2 SYNOPSIS

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** NA **Name of Active Ingredients:** Aclidinium bromide/Formoterol fumarate	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Title of study: Efficacy and Safety of Aclidinium Bromide/Formoterol Fumarate Fixed Dose Combinations Compared with Individual Components and Placebo When Administered to Patients with Stable Chronic Obstructive Pulmonary Disease

Investigators:

Study sites:

Publication (reference):
None

Studied period (years): Date study initiated (first patient screened): 26 October 2011 Date study finalised (last patient last visit): 4 January 2013	**Phase of development:** III

Objectives:

- To assess the long-term bronchodilation of aclidinium/formoterol fixed dose combination (FDC) compared with individual components and placebo, when administered twice daily (bid) via inhalation to chronic obstructive pulmonary disease (COPD) patients.
- To assess the benefits of aclidinium bromide/formoterol FDC in COPD symptoms, disease-related health status and COPD exacerbations compared with individual components and placebo, when administered bid via inhalation to COPD patients.
- To evaluate the long-term safety and tolerability of aclidinium bromide/formoterol FDC compared with individual components and placebo when administered bid via inhalation to COPD patients.

Methodology:
This was a 24-week prospective, randomised, parallel-group, double-blind, placebo and active-controlled, multinational Phase III clinical study conducted in patients with stable moderate to severe COPD.

Patients provided signed and dated informed consent before any study-related procedures were conducted. The study consisted of a 2 to 3-week run-in period designed to assess the stability of the patients' disease, thus ensuring the suitability of the patients for the study, and to establish the patients' baseline characteristics. Patients who were using any prohibited concomitant medication were to enter a washout period (1 day to 1 month long, depending on the specific medication to be washed-out) prior to the run-in period. The run-in period was followed by a 24-week double-blind treatment period (Visit 1 to Visit 6). Patients completed a follow-up contact (Visit 7) 2 weeks after the last study medication administration.

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Eligible patients were randomised in a 2:2:2:2:1 ratio (aclidinium bromide/formoterol FDC 400/12 µg [hereafter referred to as FDC 400/12 µg]: aclidinium bromide/formoterol FDC 400/6 µg [hereafter referred to as FDC 400/6 µg]: aclidinium bromide monotherapy 400 µg [hereafter referred to as aclidinium]: formoterol fumarate monotherapy 12 µg [hereafter referred to as formoterol]: placebo), respectively. Eligible patients were randomly stratified to 1 of the 5 treatment groups based on their smoking status (current or ex smokers). Thus, 1 out of 9 patients received placebo.

The study medication was administered bid by inhalation, in the mornings and evenings using a novel multidose dry powder inhaler (Genuair®).

The efficacy of the FDC was assessed by pulmonary function tests, COPD symptoms, COPD exacerbations, health-related questionnaires, and the assessment of the amount of relief medication required by patients. The safety of each patient was assessed by monitoring of adverse events (AEs), 12-lead electrocardiograms (ECGs) and 24-hour Holter (substudy only), laboratory tests, and vital signs (blood pressure).

The study duration for each patient was approximately 29 weeks (from screening to follow-up), in addition to the washout period prior to screening, if needed.

Two subsets of patients, each approximately 20% of the total study population, participated in 24-hour Holter or 12-hour spirometry substudies involving additional visits and/or assessments.

Number of patients (planned and analysed):

Planned number:

Approximately 1575 patients were planned to be randomised, of whom approximately 315 patients were to participate in a Holter substudy and another 315 patients in a spirometry substudy.

Patients analysed:

Screened: 2443 patients
Randomised: 1729 patients (including 366 in the spirometry substudy and 317 in the Holter substudy)
Completed treatment: 1526 patients
Completed study: 1524 patients
Evaluated for safety: 1729 patients
Evaluated for efficacy (Intent-to-Treat [ITT] population): 1726 patients
Evaluated for efficacy (Per Protocol [PP] population): 1633 patients
Evaluated for efficacy (ITT-Exacerbation population): 1729 patients

Diagnosis and main criteria for inclusion:

- Adult male and female patients aged 40 years or older with stable moderate to severe COPD (as defined by the Global Initiative for Chronic Obstructive Lung Disease guidelines).
- Current or ex-smokers of ≥10 pack-years.
- Postbronchodilator forced expiratory volume in one second (FEV_1) ≥30% and <80% of predicted normal value, and FEV_1/forced vital capacity (FVC) <70%.
- No history or current diagnosis of asthma.
- No signs of COPD exacerbation within 6 weeks prior to screening.

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- No evidence of clinically significant respiratory and/or cardiovascular conditions or laboratory abnormalities.
- No expectations of starting a pulmonary rehabilitation program during the clinical study, nor those who finished or started it within 3 months prior to screening.
- No contraindication to the use of anticholinergic drugs. Patients with bladder neck obstruction, acute urinary retention, symptomatic non-stable prostate hypertrophy or (known) narrow-angle glaucoma were not eligible.
- No previous participation in studies involving the FDC.

Test product, dose and mode of administration, batch number, expiry date:
Name: Aclidinium bromide/formoterol fumarate FDC 400/12 µg
Batch number: ABFF015-L52, 1090483-L72, 1090742-L74 Expiry date: August 2013

Name: Aclidinium bromide/formoterol fumarate FDC 400/6 µg
Batch number: ABFF009-L51, 1090238-L71, 1090739-L73 Expiry date: August 2013

Name: Aclidinium bromide monotherapy 400 µg
Batch number: DPI061-L50, DPI061-L69 Expiry date: August 2013

Name: Formoterol fumarate monotherapy 12 µg
Batch number: K16-185-L53, K16-185-L75, K16-213-L76 Expiry date: August 2013

Administration route: oral inhalation by Genuair® multi-dose dry powder inhaler
Dosage form: inhalation powder
Dose and regimen: 1 inhalation in the morning (08:00 to 10:00) and in the evening (20:00 to 22:00).

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Placebo
Batch number: DPI055-L48, DPI055-L68 Expiry date: August 2013
Administration route: oral inhalation by Genuair® multi-dose dry powder inhaler
Dosage form: inhalation powder
Dose and regimen: 1 inhalation in the morning (08:00 to 10:00) and in the evening (20:00 to 22:00).

Duration of treatment:
The treatment duration for this study was 24 weeks.

Criteria for evaluation:

Efficacy:
Co-primary efficacy variables:

- Change from baseline in 1-hour morning post-dose FEV_1 of each FDC dose compared to aclidinium monotherapy at Week 24.
- Change from baseline in morning pre-dose (trough) FEV_1 of each FDC dose compared to formoterol monotherapy at Week 24.

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Secondary efficacy variables:

- Improvement of Transition Dyspnoea Index (TDI) focal score for each FDC dose compared with placebo at Week 24.
- Change from baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score for each FDC dose compared with placebo at Week 24.

In addition to the above, for United States (US) filing purposes only:

- Reduction in the rate of moderate or severe COPD exacerbations per patient per year based on pooled data from the M/40464/30 and LAC-MD-31 studies, for each FDC dose compared with placebo, and aclidinium monotherapy compared with placebo.
- Change from baseline in SGRQ total score of aclidinium monotherapy compared with placebo at Week 24.

Additional efficacy variables (main additional variables are listed):
Pulmonary function tests (FEV_1, FVC and inspiratory capacity [IC]) at each time point and average (ie, area under the curve), time to peak FEV_1; COPD exacerbations; symptomatic and health related Quality of Life outcomes (TDI, SGRQ, European Quality of Life Scale 5-dimension, Exacerbations of Chronic Pulmonary Disease Tool [EXACT] and Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms [E-RS], and night-time and early morning symptoms); and use of relief medication.

Safety:
Safety assessments in this study included evaluation of AEs, serious AEs (SAEs), clinical laboratory tests, vital signs, 12-lead ECGs and 24-hour Holter (substudy only).

Statistical methods:

All efficacy analyses were performed using the ITT population except COPD exacerbation variables, which were analysed using the ITT-Exacerbation population. Analyses of the co-primary and secondary efficacy variables were also carried out using the PP population to assess the robustness of the findings. Safety outcomes were analysed using the Safety population.

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

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

The within-patient correlation was modeled using the unstructured covariance matrix in the mixed model.

The rate of COPD exacerbation per patient per year was analysed by means of negative binomial (NB) regression models including age as a covariate, and treatment group, gender, baseline ICS use,

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baseline COPD severity, and smoking status as factors (the log exposure in years was included as an offset). However, when the NB model failed to converge, COPD rates of exacerbation analysis was performed by a Poisson regression model with robust variance estimate using the sandwich method.

Safety outcomes were summarised by descriptive statistics across time by treatment group.

SUMMARY – CONCLUSIONS

Disposition:

In total 2443 patients were screened, of whom, 1729 patients were considered eligible and were randomised into the study. In total, 714 (29.2%) patients were considered screen failures, the main reason being non-fulfilment of inclusion/exclusion criteria (88.9%).

Most patients completed study treatment (88.3%); a lower percentage of patients in the placebo group completed study treatment (82.5%) compared with the active treatment groups (87.0% to 91.2%). Patients' personal request was the most frequent reason given for discontinuation (4.2% patients), followed by AE (other than COPD exacerbation) (2.9%), and protocol non-compliance (2.0%). In general, the reasons for discontinuation reported were for a low and similar percentage of patients across the 5 treatment groups.

Demographic and baseline characteristics:

The treatment groups were in general comparable for demographic and baseline characteristics. Patients randomised into the study were aged between 40 and 85 years of age; mean age was 63.2 years. The majority of patients were male (67.6%) and Caucasian (94.9%). Overall, the mean BMI was 27.1 kg/m^2 and this was similar across the 5 treatment groups; the majority of patients were overweight or obese (62.2%). Smoking status, duration and consumption were similar across the 5 treatment groups. Overall, 47.3% patients were current smokers and the overall smoking history was 40.3 pack-years.

All but 3 of the patients with available data had either moderate (60.1%) or severe (39.7%) COPD. Patients had a mean duration of COPD of 8.57 years and this was similar across the 5 treatment groups. Approximately one third of the patients (37.0%) had at least one COPD exacerbation within the 12 months prior to study entry; the overall rate of COPD exacerbations was 0.54 patient-years in the previous year.

At screening, the mean post-bronchodilator percent predicted normal FEV_1 was 54.3% and the mean FEV_1/FVC ratio was 48.1%. Post-bronchodilator lung function data at screening were similar across the 5 treatment groups. Mean bronchodilator reversibility (calculated as a percentage of the pre-bronchodilator value) was 12.7% and was similar across the 5 treatment groups.

Before study medication administration on Day 1, the overall mean baseline FEV_1 value was 1.408 L and was similar across the 5 treatment groups. The overall percent predicted FEV_1 value was 49.8% and was similar across the 5 treatment groups.

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Efficacy results:

Co-primary endpoint:

The co-primary endpoint of the study was met with values indicating superior bronchodilation with both FDC doses compared with each of the relevant monotherapies. Treatment with both FDC doses statistically significantly increased FEV_1 at 1-hour post-dose at Week 24 compared with aclidinium (adjusted mean treatment difference for FDC 400/12 µg 0.125 L and 0.069 L for FDC 400/6 µg; p≤0.0001 for both comparisons). Treatment with both FDC doses statistically significantly increased trough FEV_1 at Week 24 compared with formoterol (adjusted mean treatment difference for FDC 400/12 µg 0.085 L and 0.053 L for FDC 400/6 µg; p<0.0001 and p=0.0022, respectively). According to both the EU and US filing approaches, both FDC doses met the co-primary endpoints in improving FEV_1 after adjustment for multiple comparisons.

Treatment				Comparison	Treatment difference		
	N	LS Means	SE		LS Means	95% CI	p-value
Primary endpoint: Change from baseline in 1-hour morning post-dose FEV_1 (L) at Week 24							
FDC 400/12 µg	347	0.269	0.013	FDC 400/12 µg vs. Aclidinium 400 µg	0.125	0.090, 0.160	<.0001
FDC 400/6 µg	339	0.213	0.013	FDC 400/6 µg vs. Aclidinium 400 µg	0.069	0.034, 0.105	0.0001
Primary endpoint: Change from baseline in morning trough FEV_1 (L) at Week 24							
FDC 400/12 µg	349	0.083	0.012	FDC 400/12 µg vs. Formoterol 12 µg	0.085	0.051, 0.119	<.0001
FDC 400/6 µg	340	0.050	0.012	FDC 400/6 µg vs. Formoterol 12 µg	0.053	0.019, 0.087	0.0022

LS = least squares; SE= standard error.

Secondary endpoints:
Treatment with both FDC doses statistically significantly improved dyspnoea as assessed by the TDI focal score; adjusted mean treatment difference for FDC 400/12 µg compared with placebo: 1.29 units and FDC 400/6 µg compared with placebo: 1.16 units (p<0.0001 for both comparisons). According to the EU filing approach both FDC doses met the TDI secondary endpoint after adjustment for multiple comparisons.

Marked reductions from baseline at Week 24 in SGRQ total score were observed in all treatment groups, including the placebo group. Indeed, the mean change from baseline at Week 24 in SGRQ total score in the placebo group was larger than the changes from baseline in SGRQ total score observed in the monotherapy groups (aclidinium monotherapy compared with placebo 0.71 units). Despite the numerical improvement in SGRQ total score observed with both FDC doses statistical significance compared to placebo was not achieved.

Additional Endpoints:

Mean increases from baseline in 1-hour post-dose FEV_1 with both FDCs were maintained from Day 1 to Week 24. The magnitude of improvement observed for FEV_1 at 1 hour post-dose for both FDC doses was statistically significantly greater than both monotherapies at all visits. Moreover, FDC 400/12 µg

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bronchodilation was numerically greater than FDC 400/6 µg at all visits (values ranged between 0.019 L to 0.055 L), and reached statistical significance at Week 1, Week 4 and Week 24 ($p<0.05$ for all comparisons).

At Week 24, patients receiving all active treatments reached peak FEV_1 (i.e. the highest FEV_1 in the 3 hours following the morning dose) at approximately 2 hours. Mean increases from baseline in peak FEV_1 with both FDC doses were maintained from Day 1 at Week 24. The magnitude of improvement observed for both FDC doses were also statistically significantly greater than placebo and both monotherapies at all visits. Similar results were observed with the normalised FEV_1 area under the concentration-time curve from time 0 to 3 hours (AUC_{0-3}) data.

Treatment differences for both FDCs and placebo in the changes from baseline in trough FEV_1 were maintained at all visits and ranged between 0.127 L and 0.147 L for the FDC 400/12 µg dose and between 0.111 L and 0.134 L for the FDC 400/6 µg dose ($p<0.0001$ for all timepoints for both doses). The magnitude of improvement observed for both FDCs were also statistically significantly greater than formoterol in trough FEV_1 at all visits. A statistically significant greater increase from baseline in trough FEV_1 was observed with the FDC 400/12 µg dose compared with the FDC 400/6 µg dose at Week 4. A numerical increase in trough FEV_1 was observed with the FDC 400/12 µg dose compared with the FDC 400/6 µg dose at Week 24 ($p=0.0590$).

The percentage of patients achieving onset of action (defined as an increase from baseline in FEV_1 of >15%) at 5 minutes post-dose on Day 1 for FDC 400/12 µg (25.3%) was higher than those in the FDC 400/6 µg group (18.6%), and was similar to the formoterol group (24.3%). Statistical significance for FDC 400/12 µg and FDC 400/6 µg compared with placebo was observed on Day 1 at 5 minutes post-dose for the change from baseline in FEV_1 by 0.108 L and by 0.100 L, respectively ($p<0.0001$ for both comparisons).

In the 12-hour spirometry substudy, statistically significant increases from baseline in the normalised FEV_1 area under the concentration-time curve from time 0 to 12 hours (AUC_{0-12}) were also observed on both Day 1 and at Week 24 with FDC 400/12 µg (Day 1 0.201 L; Week 24 0.221 L) and FDC 400/6 µg (Day 1 0.191 L; Week 24 0.189 L) compared with placebo ($p<0.0001$ for all comparisons). The magnitude of improvements observed with both FDC doses were numerically greater than aclidinium monotherapy, and reached statistical significance for the comparison with formoterol monotherapy.

Results for FVC and IC parameters supported those observed with FEV_1.

At Week 24, a higher percentage of patients receiving FDC 400/12 µg (64.8%) and FDC 400/6 µg (63.7%) had a clinically meaningful improvement (≥1 unit) in TDI focal score compared with placebo (45.5%). The odds ratios were 2.54 for the FDC 400/12 µg group compared with placebo and 2.57 for the FDC 400/6 µg group compared with placebo ($p=0.0001$ for both comparisons).

At Week 24, a higher percentage of patients receiving FDC 400/12 µg (55.3%) and FDC 400/6 µg (64.2%) had a clinically meaningful improvement (≥4 units) in SGRQ total score compared with placebo (53.2%). The odds ratios compared with placebo were 1.12 for the FDC 400/12 µg and 1.77 for the FDC 400/6 µg ($p<0.05$ for the FDC 400/6 µg group only).

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Statistically significant decreases in daily, day-time, and night-time relief medication use for each FDC dose compared with placebo were observed from Week 4 and the effect was maintained through to Week 24 ($p<0.05$ for all comparisons with the exception of night-time use for the FDC 400/12 µg group [$p=0.0579$]). The adjusted mean treatment differences between FDC 400/12 µg and FDC 400/6 µg for overall daily use of relief medication compared with placebo were -0.66 and -0.73 inhalations, respectively ($p<0.001$ for both comparisons).

Based on Health Care Resource Utilisation, patients in both FDC groups had slightly fewer COPD exacerbations (9.4% for FDC 400/12 µg and 9.7% for FDC 400/6 µg) than those receiving aclidinium monotherapy, formoterol monotherapy or placebo (10.9%, 13.5% and 13.4%, respectively). Numerical reductions were observed with FDC 400/12 µg or FDC 400/6 µg compared with placebo in the rate of exacerbations of any severity of 27% (rate ratio [RR] of 0.73) and 20% (RR 0.80), respectively, and in the rate of moderate or severe exacerbations of 23% (RR 0.77) and 15% (RR 0.85), respectively.

Similarly, based on the EXACT questionnaire, a lower percentage of patients in the FDC 400/12 µg (30.9%) and FDC 400/6 µg (36.0%) groups had at least one COPD exacerbation compared with patients receiving placebo (38.1%). A statistically significant reduction in exacerbation rate of 29% was observed with FDC 400/12 µg compared with placebo (RR 0.71), but not with the FDC 400/6 µg dose (RR 0.83).

Both FDC 400/12 µg and FDC 400/6 µg improved the overall E-RS total score compared with placebo at all timepoints over the 24-week treatment period. The overall treatment differences for FDC 400/12 µg (adjusted mean for the treatment difference: -0.82) and FDC 400/6 µg (-1.16) compared with placebo were statistically significant ($p<0.05$ for both comparisons).

Both FDC doses showed numerical improvements compared with placebo and reached statistical significance in most of the night-time and early morning symptoms.

Safety results:

A total of 2359 treatment-emergent adverse events (TEAEs) were reported for 51.9% of patients, with a similar percentage reported across the 5 treatment groups. The most common TEAEs (reported in ≥5% of patients overall) were COPD (exacerbation), headache, and nasopharyngitis. In general, the frequency of TEAEs was similar for each of the 5 treatment groups. A numerically lower percentage of patients in the FDC groups (FDC 400/12 µg: 9.4%; FDC 400/6 µg: 10.0%) had TEAEs of COPD (exacerbation) compared with the aclidinium (11.9%), formoterol (15.6%) and placebo (13.9%) groups. Of the most common TEAEs (reported in at least 2% of patients in any treatment group) oropharyngeal pain (FDC 400/12 µg: 2.6%), sinusitis (FDC 400/6 µg: 2.6%), and rhinitis (FDC 400/6 µg: 1.6%) were the only TEAEs reported in any of the FDC groups at twice the frequency of that reported for placebo (0.5%, 0.5%, and 0.5%, respectively).

Most of the TEAEs reported were mild or moderate in intensity; a low percentage of patients (5.3%) had TEAEs considered to be severe, with a similar percentage of patients across the 5 treatment groups. Severe TEAEs of COPD (exacerbation) were reported in a slightly lower percentage of patients in the active treatment groups (1.0% of patients in each of the FDC groups, 1.8% and 0.3% patients receiving aclidinium or formoterol, respectively) compared with the placebo group (2.6%).

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Most TEAEs were not considered to be related to treatment by the reporting investigator and the majority of TEAEs resolved or were resolving at the time of the last patient visit.

A low number of TEAEs with a fatal outcome were reported in this study (4 patients; COPD exacerbation in the FDC 400/12 µg group; cardiac failure in the FDC 400/6 µg group; COPD exacerbation in the FDC 400/6 µg group; cardiac failure in the formoterol group). None of these were considered to be related to the study medication by the reporting investigator. The percentage of patients with treatment-emergent SAEs was low (4.8%) and similar across the treatment groups. The most commonly reported SAE by PT was COPD (exacerbation); which was reported in a lower percentage of patients in the active treatment groups (1.0% FDC 400/12 µg; 1.0% FDC 400/6 µg; 1.8% aclidinium; 0.3% formoterol) compared with patients who received placebo (2.6%).

The percentage of patients with TEAEs leading to withdrawal was low (3.9%) and similar across the treatment groups. The most common TEAE leading to discontinuation from the study was COPD (exacerbation) (1.2% overall). A similar percentage of patients discontinued the study due to COPD (exacerbation) in each treatment group.

Overall, the percentage of patients with cardiac or cerebrovascular TEAEs, or major adverse cardiac events was low and similar across the 5 treatment groups (4.6%, 0.2%, and 0.6% overall, respectively). A low percentage of patients reported possible anticholinergic and/or β_2-adrenergic agonist events during the study and incidences of PTs were in general low and similar between the 5 treatment groups (<3% in any treatment group). There were no pregnancies during the study.

Overall, there was no evidence of a dose-related trend for the FDC in the percentage of patients with at least one TEAE, treatment-emergent SAEs, or TEAEs leading to withdrawal. The safety profile from both FDC doses was similar to those of the monotherapies (aclidinium 400 µg and formoterol 12 µg).

The changes from baseline in clinical laboratory tests, vital signs and ECGs (including 24-hour Holter ECG monitoring) parameters showed no clinically significant differences between the treatment groups. Overall, the changes were generally small, with no evidence of a dose-related change for the FDC at Week 24 or at the end of the study. There was no evidence to suggest the administration of aclidinium and formoterol in combination led to an increased incidence of clinically significant laboratory, vital signs or ECG abnormalities. Administration of the FDC at either dose was well tolerated and not clinically significantly different to the administration of placebo.

CONCLUSIONS:

DATE OF REPORT:
Final, 19 August 2013