2 SYNOPSIS

Name of Sponsor/Company: AstraZeneca **Name of Finished Product:** N.A. **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, SAFETY AND TOLERABILITY OF TWO FIXED-DOSE COMBINATIONS OF ACLIDINIUM BROMIDE WITH TWO DOSES OF FORMOTEROL FUMARATE COMPARED WITH ACLIDINIUM BROMIDE, FORMOTEROL FUMARATE AND PLACEBO ALL ADMINISTERED TWICE DAILY IN STABLE, MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS		
Investigators: **Co-ordinating Investigator:**		
Study centres:		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 18 February 2010 Date study finalised (last patient last visit): 23 September 2010	**Phase of development:** IIb	

Objectives:

- To assess the efficacy, safety and tolerability of the 2 fixed-dose combinations (FDCs) of aclidinium bromide and formoterol fumarate compared to placebo, all administered twice daily (BID) in patients with moderate to severe chronic obstructive pulmonary disease (COPD).
- To determine which of the 2 combinations provide the greater benefit in terms of efficacy, safety and tolerability.

Methodology:

This was a multicentre, randomised, double-blind, placebo-controlled, 4-period cross-over study. The study consisted of a Screening Visit conducted after the informed consent form was signed, where patients' medical history, COPD severity stage and physical examination were assessed, among other common measurements. Patients meeting eligibility criteria were randomised to 1 of the 20 possible treatment sequences using a balanced incomplete cross-over design. Each sequence consisted of 4 periods, and a different treatment was administered at each period. All patients participating in this clinical study were to attend a maximum of 18 visits over a maximum of 18 weeks. Each treatment was administered BID through the Genuair® inhaler for 13 consecutive days and 1 dose in the morning on the 14th day, separated by a washout period of 7 to 10 days between each treatment period. Additionally, patients were provided with relief medication (salbutamol pressurised metered dose inhaler 100µg/puff) to be used on an as needed basis, from the time of the informed consent signature until the end of treatment period.

During each period, assessments took place prior to the morning dose and up to 3 hours later (Day 1), and assessments continued up to 12 hours post-morning dose on Days 7 and 14. During the treatment periods, blood pressure (BP), 12-lead electrocardiogram (ECG), laboratory and pulmonary function tests ([PFTs], spirometry tests) were performed. In addition, 24-hour ECG Holter was assessed on 2 occasions. Patients were instructed to record their COPD symptoms, relief medication use and BID intake of the study drug in a Patient Diary until the end of the treatment phase. A follow-up contact was performed 2 weeks after the last study drug administration. During the entire duration of the study adverse events (AEs) and the use of any concomitant medication were recorded.

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Number of patients (planned and analysed):
Planned to randomise: 120
Screened: 176
Randomised: 135
Completed study: 119
Evaluated for safety: 135
Evaluated for efficacy (Intent-to-Treat [ITT] analysis): 135
Evaluated for efficacy (Per-Protocol [PP] analysis): 122

Diagnosis and main criteria for inclusion:

- Adult male and female patients aged between 40 and 80 years, inclusive.
- Stable moderate to severe COPD (stages II and III according to the Global Initiative for Chronic Obstructive Lung Disease [GOLD guidelines]): forced expiratory volume in 1 second (FEV_1) at Screening 30%≤FEV_1 <80% of the predicted normal value and FEV_1/forced vital capacity (FVC) <70%.
- Current or ex-smokers with a ≥10 pack-years smoking history.
- Patients with no history or current diagnosis of asthma or exercise-induced bronchospasm.
- No signs of COPD exacerbation within 6 weeks prior to the Screening Visit.
- No evidence of clinically significant respiratory and/or cardiovascular conditions or laboratory abnormalities.
- No history of untoward reactions or known hypersensitivity to inhaled anticholinergic drugs.

Test product, dose and mode of administration, batch number, expiry date:
Name: Aclidinium bromide 200 µg + formoterol fumarate 6 µg (FDC 200/6 µg)
Administration route: Oral inhalation using the Genuair® multidose dry powder inhaler
Dosage form: Dry powder for inhalation
Dose and regimen: 1 puff of 200 µg aclidinium bromide and 6 µg formoterol fumarate BID (12 hours apart)
Batch number: K16-144-L14
Expiry date: February 2011

Name: Aclidinium bromide 200 µg + formoterol fumarate 12 µg (FDC 200/12 µg)
Administration route: Oral inhalation using the Genuair® multidose dry powder inhaler
Dosage form: Dry powder for inhalation
Dose and regimen: 1 puff of 200 µg aclidinium bromide and 12 µg formoterol fumarate BID (12 hours apart)
Batch number: K16-129-L15
Expiry date: February 2011

Name: Aclidinium bromide 200 µg
Administration route: Oral inhalation using the Genuair® multidose dry powder inhaler
Dosage form: Dry powder for inhalation
Dose and regimen: 1 puff of 200 µg aclidinium bromide BID (12 hours apart)
Batch number: B2-L11
Expiry date: February 2011

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Name: Formoterol fumarate 12 µg
Administration route: Oral inhalation using the Genuair® multidose dry powder inhaler
Dosage form: Dry powder for inhalation
Dose and regimen: 1 puff of 12 µg formoterol fumarate BID (12 hours apart)
Batch number: K16-127-L13
Expiry date: February 2011

Duration of treatment:
Fourteen (± 2) days of treatment per period; 4 periods per patient.

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Placebo
Administration route: Oral inhalation using the Genuair® multidose dry powder inhaler
Dosage form: Dry powder for inhalation
Dose and regimen: 1 puff of placebo BID (12 hours apart)
Batch number: DPI022-L10
Expiry date: February 2011

Criteria for evaluation:

Efficacy:

Efficacy was assessed by PFTs (FEV_1, FVC and inspiratory capacity [IC]), by the patient COPD symptoms (breathlessness, cough and nocturnal symptom) and relief medication usage (day-time, night-time and daily).

Primary efficacy variable:

- Change from baseline in normalised FEV_1 area under the curve (AUC) over the 12 hours after morning study drug administration (FEV_1 AUC_{0-12h}) at Day 14.

Secondary efficacy variables:

- Change from baseline in morning pre-dose FEV_1 at Day 14.
- Change from baseline in morning peak FEV_1 at Day 14.

Safety:

Safety assessments included eliciting of AEs, including COPD exacerbations, serious AEs (SAEs), laboratory parameters (including glucose and potassium), physical examination, BP measurements, 12-lead ECG recordings, and 24-hour Holter ECG. Pregnancy tests were performed in females of child-bearing potential.

Other variables:

- Exposure to study drug, treatment compliance, prior and concomitant medication.

Statistical methods:

The analysis of efficacy variables was performed on the ITT population. Analysis of the primary and secondary efficacy variables was also carried out on the PP population in order to assess the robustness of the findings from the ITT population. All the safety and tolerability analyses were performed on the safety population.

The primary and secondary efficacy variables were analysed by means of a mixed model for repeated measures for crossover designs with treatment and period as fixed effect factors, patient as random effect, and baseline value at each period as the covariate.

All additional variables were analysed by using the same mixed model with the corresponding baseline, except for the time to peak FEV_1, which was analysed descriptively; AEs, SAEs, laboratory parameters (including glucose and potassium), BPs, 12-lead ECGs and 24-hour ECG Holter recordings were analysed by means of descriptive statistics and shift tables. Exposure to the study drug and treatment

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compliance, prior and concomitant medication, withdrawals and reason for withdrawals were summarised descriptively.

SUMMARY – CONCLUSIONS

Disposition (All patients):

Patient status (statistic)	Number of patients
Patients screened (n)	176
Patients randomised (n)	135
Study completed (n [%])	119 (88.1%)
Treatment completed (n [%])	119 (88.1%)
Discontinued (n [%])	16 (11.9%)
Adverse Events	11 (8.1%)
Patient's personal request	4 (3.0%)
Protocol non-compliance (other than entry criteria)	1 (0.7%)

Demographics and Baseline Characteristics (Safety population):

		Overall N=135	
		n	Mean (SD)
Age	[years]	135	60.4 (7.93)
Smoking duration	[years]	135	35.3 (10.27)
Smoking consumption	[pack-years]	135	38.8 (18.97)
Duration of COPD	[years]	135	7.80 (6.63)
Pre-bronchodilator FEV_1	[L]	135	1.430 (0.476)
FEV_1 of predicted post bronchodilator	[%]	135	54.3 (13.3)
		n (%)	
Sex	Female	40 (29.6%)	
	Male	95 (70.4%)	
Race	Caucasian	135 (100.0%)	
Smoking status	Current smoker	65 (48.1%)	
	Ex-smoker	70 (51.9%)	
COPD severity (GOLD stage) [Note: Data missing for one patient]	Stage II (Moderate)	77 (57.5%)	
	Stage III (Severe)	57 (42.5%)	

Efficacy Results:

All active treatments BID (FDC 200/12 µg, FDC 200/6 µg, aclidinium bromide 200 µg or formoterol fumarate 12 µg) demonstrated statistically significant bronchodilation compared to placebo, on the primary endpoint the change from baseline in normalised FEV_1 AUC_{0-12h} at Day 14.

The magnitude of the bronchodilatory effect of FDC 200/12 µg and FDC 200/6 µg were similar (0.221 L and 0.234 L, respectively compared to placebo), both doses being statistically superior to formoterol fumarate 12 µg (p=0.0008 and p=0.0001, respectively). However, although both FDCs provided higher bronchodilation than aclidinium bromide 200 µg (0.042 L for FDC 200/12 µg and 0.054 L for FDC 200/6 µg), only FDC 200/6 µg reached statistical significance (p=0.0246).

Similar trends were observed in the PP population analyses and also for results at Day 7 as well as for mean normalised FEV_1 AUC over the 3 hours after morning study drug administration values at Days 1, 7 and 14.

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Treatment (A)	Treatment (B)	LSMean Difference A–B (SE)	95% CI for the Difference (Lower, Upper)	p-value
Primary treatment comparisons				
FDC 200/12 µg	Placebo	0.221 (0.024)	(0.174, 0.268)	<0.0001
FDC 200/6 µg	Placebo	0.234 (0.024)	(0.186, 0.281)	<0.0001
Secondary treatment comparisons				
FDC 200/12 µg	Aclidinium bromide 200 µg	0.042 (0.024)	(-0.005, 0.089)	0.0821
FDC 200/6 µg	Aclidinium bromide 200 µg	0.054 (0.024)	(0.007, 0.102)	0.0246
FDC 200/12 µg	Formoterol fumarate 12 µg	0.081 (0.024)	(0.034, 0.128)	0.0008
FDC 200/6 µg	Formoterol fumarate 12 µg	0.093 (0.024)	(0.046, 0.140)	0.0001
Additional treatment comparisons				
Aclidinium bromide 200 µg	Placebo	0.179 (0.024)	(0.132, 0.227)	<0.0001
Formoterol fumarate 12 µg	Placebo	0.140 (0.024)	(0.093, 0.187)	<0.0001

Changes in morning pre-dose FEV_1 at Days 7 and 14 for active treatments compared to placebo, although statistically significant were inconsistent. Similarly inconclusive results were observed when both FDCs were compared to monotherapies at Days 7 and 14.

Changes from baseline in morning peak FEV_1 at Days 1, 7 and 14 for active treatments were statistically superior to placebo. At Day 14 changes from baseline ranged from 0.255 L for both monotherapies to 0.347 L for FDC 200/6 µg. A small increase compared to baseline was seen in the placebo group (0.052 L). Both FDCs were statistically significant and superior to both monotherapies with a comparable magnitude at Day 14 (0.080 L for FDC 200/12µg versus [vs] monotherapies and 0.092 L for FDC 200/12µg vs monotherapies).

The change from baseline in FEV_1 curve over 12 hours demonstrated a bronchodilator effect of all active treatments starting rapidly (30 minutes post-morning dose, first timepoint assessed), reaching a plateau at approximately 3 hours post-dose before slowly decreasing until almost reaching pre-dose values at 12 hours post-dose. All active treatments were statistically superior to placebo at all timepoints. Both FDCs were statistically superior to both monotherapies between 1 to 4 hours post dose and were numerically superior at the remaining timepoints. The curves for formoterol fumarate 12 µg and aclidinium bromide 200 µg were comparable up to the 3-hour point, after which aclidinium bromide 200 µg was superior. Time to peak FEV_1 was achieved at 3 hours post-dose.

Other lung function improvements (FVC, IC) followed the same trend as normalised FEV_1 AUC_{0-12h} with a similar magnitude of effects with both FDCs.

When compared to placebo, a statistically significant reduction in use of daytime relief medication was demonstrated for all active treatments. Overall, the mean daytime use of relief medication dropped for all treatments, with the decreases ranging from 1.36 puffs for formoterol fumarate 12 µg to 1.57 puffs for FDC 200/12 µg compared to a decrease for placebo (0.55 puffs). No notable differences were observed in the overall use of night-time relief medication.

Improvements in daily COPD symptom were observed in all treatments groups including placebo, and these were generally larger for all active treatments compared to placebo (an exception being an increase in daily cough for formoterol fumarate 12 µg compared to placebo). However, only on rare occasions did the FDCs reach statistical significance vs placebo.

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Each component of the FDC treatments demonstrated their contribution to the bronchodilation efficacy when compared to both monotherapies (aclidinium bromide 200 µg or formoterol fumarate 12 µg). Overall, FDC 200/12 µg and FDC 200/6 µg provided a comparable bronchodilation effect.

Safety Results:
All treatments, given BID, were shown to be safe and well tolerated in patients with moderate to severe COPD. The safety profile of both FDC doses was, in general, comparable to that of each monotherapy (aclidinium bromide 200 µg and formoterol fumarate 12 µg) and placebo.

The percentage of patients experiencing treatment-emergent AEs (TEAEs) was similar in all treatment groups, including placebo, being the highest with aclidinium bromide 200 µg BID (17.0%) and the lowest with FDC 200/12 µg BID (11.9%).

The most frequently reported TEAEs mapped mainly to the system organ class "Respiratory, Thoracic and Mediastinal Disorders", followed by "Cardiac Disorders", "Infections and Infestations" and "Investigations". The most commonly reported TEAEs (reported by at least 2 patients in any treatment) were cough, COPD, dyspnoea, headache, hypertension, ventricular extrasystoles, rhinorrhoea, ventricular tachycardia, muscle spasms, musculoskeletal chest pain, and toothache.

The incidence of individual TEAEs typically associated with anticholinergic agents and β_2-adrenergic agonists was low (≤2.0% in any treatment group), and no differences between the FDC and monotherapy or placebo groups were observed.

The number of patients experiencing on-treatment SAEs or those patients discontinuing treatment due to TEAEs was low for all treatments. There were no deaths during the study.

No overall clinically relevant differences were observed among treatment groups, including placebo, in the change from baseline over time for systolic and diastolic BP, ECG parameters including ECG outliers (heart rate and Fridericia corrected QT interval), 24-hour Holter ECG monitoring or laboratory safety parameters (serum glucose and potassium). Values determined in the FDC groups were shown to be comparable to those obtained for placebo. Only a few abnormalities in laboratory safety parameters were detected at the end of the study, but were also of no clinical relevance.

CONCLUSIONS:
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DATE OF REPORT:

Final (08/07/2011)