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-31

Title of Study: A Phase III, Randomized, Double-blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Tolerability of Two Fixed-Dose Combinations of Aclidinium Bromide/Formoterol Fumarate Compared With Aclidinium Bromide, Formoterol Fumarate and Placebo for 24-Weeks Treatment in Patients With Moderate to Severe, Stable Chronic Obstructive Pulmonary Disease (COPD) (AUGMENT COPD)

Investigators:

Study Centers:

Publication (reference): Not applicable

Study Period: First Patient First Visit: 04 Oct 2011 Last Patient Last Visit: 06 Feb 2013	**Development Phase:** 3

Objectives:

1. Assess the maintenance bronchodilator effect of the FDC versus monotherapies
2. Assess the effects of the FDC in terms of COPD symptoms and disease-related health status (versus placebo)
3. Evaluate the safety and tolerability of the FDC (versus monotherapies and placebo)

Study Design: This was a multicenter, multinational, randomized, double-blind, placebo- and active-controlled, parallel-group, 24-week treatment study. Patients were randomized at a 1:1:1:1:1 ratio to an FDC of aclidinium bromide/formoterol fumarate 400/12 µg, an FDC of aclidinium bromide/formoterol fumarate 400/6 µg, monotherapy aclidinium 400 µg, monotherapy formoterol 12 µg, or placebo, all administered twice daily via investigational inhaler.

Diagnosis and Main Criteria for Inclusion: Male and female patients, ≥ 40 years of age, a diagnosis of stable moderate to severe COPD as defined by criteria of the Global Initiative for Chronic Obstructive Lung Disease (post-albuterol/salbutamol forced expiratory volume in 1 second [FEV_1] ≥ 30% to < 80% predicted and FEV_1/forced vital capacity < 70% predicted) and a smoking history of ≥ 10 pack-years.

Number of Patients: A total of 3260 patients were screened and 1692 were randomized into the study.

	Placebo	*FDC 400/12 µg*	*FDC 400/6 µg*	*Aclidinium 400 µg*	*Formoterol 12 µg*	*Total*
Total number of patients screened = 3260						
Randomized Population, N	337	338	338	340	339	1692
Safety Population, N	332	335	333	337	332	1669
Holter Substudy Population	44	44	48	47	48	231
Intent-to-Treat (ITT) Population, N	331	335	333	337	332	1668
Spirometry Substudy Population	58	53	50	52	57	270
ITT-Exacerbations Population, N	332	335	333	337	332	1669
Per-Protocol (PP) Population, N	296	302	300	292	301	1491

The Screened Population consisted of all patients who signed a written informed consent form and received a patient identification number.

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

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

The ITT Population for all efficacy endpoints except for COPD exacerbations and Exacerbation of Chronic Pulmonary Disease Tool–Respiratory Symptoms (E-RS) consisted of all patients in the Safety Population who had at least 1 baseline and 1 postbaseline assessment of FEV_1.

The ITT Population for COPD exacerbation endpoints and E-RS (ITT-Exacerbations) consisted of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product.

The PP Population consisted of the subset of patients from the ITT Population who:

a. Met all inclusion/exclusion criteria liable to affect the efficacy assessments
b. Sufficiently complied with the study treatment
c. Did not present major deviations from the protocol that may have affected efficacy.

Investigational Product, Dose and Mode of Administration, Batch Number:

- Aclidinium/formoterol FDC 400/12 µg, lots ABFF015 and 1090483
- Aclidinium/formoterol FDC 400/6 µg, lot ABFF009
- Aclidinium monotherapy 400 µg, lot DPI061
- Formoterol monotherapy 12 µg, lots K16-185 and K16-213

All administered twice daily (once in the morning and once in the evening) via investigational inhaler

Reference Therapy, Dose and Mode of Administration, Batch Number:
Placebo administered twice daily (once in the morning and once in the evening) via investigational inhaler, lot DPI05

Duration of Treatment: 24-week double-blind treatment period

Criteria for Evaluation:

Efficacy

Primary:

- Change from baseline in 1-hour morning postdose FEV_1 at Week 24 (each dose of FDC versus aclidinium 400 µg)
- Change from baseline in morning predose (trough) FEV_1 at Week 24 (each dose of FDC versus formoterol 12 µg)

Secondary:

- Improvement of Transition Dyspnea Index (TDI) focal score at Week 24 (each dose of FDC versus placebo)
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24 (each dose of FDC versus placebo; aclidinium 400 µg versus placebo for US filing only)
- Reduction in rate of moderate or severe COPD exacerbation per patient per year due to the effect of aclidinium 400 µg (assessed using patients on aclidinium 400 µg relative to placebo based on pooled data from M/40464/30 and LAC-MD-31)
- Reduction in rate of moderate or severe COPD exacerbation per patient per year in each dose of FDC relative to placebo based on pooled data from M/40464/30 and LAC-MD-31

Additional:

- Pulmonary function (pre-morning and post-morning dose pulmonary function tests; FEV_1, FVC, inspiratory capacity are done at every visit except at Week 18 for the post-morning dose pulmonary function tests)
- Dyspnea
- Health-related quality of life
- COPD exacerbations based on the electronic case report form
- COPD exacerbations derived from the Exacerbation of Chronic Pulmonary Disease Tool

Safety: Adverse events (AEs) recording, physical examinations, clinical laboratory evaluations (hematology, chemistry, urinalysis, theophylline), electrocardiograms, vital signs (including pulse rate, sitting systolic and diastolic blood pressure, respiratory rate, weight, and body mass index), Holter monitoring (substudy patients only)

Health economics and outcomes research (HEOR)*:* Nighttime Symptoms of COPD Instrument (NiSCI), Early Morning Symptoms of COPD Instrument (EMSCI), exploratory nighttime and early morning symptom questions, Patient Global Impression of Change (PGIC), Health Resource Utilization Questionnaire

Statistical Methods:

Disposition: All patient disposition analyses were based on the Randomized Population. The percentage of patients who prematurely discontinued was calculated for each of the treatment groups. No statistical tests were performed.

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

Efficacy: The coprimary efficacy parameters (change from baseline in 1-hour morning postdose FEV_1 at Week 24 and change from baseline in morning predose [trough] FEV_1 at Week 24) were analyzed by means of mixed model for repeated measures (MMRM), with pre- and postbronchodilator FEV_1, age, baseline FEV_1, as covariates and treatment group, sex, smoking status, visit and treatment group-by-visit interaction as fixed effect factors.

The secondary efficacy parameters (change from baseline in SGRQ total score and improvement in TDI focal score at Week 24) were analyzed by means of MMRM, adjusted for the corresponding baseline value (SGRQ total score at baseline or BDI focal score) and age as covariates, and treatment group, sex, smoking status, visit, and treatment group=by-visit interaction as fixed-effect factors. The statistical methods and results for the secondary enpoint of moderate or severe COPD exacerbation are reported in the integrated summary of efficacy since they are based on the pooled data from studies M/40464/30 and LAC-MD-31.

Safety: Safety parameters were summarized for each treatment group with descriptive statistics that were based on the Safety Population.

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 3260 patients were screened and 1692 patients were randomized into the study. FDC 400/12 µg and FDC 400/6 µg had the highest incidences of study completion (80.5% and 81.7%, respectively). Comparatively, 70.0%, 78.8%, and 79.6% of patients in the placebo, aclidinium 400 µg, and formoterol 12 µg treatment groups, completed the study.

Demographics and Other Baseline Characteristics: All active and placebo treatment groups were comparable with respect to demographic and baseline characteristics.

Efficacy Results:

Discussion of Efficacy Results:

Treatment with FDC 400/12 µg or FDC 400/6 µg BID (once in the morning and once in the evening) for 24 weeks is effective therapy for patients with moderate to severe COPD as compared to placebo or monotherapies, as was demonstrated across multiple efficacy parameters. The totality of data from this study demonstrate the efficacy of aclidinium/formoterol FDC 400/12 µg for the maintenance treatment of COPD across spirometric and supportive nonspirometric endpoints (COPD exacerbations, E-RS symptoms, rescue medication) and support the selection of FDC 400/12 µg as the intended dose for clinical use.

Patients treated with aclidinium/formoterol FDC 400/12 µg BID demonstrated statistically significant improvements in airflow limitation compared to patients treated with placebo and the aclidinium 400 µg and formoterol 12 µg monotherapies, as well as statistically significant and clinically meaningful improvements in health outcomes as measured by SGRQ total score and symptom frequency as measured by the TDI focal score. Additionally, a trend towards reduction in COPD exacerbations was noted, although the study lacked sufficient statistical power to detect a difference in exacerbations. In contrast, the efficacy of aclidinium/formoterol FDC 400/6µg BID failed to meet 1 of the spirometric coprimary endpoints and did not achieve clinically meaningful improvements in SGRQ, although a clinically meaningful improvement in dyspnea, as measured by TDI, was shown.

Efficacy Conclusions:

When results presented in this section are adjusted for the multiplicity it will be explicitly stated in text. If not explicitly stated, all results presented in this section are not adjusted for the multiplicity, and all reported p-values are considered to be nominal.

Efficacy of aclidinium/formoterol FDC 400/12 µg and FDC 400/6 µg BID was demonstrated across the coprimary endpoints as follows:

- The FDC 400/12 µg BID treatment achieved statistical significance in both coprimary efficacy endpoints: change from baseline in FEV_1 at 1-hour postdose versus aclidinium 400 µg (0.108 L [$p < 0.0001$]) and change from baseline in morning predose (trough) FEV_1 versus formoterol 12 µg (0.045 L [$p = 0.0102$]) at Week 24. The results for both tests met both coprimary endpoints for the FDC 400/12 µg and are statistically significant after multiplicity adjustment for the US and the EU filings
- The bronchodilatory effect of FDC 400/12 µg BID versus placebo was shown to be clinically important and statistically significant (the difference between FDC 400/12 µg BID and placebo at Week 24 based on change from baseline in FEV_1 was 0.130 L at predose and 0.284 L at 1-hour postdose)
- The FDC 400/6 µg BID treatment achieved statistical significance in bronchodilation over aclidinium 400 µg (0.087 L [$p < 0.0001$]) based on the change from baseline in FEV_1 at 1-hour postdose at Week 24, but failed to reach statistical significance in bronchodilation over formoterol 12 µg (0.026 L [$p = 0.1325$]) based on change from baseline in morning predose (trough) FEV_1 at Week 24. The first coprimary endpoint for the FDC 400/6 µg is statistically significant for 1-hour postdose after multiplicity adjustment, but the effect failed to meet statistical significance on the second coprimary endpoint (morning predose [trough] FEV_1) for the US as well as for the EU filings

Efficacy of aclidinium/formoterol FDC 400/12 µg and FDC 400/6 µg BID was demonstrated across the secondary endpoints as follows:

- The placebo-adjusted improvement in SGRQ total score observed with FDC 400/12 µg (–4.35 units) was statistically significant and of a magnitude that is considered clinically meaningful (minimal clinically important difference [MCID] of ≥ 4 units). The FDC 400/12 µg also demonstrated statistically significant ($p < 0.0001$) improvements in health outcomes (SGRQ total score) as compared with placebo after adjustment for multiple comparisons for the US filing. This improvement was nominally significant for the EU filing, but such significance level, $p < 0.0001$, supports that the effect on SGRQ is true
- At Week 24, patients receiving FDC 400/12 µg showed statistical significance and clinically meaningful (MCID of ≥ 1 unit) improvements in dyspnea (TDI focal score) compared with placebo (by 1.44 units). FDC 400/12 µg achieved statistical significance after adjusting for multiplicity ($p < 0.0001$) for the EU filing, but only nominal significance for the US filing since it was not controlled for multiplicity by study design
- The placebo-adjusted improvement in SGRQ total score observed with FDC 400/6 µg (–3.73 units) reached statistical significance, and almost reached the magnitude that is considered clinically meaningful (MCID of ≥ 4 units). The FDC 400/6 µg achieved nominal significance for the SGRQ ($p = 0.0005$)
- At Week 24, patients receiving FDC 400/6 µg showed statistical significance and clinically meaningful (MCID of ≥ 1 unit) improvements in dyspnea (TDI focal score) compared with placebo (by 1.40 units). FDC 400/6 µg achieved nominal significance for TDI ($p < 0.0001$)

Additionally, the secondary efficacy endpoint for aclidinium 400 µg showed that the placebo-adjusted improvement in SGRQ total score observed with aclidinium 400 µg (–4.22 units) reached clinical significance. The aclidinium 400 µg achieved nominal statistical significance for the SGRQ hypotheses ($p < 0.0001$), however the strength of significance suggests such effect is a true one.

Additional Efficacy Parameters

Results of the additional efficacy parameters further support the selection of FDC 400/12 µg, as was also demonstrated by results of the coprimary and secondary efficacy endpoints.

Pulmonary Function:

Both of the FDCs achieved statistical significance over placebo in each of the analyses of the spirometric parameters based on FEV_1 and FVC. Statistically significant differences were observed in the change from baseline in peak FEV_1 at Day 1 and on Week 24 for FDC 400/12 µg versus placebo by 0.216 L ($p < 0.0001$) and by 0.285 L ($p < 0.0001$), respectively, demonstrating a sustained effect over the 24 weeks of treatment. FDC 400/12 µg consistently showed numerically greater differences for change from baseline in peak FEV_1 and peak FVC when compared to FDC 400/6 µg at all visits. Both of the FDCs achieved statistical significance over placebo in each of the analyses of the spirometric parameter based on IC and statistical significance was achieved by the FDCs over the monotherapies at few timepoints.

The difference in the number of patients treated with the FDCs versus patients treated with placebo who achieved onset of action of bronchodilation in FEV_1 (defined as > 15% increase from baseline in FEV_1 on the first day after administration of investigational product) was statistically significant at all timepoints including at +5 minutes. At each timepoint, a higher percentage of patients treated with FDC 400/12 µg achieved onset of action of bronchodilation in FEV_1 as compared to patients treated with FDC 400/6 µg. Additionally, serial FEV_1 measurements in patients treated with FDC 400/12 µg demonstrated a bronchodilator treatment effect after the first dose compared to placebo at 5 minutes postdose of 0.128 L.

In patients participating in the 12-hour serial spirmoetry stubstudy, both of the FDCs achieved statistical significance over placebo for most timepoints in each of the analyses of the spirometric parameters based on FEV_1 and FVC; and numerically over the monotherapies. Data from the serial spirometry substudy support the results observed in the whole ITT Population and also substantiates a BID dosing regimen as demonstrated by the FEV_1 curves over time.

Dyspnea and Health Outcomes:

The LS mean difference in TDI focal score between the FDCs and placebo was statistically significant at all visits with all differences > 1 unit (1 unit change in TDI focal score is considered to be the MCID). Numerically greater improvements in TDI focal score were also observed in the FDCs compared to the monotherapies at all visits. Additionally, the FDC 400/12 µg treatment group showed greater improvements in TDI focal score when compared to the FDC 400/6 µg treatment group at Weeks 12 and 24. The number of patients who achieved a clinically meaningful difference in TDI focal score at all visits was consistent with results observed in the improvement in dyspnea status as measured by the TDI focal score.

Both of the FDCs achieved statistical significance over placebo in the number of patients with ≥ 4-unit decreases from baseline in SGRQ total score (MCID ≥ 4-unit decrease) at all visits. The percentage of patients who achieved these decreases was consistently greater in the FDC 400/12 µg treatment group as compared to the monotherapies.

COPD Exacerbations:

A clinically important reduction of 31% in the rate of moderate or severe exacerbations (eCRF) per patient per year was observed in the FDC 400/12 µg treatment group compared with placebo (FDC 400/12 µg rate = 0.37; placebo rate = 0.54; rate ratio of 0.69 [95% CI 0.46, 1.02]), however, this reduction did not reach statistical significance (p = 0.0655) due to the limited sample size of the study. Also, a reduction of 22% was observed in the FDC 400/6 µg treatment group relative to placebo (rate ratio of 0.78 [95% CI 0.53, 1.14]).

Daily COPD Symptoms (E-RS):

Overall, patients treated with FDC 400/12 µg or FDC 400/6 µg had greater improvements in total E-RS and each of the 3 symptoms domains as compared to placebo or either of the monotherapies.

Rescue Medication:

Significant reductions of overall daily total rescue medication use were observed in all active treatment groups (p < 0.0001) compared with placebo. Treatment differences were highest in the FDC 400/12 µg and 400/6 µg treatment groups (–1.1 puffs for both groups vs placebo). This finding is complementary and supportive of the bronchodilatory and symptomatic improvements in SGRQ and TDI with FDC treatment.

Health economics and outcomes research: At Week 24, both of the FDC doses provided statistically significant improvements in nighttime and morning symptoms severity of wheezing, breathlessness, tightness of chest, and overall symptoms compared to placebo.

Safety Results:

The following conclusions can be drawn from the safety data:

- The administration of aclidinium/formoterol FDCs at doses of 400/12 µg or 400/6 µg was well tolerated in patients with moderate to severe COPD; the safety profile for the FDC was comparable to that of the individual monotherapies. In general, there was no dose response observed between FDC 400/12 µg and 400/6 µg
- The incidence of treatment-emergent adverse events (TEAEs) observed with FDC treatment was similar to that observed with aclidinium monotherapy (ranging from 61% [FDC 400/6 µg] to 64.2% [FDC 400/12 µg]) and numerically higher than that observed with placebo or formoterol monotherapy (54.5% and 56.9%, respectively), however, there was no indication of an overall dose-response trend for the FDC 400/12 µg and 400/6 µg doses. Nasopharyngitis and cough were the most frequently reported TEAEs, reported at similar rates across treatment groups. The majority of TEAEs were mild or moderate in severity and unrelated to treatment with investigational product
- A total of 5 patients died during the treatment period or within 30 days of the last dose of investigational product: 1 treated with FDC 400/12 µg, 3 treated with aclidinium 400 µg, and 1 treated with formoterol 12 µg. None of the deaths were considered related to treatment with investigational product
- Serious adverse events (SAEs) were reported more frequently in the active treatment groups (ranging from 4.5% to 5.7%) than with placebo (3.6%). Pneumonia, the most commonly reported SAE, was reported in < 1% of patients in any treatment group. The percentage of patients who discontinued treatment with investigational product due to AEs was similar between the FDCs and placebo treatment groups and slightly lower in the monotherapy treatment groups
- There was no apparent dose-related increase in MACEs for FDC 400/12 µg compared to FDC 400/6 µg, and no evidence of an additive effect of combining aclidinium and formoterol. MACEs were infrequent and the MACE composite for FDC 400/12 µg was comparable with that of the placebo and formoterol 12 µg treatment arms

- Examination of events potentially associated with anticholinergic or β_2-agonist effects showed no observations of potassium or glucose-related events. Urinary tract infection, headache, and cough were reported slightly more often in the FDC 400/12 µg treatment group than other treatment groups (approximately 5% with FDC 400/12 µg compared to 3% – 4% in the other treatment groups). Other potential anticholinergic TEAEs that were reported more often in the FDC 400/12 µg and/or the FDC 400/6 µg treatment groups than other treatment groups were dry mouth, tachycardia, urinary retention, dysphonia, and throat irritation; however, the overall incidence of these events was low. Other potential β_2-agonist TEAEs that were reported more often in either FDC 400/12 µg or FDC 400/6 µg treatment groups than the placebo or aclidinium treatment groups were muscle spasm, tremor, and anxiety; however, the overall incidence of these events was low
- Mean changes from baseline in laboratory parameters were generally small and of no clinical relevance
- Assessment of vitals sign data, including blood pressure, pulse rate, respiratory rate, and body weight, showed no findings of a treatment effect in any of the treatment groups. Mean changes from baseline in vital signs values were of no clinical relevance and few patients met PCS criteria during the study
- Mean changes from baseline for ECG parameters were small and of no clinical relevance. The incidence of patients who met PCS criteria during the study was generally similar among treatment groups
- The Holter monitoring performed in this study did not produce any findings of an ECG effect for patients in any of the treatment groups. There were no differences in 12-lead Holter monitoring results between the treatment groups

CONCLUSIONS:

Date of the Report: XX Aug 2013