDC 400/12 µg treatment group and COPD exacerbation in the formoterol 12 µg treatment group. When considering the 2:1 randomization ratio used in this study, the outcome of 5 observed deaths in the FDC 400/12 µg group and 1 in the formoterol 12 µg group did not emerge as a signal in this 52-week study.

A similar percentage of patients discontinued the study due to an AE (6.6% in the FDC 400/12 µg treatment group and 7.1% in the formoterol 12 µg treatment group). The most commonly reported TEAEs resulting in discontinuation were death and ventricular tachycardia (2 patients [0.5%] each, both in the FDC 400/12 µg treatment group) and dyspnea (2 patients [1.0%], both in the formoterol 12 µg treatment group).

The number of major adverse cardiovascular events (MACEs) based on the adjudication committee was low and reported at similar incidences between treatment groups. A total of 3 patients had 1 or more MACEs: 2 patients (0.5%) were from the FDC 400/12 µg treatment group and 1 patient (0.5%) was from the formoterol 12 µg treatment group. The incidence of MACEs by adjudicated subcategory was the same for both TEAEs and SAEs. All MACEs were considered to be unrelated to treatment with investigational product.

The incidence of cardiac events by SMQ for FDC 400/12 µg was numerically lower than or comparable with that observed in the formoterol 12 µg group suggesting no added safety risk for FDC 400/12 µg compared with formoterol 12 µg. Cardiac events based on adjudicated SAEs were reported in the SMQs of ischemic heart disease, supraventricular tachyarrhythmia, and cardiac failure. For the ischemic heart disease SMQ, 2 cardiac events (0.6%) were reported in the FDC 400/12 µg treatment group and 1 cardiac event (0.5%) was reported in the formoterol 12 µg treatment group. For the supraventricular tachyarrhythmia SMQ, a total of 2 cardiac events (0.5%) were reported in the FDC 400/12 µg treatment group and 1 cardiac event (0.5%) was reported in the formoterol 12 µg treatment group. For the cardiac failure SMQ, a total of 1 cardiac event (0.3%) was reported in the FDC 400/12 µg treatment group and 1 cardiac event (0.5%) was reported in the formoterol 12 µg treatment group. These events were not considered by the Investigator to be related to the investigational product.

The incidence of hemorrhagic cerebrovascular conditions by SMQ was comparable between the FDC 400/12 µg (0%) and formoterol 12 µg (0.5%) treatment groups. The incidence of ischemic cerebrovascular conditions in the FDC 400/12 µg treatment group was low (0.5%). There were no serious adjudicated events of ischemic cerebrovascular SMQ reported in the formoterol 12 µg treatment group. However, when analyzing the rates, it is important to take into consideration the 2:1 randomization ratio between the FDC 400/12 µg and formoterol 12 µg treatment groups. The safety risks were comparable between the 2 treatment arms.

Overall, UTI was the most frequently reported (in 2% or more of the patients in either group) potential anticholinergic TEAE (6.6% and 5.6% for FDC 400/12 µg and formoterol 12 µg, respectively) followed by dizziness (2.6% and 4.0% for FDC 400/12 µg and formoterol 12 µg, respectively), and constipation (1.5% vs 3.5% for FDC 400/12 µg and formoterol 12 µg, respectively). UTI was predominately noted in female patients who are generally more prone to develop UTIs, and the majority of the cases were unrelated to investigational product, and mild or moderate in intensity. The same patients having UTI, constipation and dizziness are included in the potential β_2-agonist TEAEs discussed below.

Potential β_2-agonist TEAEs that occurred in 2% or more of the patients in the FDC 400/12 µg treatment group vs formoterol 12 µg treatment group were UTIs (6.6% vs 5.6%), anxiety (5.9% vs 2.5%), muscle spasms (3.8% vs 2.0%), headache (2.8% vs 2.5%), hypertension (2.8% vs 4.0%), insomnia (2.6% vs 3.0%),dizziness (2.6% vs 4.0%), cough (2.6% vs 5.1%), peripheral edema (2.0% vs 2.5%), constipation (1.5% vs 3.5%), hyperglycemia (1.3% vs 2.5%), myalgia (1.0% vs 2.0%), and tremor (1.0% vs 2.5%). These types of TEAEs are often encountered with this class of drugs.

The change from baseline in clinical laboratory tests, vital signs, and ECG parameters, including Holter monitoring in a subset of patients, was similar between treatment groups and of no clinical relevance.

The proportions of patients with potentially clinically significant (PCS) postbaseline laboratory, vital signs, and ECG values were similar in each treatment group. Creatine kinase was the PCS laboratory parameter most often reported as a TEAE (7 patients in the FDC 400/12 µg and 5 patients in the formoterol 12 µg treatment group). None of these events were SAEs. The majority of the patients had either recently undergone strenuous manual work/strenuous exercise or had concomitantly received statin medications that are known to increase creatine phosphokinase levels in the blood. Elevated blood creatine phosphokinase TEAEs in 2 patients in the FDC 400/12 µg group were considered by the Investigator to be related to the investigational product; 1 of these patients discontinued the study due to the TEAE. Tachycardia or sinus tachycardia (3 patients for FDC 400/12 µg) and hypertension or orthostatic hypotension (3 patients for formoterol 12 µg) were the only PCS postbaseline vital signs reported as TEAEs. Tachycardia or sinus tachycardia (3 patients) and ECG QT prolonged (2 patients for FDC 400/12 µg) were the only PCS postbaseline ECG findings reported as TEAEs.

CONCLUSIONS: • [redacted] • [redacted] • [redacted] • [redacted]
Date of the Report 19 Sep 2013