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 FDC	**Volume:**	
Name of Active Ingredient: Aclidinium Bromide/ Formoterol Fumarate	**Page:**	

Title of Study: Efficacy and Safety Study of Two Fixed-Dose Combinations of Aclidinium Bromide With Formoterol Fumarate Compared With Aclidinium Bromide, Formoterol Fumarate, and Placebo All Administered Twice Daily (BID) to Patients With Stable, Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)	
Investigators: [redacted]	
Study Centers: [redacted]	
Publication (reference): None	
Study Period (years): First Patient First Visit 23 Dec 2009 Last Patient Last Visit/Early Termination 5 Aug 2010	**Development Phase:** 2B
Objective: To assess the efficacy and safety of 2 fixed-dose combinations (FDCs) of aclidinium bromide with formoterol fumarate (400/6 µg or 400/12 µg) compared with placebo, aclidinium bromide (400 µg), and formoterol fumarate (12 µg), all administered BID in patients with stable, moderate to severe COPD	
Study Design: Multicenter, randomized, double-blind, placebo-controlled, 4-period, incomplete block crossover, dose-ranging study with 8 weeks of treatment (2 weeks per treatment regimen) and a 7- to 10-day washout period between treatment periods	
Diagnosis and Main Criteria for Inclusion Male and female patients, aged ≥ 40 to 80 years, inclusive, who had a clinical diagnosis of stable, moderate to severe COPD as defined by criteria of the Global Initiative for Chronic Obstructive Lung Disease (forced expiratory volume in 1 second [FEV_1] ≥ 30% to < 80% predicted, FEV_1/forced vital capacity [FVC] < 70%, and a smoking history of 10 pack-years or more)	
Number of Patients: A total of 225 patients were screened for the study, and 128 (56.9%) were randomized to treatment. All randomized patients were included in the Safety and Intent-to-Treat (ITT) populations. There were 114 (89.1%) randomized patients in the Per Protocol population.	
Investigational Product, Dose and Mode of Administration, Batch Number: Please note: Throughout this study, the Sponsor's multidose dry-powder inhaler is referred to by its new intended US trademark name, Pressair. This device was previously referred to as the Almirall Inhaler at the end of Phase 2 studies, and it is still referred to by the name Genuair in Europe and the rest of the world. Pressair, Genuair, and Almirall Inhaler all represent the exact same device. Aclidinium bromide 400 µg in combination with formoterol fumarate 12 µg administered BID, once in the morning and once in the evening, via inhalation through the Pressair inhaler; Lot #K16-130 Aclidinium bromide 400 µg in combination with formoterol fumarate 6 µg administered BID, once in the morning and once in the evening, via inhalation through the Pressair inhaler; Lot #K16-146 Aclidinium bromide 400 µg administered BID, once in the morning and once in the evening, via inhalation through the Pressair inhaler; Lot #DPI028 Formoterol fumarate 12 µg administered BID, once in the morning and once in the evening, via inhalation through the Pressair inhaler; Lot #K16-127 **Rescue medication** ProAir® HFA (albuterol sulfate) Inhalation Aerosol 90 µg; Lot #AED54A	

Reference Therapy, Dose and Mode of Administration, Batch Number:
Blinded placebo was administered once in the morning and once in the evening, via inhalation through the Pressair inhaler; Lot #DPI022

Duration of Treatment: Patients received double-blind investigational product for 8 weeks (2 weeks per treatment regimen) with a 7- to 10-day washout period between each treatment period. Total treatment period: 3 months

Criteria for Evaluation:
Efficacy:
Primary: Change from baseline in normalized FEV_1 area under the curve over the 12 hours (AUC_{0-12}) after the morning dose of investigational product at Day 14

Secondary: Change from baseline in morning predose (trough) FEV_1 at Day 14 and change from baseline in morning peak FEV_1 at Day 14

Additional: Pulmonary function tests (FEV_1 AUC_{0-3}, FVC AUC_{0-3}, FVC AUC_{0-12}, FEV_1, FVC, inspiratory capacity [IC] at peak, trough, and by time point); COPD symptom scores; and rescue medication use.

Safety Adverse event recording, clinical laboratory assessments, vital sign parameters, electrocardiograms, Holter monitoring, and physical examinations

Statistical Methods:
Demographics and Other Baseline Characteristics: Demographic parameters and other baseline characteristics were summarized overall for the Safety Population. No statistical tests were performed.

Efficacy: All efficacy analyses were based on the ITT Population using the observed-case approach. The primary efficacy parameter (change from baseline in FEV_1 AUC_{0-12} at Day 14) was analyzed by mean of a mixed-effects model for repeated measures (MMRM) with treatment and period as fixed effects, subject as a random effect, and baseline values at each period as covariates. The primary efficacy parameter was also analyzed using the same MMRM based on the Per-Protocol Population to assess the robustness of the findings from the ITT Population. An additional sensitivity analysis was performed on the change from baseline of Period 1 in FEV_1 AUC_{0-12} at Day 14 and the change from baseline of Period 1 in morning predose FEV_1 at Day 14 using the same MMRM based on the ITT Population.

Safety: All safety parameters were analyzed descriptively based on the Safety Population.

SUMMARY OF RESULTS
Disposition: A total of 225 patients were screened for eligibility, and 128 were randomized to a study treatment sequence. The percentage of randomized patients who completed the study was 81.3% (104/128).

Demographic and Physical Characteristics:
The average patient was approximately 61.5 years of age; the majority of patients were Caucasian (93.8%), female (57%), and non-Hispanic (96.1%). For patients in the ITT/Safety Population, the average weight was 80.1 kg, the average height was 168 cm, and the average body mass index was 28.2 kg/m^2. Mean COPD duration was 8.6 years. The majority (55.5%) of patients were current smokers. Mean smoking duration for all patients was approximately 40 years with a range of 20 to 63 years.

Efficacy Results:
Primary Efficacy Parameter: Change from baseline in normalized FEV_1 AUC_{0-12} measured over the 12 hours after the morning dose of investigational product at Day 14

The FDCs of aclidinium/formoterol 400/12 µg and aclidinium/formoterol 400/6 µg and their monotherapy components (aclidinium 400 µg and formoterol 12 µg) were statistically significant ($p < 0.0001$) versus placebo in change from baseline in normalized FEV_1 AUC_{0-12} at Day 14. The changes from baseline in normalized FEV_1 AUC_{0-12} compared with placebo were 0.200 L and 0.202 L for FDCs 400/12 µg and 400/6 µg, respectively, and were 0.157 L and 0.127 L for aclidinium 400 µg and formoterol 12 µg, respectively.

FDC 400/6 µg was statistically significant versus aclidinium 400 µg ($p = 0.0437$) and formoterol 12 µg ($p = 0.0011$). FDC 400/12 µg was statistically significant versus formoterol 12 µg ($p = 0.0015$) and approached statistical significance in FEV_1 change from baseline over aclidinium 400 µg ($p = 0.0540$).

Treatment (A)	*Treatment (B)*	*Least Squares Mean Difference, L A–B (SE)*	*95% CI for the Difference (Lower, Upper)*	*p-Value*
FDC (µg) Versus Placebo				
FDC 400/12	Placebo	0.200 (0.022)	(0.156, 0.245)	< 0.0001
FDC 400/6	Placebo	0.202 (0.022)	(0.158, 0.245)	< 0.0001
FDC (µg) Versus Monotherapy (µg)				
FDC 400/12	Aclidinium bromide 400	0.043 (0.022)	(0.001, 0.087)	0.0540
FDC 400/6	Aclidinium bromide 400	0.045 (0.022)	(0.001, 0.088)	0.0437
FDC 400/12	Formoterol fumarate 12	0.074 (0.023)	(0.029, 0.119)	0.0015
FDC 400/6	Formoterol fumarate 12	0.075 (0.023)	(0.030, 0.120)	0.0011
Monotherapy (µg) Versus Placebo				
Aclidinium bromide 400	Placebo	0.157 (0.022)	(0.113, 0.201)	< 0.0001
Formoterol fumarate 12	Placebo	0.127 (0.023)	(0.082, 0.172)	< 0.0001

Secondary Efficacy Parameters:
(1) Change from baseline in morning predose FEV_1 at Day 14

As with the primary efficacy parameter, all 4 active treatments were statistically significant ($p \leq 0.0017$) versus placebo in change from baseline in morning predose FEV_1. The changes from baseline compared with placebo were 0.132 L and 0.137 L for FDC 400/12 and FDC 400/6 µg, respectively, and were 0.088 L and 0.079 L for aclidinium 400 µg and formoterol 12 µg, respectively. The FDCs were also statistically significant versus their components in increasing morning predose FEV_1 over baseline. The change from baseline was statistically significant for both FDCs compared with formoterol 12 µg (0.053 L [p = 0.0381] for FDC 400/12 µg and 0.057 L [p = 0.0218] for FDC 400/6 µg). Compared with aclidinium 400 µg, FDC 400/6 µg was statistically significant (0.049 L [p = 0.0480]) in change from baseline. FDC 400/12 µg did not reach statistical significance (0.044 L [p = 0.0792]) compared with aclidinium 400 µg.

(2) Change from baseline in morning peak FEV_1 at Day 14

Again, all 4 active treatments were statistically significantly higher ($p < 0.0001$) compared to placebo in change from baseline in morning peak FEV_1 at Day 14. Compared with placebo, the changes from baseline were 0.281 L and 0.275 L for FDC 400/12 and FDC 400/6 µg respectively, and were 0.187 L and 0.171 L for aclidinium 400 µg and formoterol 12 µg, respectively. Both FDCs were also statistically significant versus their monotherapy components (0.095 mL [p = 0.0003] for FDC 400/12 and 0.088 L [p = 0.0006] for FDC 400/6 µg compared with aclidinium and 0.110 L [p < 0.0001] for FDC 400/12 µg and 0.103 L [p < 0.0001] for FDC 400/6 µg compared with formoterol) in change from baseline in morning peak FEV_1 at Day 14.

Additional Efficacy Parameters

Consistent with the primary and secondary efficacy parameters, both FDCs showed statistically significant changes from baseline versus both placebo and their monotherapy components for the majority of assessments for the additional efficacy parameters.

Additional efficacy parameters were measurements of change from baseline in normalized FEV_1 AUC_{0-3} after morning investigational product administration at Day 1 and Day 14, change from baseline in normalized FVC AUC_{0-12} after morning investigational product administration at Day 14; changes from baseline in the following: morning predose FVC at Day 14; morning predose IC at Day 14; morning peak FEV_1 at Day 1; morning peak FVC at Days 1 and 14; FEV_1 and FVC at each specific time point at Days 1 and 14; and IC at 3 hours after morning investigational product administration at Days 1 and 14; COPD symptoms; and rescue medication use. Consistent with the primary and secondary objectives, the FDCs of aclidinium and formoterol were statistically significant versus both placebo and to 1 or both monotherapy components for the majority of the time points for each spirometric evaluation. Assessments of COPD symptom scores (nocturnal, cough and breathlessness symptom scores) during the first week and the second week of treatment, and during the overall treatment period also showed statistically significant reductions in the majority of symptom scores for both FDCs compared with placebo at most time points.

Safety Results:
Treatment with FDCs of aclidinium and formoterol and with their monotherapy components (400 µg for aclidinium and 12 µg for formoterol) was generally well tolerated, with a comparable safety profile across all treatments. Treatment-emergent adverse events (TEAEs) and laboratory and electrocardiographic abnormalities that occurred were not unexpected in this population of patients ≥ 40 to 80 years of age with moderate to severe COPD.

Overall, a higher proportion of patients receiving active treatments than of patients receiving placebo treatment reported any TEAE: 19.5%-29.3% during active treatments versus 9.8% during placebo treatment. Additionally, formoterol 12 µg monotherapy was associated with a higher incidence of TEAEs (29.3%) than the FDCs (19.5% for FDC 400/12 µg and 22.0% for FDC 400/6 µg). The large majority of the TEAEs were mild in severity, and only 7 were considered severe: 4 (14.3%) during treatment with FDC 400/12 µg and 3 (8.8%) during treatment with aclidinium 400 µg. The 4 severe TEAEs during FDC 400/12 µg treatment occurred in 2 patients and were bronchitis, hypoglycemia, and COPD in 1 patient and COPD in the second patient. The 3 severe TEAEs during aclidinium 400 µg treatment were in 1 patient and were metastases to spine, metastatic renal cell carcinoma, and spinal laminectomy. Most TEAEs were considered not related to treatment by the Investigator. Overall, 3 (21.4%) of the TEAEs during placebo treatment, 10 (35.7%) during FDC 400/12-µg treatment, 8 (30.8%) during FDC 400/6-µg treatment, 10 (29.4%) during aclidinium 400 µg treatment, and 6 (16.2%) during formoterol 12 µg treatment were considered possibly or probably related to treatment.

Number (%) of Patients With Adverse Events Occurring in at Least 2% of Patients During Any Treatment by Preferred Term

Treatments	***Number (%) of Patients***				
	Placebo (N = 92)	***Aclidinium/Formoterol***		***Aclidinium 400 µg (N = 94)***	***Formoterol 12 µg (N = 92)***
		400/12 µg (N = 87)	***400/6 µg (N = 91)***		
Any TEAE	9 (9.8)	17 (19.5)	20 (22.0)	19 (20.2)	27 (29.3)
Preferred Term (Incidence ≥ 2%)					
Abdominal Pain	0	0	0	1 (1.1)	2 (2.2)
Nausea	0	0	0	3 (3.2)	1 (1.1)
Oedema peripheral	1 (1.1)	0	1 (1.1)	2 (2.1)	0
Bronchitis	0	2 (2.3)	0	0	0
Nasopharyngitis	0	1 (1.1)	3 (3.3)	0	1 (1.1)
Upper respiratory tract infection	1 (1.1)	0	0	2 (2.1)	2 (2.2)
Urinary tract infection	0	0	0	1 (1.1)	2 (2.2)
Hypoglycaemia	1 (1.1)	1 (1.1)	0	1 (1.1)	3 (3.3)
Hyperkalaemia	0	1 (1.1)	0	2 (2.1)	1 (1.1)
Headache	1 (1.1)	0	1 (1.1)	0	2 (2.2)
Chronic obstructive pulmonary disease	1 (1.1)	2 (2.3)	1 (1.1)	1 (1.1)	4 (4.3)
Hypertension	1 (1.1)	0	1 (1.1)	0	2 (2.2)

TEAE = treatment-emergent adverse event.

No deaths were reported during the study. The incidence of serious adverse events (SAEs) was low. Four patients had a total of 6 SAEs: 2 (2.3%) of the 87 patients during treatment with FDC 400/12 µg, 1 (1.1%) of the 94 patients during treatment with aclidinium 400 µg, and 1 (1.1%) of the 92 patients during treatment with formoterol 12 µg. One patient during treatment with FDC 400/12 µg had 3 SAEs: hypoglycemia, acute renal failure, and COPD. The COPD in this patient was considered related to treatment by the investigator, as was the SAE of COPD in 1 other patient during FDC 400/12 µg treatment. None of the other SAEs were considered to be related to treatment. Nine patients, all receiving active treatments, discontinued treatment because of TEAEs. One other patient discontinued because of a TEAE that had begun at baseline before treatment.

Few patients in any treatment sequence reported possible anticholinergic and/or β-adrenergic TEAEs. Overall, the monotherapy treatments had a slightly higher incidence of possible anticholinergic and/or β-adrenergic TEAEs during the study compared with the placebo and the FDC treatments.

A number of laboratory abnormalities were noted both at study entry and at the final evaluation, but these were not considered clinically relevant. Changes in fasting glucose and potassium, which were assessed at each visit, appeared to be minimal and comparable across treatments. Changes in vital signs also did not appear to be associated with any treatment. Only 1 patient (FDC 400/12 µg) had a postbaseline electrocardiographic abnormality that was determined to be clinically significant. This patient had frequent ventricular premature complexes at Visit 13, including an 8-beat run of supraventricular tachycardia.

Although a number of abnormalities were noted on the 12-lead Holter monitoring assessments, the overall analysis of the data did not show that active treatments were associated with a higher incidence of abnormal changes than placebo treatment**.**

Conclusions:

[redacted]

Date of the Report: 05 Mar 2012