2.0 SYNOPSIS

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

Title of Study: A RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED, PARALLEL-GROUP, MULTICENTER, 4-WEEK PILOT STUDY TO ASSESS SYMPTOMS IN STABLE, MODERATE-TO-SEVERE COPD PATIENTS TAKING ACLIDINIUM BROMIDE 200 MG ONCE-DAILY IN COMBINATION WITH FORMOTEROL FUMARATE 12 µG ONCE-OR TWICE-DAILY VERSUS FORMOTEROL FUMARATE 12 µG TWICE-DAILY

Investigators:

[redacted]

Study centre (s):

[redacted]

Publication (reference):
None

Studied period (years): Date study initiated (first screening): March 5th 2008 Date of early study termination: November 17th 2008 Date of completion of the Study (last patient last visit): February 12th 2009	Phase of development: IIb exploratory study

Objectives:
The objective of this study was to assess the safety, efficacy, pharmacokinetics (PK), and symptom changes associated with administering aclidinium bromide and formoterol fumarate fixed dose combination (FDC) once-daily in the morning compared with the FDC once-daily in the morning plus formoterol fumarate once every evening in patients with stable, moderate-to-severe chronic obstructive pulmonary disease (COPD). Also, to use data collected from the Activity-Related Dyspnea and Fatigue (ARDF) instrument to determine the initial measurement properties of the instrument as a part of its validation process.

Methodology:
This clinical study was conducted as a multicenter, randomized, double-blind, active-controlled, three-arm, parallel-group study comparing aclidinium bromide 200 µg and formoterol fumarate 12 µg FDC once-daily in the morning plus placebo once every evening (FDC 12 µg Q_{AM} plus placebo Q_{PM}), aclidinium bromide 200 µg and formoterol fumarate 12 µg FDC once-daily in the morning plus formoterol fumarate 12 µg once every evening (FDC 12 µg Q_{AM} plus formoterol fumarate 12 µg Q_{PM}), or formoterol fumarate 12 µg twice-daily (formoterol fumarate 12 µg Q_{AM} and Q_{PM}) in patients diagnosed with moderate-to-severe stable COPD.

The study consisted of a 1-week screening period followed by 4-week double-blind treatment. At the end of the screening period, patients meeting the entry criteria for this study were randomized (2:2:1) to FDC 12 µg Q_{AM} plus placebo Q_{PM}, FDC 12 µg Q_{AM} plus formoterol fumarate 12 µg Q_{PM} or formoterol fumarate 12 µg Q_{AM} and Q_{PM}. The date of the last patient visit was a follow-up telephone contact 1 week after the last dose of study drug.
Number of subjects (planned and analyzed): Planned: 200 randomized in a 2:2:1 ratio, aclidinium bromide 200 µg and formoterol fumarate 12 µg FDC once-daily in the morning plus placebo once every evening, aclidinium bromide 200 µg and formoterol fumarate 12 µg FDC once-daily in the morning plus formoterol fumarate 12 µg once every evening, or formoterol fumarate 12 µg twice-daily Screened: 270 patients Randomized: 156 (63 to FDC 12 µg Q_{AM} plus placebo Q_{PM} [FDC + placebo], 62 to FDC 12 µg Q_{AM} plus formoterol fumarate 12 µg Q_{PM} [FDC + formoterol], and 31 to formoterol fumarate 12 µg Q_{AM} and Q_{PM} [formoterol + formoterol]). Completed study: 145 (92.9%) (FDC + placebo: 57 [90.5%], FDC + formoterol: 58 [93.5%], formoterol + formoterol: 30 [96.8%]). Evaluated for safety: 156 (FDC + placebo: 63 [100%], FDC + formoterol: 62 [100%], formoterol + formoterol: 31 [100%]). Evaluated for efficacy (Randomized population): 156 (FDC + placebo: 63 [100%], FDC + formoterol: 62 [100%], formoterol + formoterol: 31 [100%]). Evaluated for efficacy (Per Protocol [PP] population): 132 (84.6%) (FDC + placebo: 47 [74.6%], FDC + formoterol: 56 [90.3%], formoterol + formoterol: 29 [93.5%]).
Diagnosis and main criteria for inclusion: Males and non-pregnant, non-lactating females aged between 40 and 80 years, inclusive, who were current or former cigarette smokers (with a ≥ 10 pack-year history), with a clinical diagnosis of stable moderate to-severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, with stable airway obstruction and who consented to participate, were eligible for the study. The patient's forced expiratory volume in one second (FEV_1) at Screening (Visit 1) measured between 30-45 minutes post inhalation of salbutamol had to be ≥ 30% and <80% of the predicted normal value, the pre-dose FEV_1 at Baseline (Visit 2) had to be within the range of 80 to 120% (inclusive) of the FEV_1 measured at Screening (Visit 1) prior to salbutamol inhalation and the post-salbutamol FEV_1/forced vital capacity (FVC) at Screening (Visit 1) had to be <70%. Patients with a history or current diagnosis of asthma were excluded as were patients who had experienced a COPD exacerbation within 6 weeks of Screening (Visit 1).
Test product, dose and mode of administration, batch number, expiry date: Name: Almirall inhaler delivering FDC of aclidinium bromide 200 µg and formoterol fumarate 12 µg dry powder Administration route: inhalation by Almirall multidose dry powder inhaler (Almirall inhaler). Dosage form: Dry powder for inhalation. Dose and regimen: one inhalation of FDC once-daily in the morning and one inhalation of placebo once in the evening (i.e., formoterol fumarate [as part of FDC] once-daily in the morning.

Aclidinium bromide 200 µg + Formoterol Fumarate Dihydrate 12 µg Batch K16-110

Formoterol Fumarate Dihydrate 12 µg Batch K16-109

Expiry date: Not applicable

Duration of treatment:
4-week treatment period. The total duration of the study for each patient was approximately 6 weeks, including the screening and follow-up visits.

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Formoterol fumarate 12 µg
Administration route: Oral inhalation by Almirall multidose dry powder inhaler (Almirall inhaler)
Dosage form: Dry powder for inhalation
Dose and regimen: One inhalation twice-daily in the morning and in the evening
Formoterol Fumarate Dihydrate 12 µg Batch K16-109
Expiry date: Not applicable

Name: Placebo to formoterol fumarate 12 µg
Administration route: Oral inhalation by Almirall multidose dry powder inhaler (Almirall inhaler)
Dosage form: Dry powder for inhalation
Dose and regimen: One inhalation once-daily in the evening
Placebo to Aclidinium Bromide/Formoterol Fumarate Dihydrate Batch K16-65
Expiry date: Not applicable

Criteria for evaluation:

Efficacy:
Efficacy was assessed by pulmonary function tests (FEV_1, FVC, inspiratory capacity [IC]), COPD symptom scores (nocturnal symptom scores, daily sputum scores, night time sputum volume scores, night time use of rescue medication, morning breathlessness symptom scores, evening breathlessness symptom scores, morning use of rescue medication, evening use of rescue medication).

Safety:
Safety assessments included the eliciting of adverse events (AEs) and serious AEs (SAEs); the monitoring of hematology, blood chemistry and urine values; physical examinations; vital signs, including blood pressure measurement; and recording of 12-lead electrocardiograms (ECGs). Pregnancy tests were performed in females of child-bearing potential.

Statistical methods:
This was an exploratory study. Therefore, all continuous efficacy parameters were summarized using descriptive statistics (mean, standard deviation, standard error of the mean, median, minimum, maximum, 95% confidence interval, and number of patients). All categorical and ordinal efficacy parameters were summarized by counts and percentages.

Furthermore, there was no hierarchical distinction among the various clinical endpoint measured.

SUMMARY – CONCLUSIONS

Efficacy Results:
The results from this study show that following 4 weeks of treatment with FDC Q_{AM} + placebo Q_{PM}, FDC Q_{AM} + formoterol Q_{PM} or formoterol Q_{AM} + formoterol Q_{PM}, lung function and most COPD symptom scores improved in all treatment groups, to varying degrees.

Lung function:
Trough FEV_1 and trough FVC increased by an average of 0.084 L to 0.118 L and 0.153 L to 0.195 L, respectively. In both cases, the increase was comparable across all treatment groups.

The increase in trough IC was smaller in magnitude, ranging from 0.016 L to 0.095 L across treatment groups. Given the magnitude of the increase, the relevance of the small differences seen among treatment groups is unclear.

Peak FEV_1 and peak FVC increased in all treatment groups, by an average of 0.280 L to 0.355 L, and 0.517 L to 0.665 L, respectively. The changes observed in the FDC-containing treatment groups, with or without formoterol Q_{PM}, were slightly greater than those observed in the formoterol only treatment group, with mean values of 0.355 L and 0.319 L versus 0.280 L for peak FEV_1, and 0.665 L and 0.562 L versus 0.517 L for peak FVC.

Changes in normalized $AUC_{0\text{-}3\ h}$ FEV_1 and FVC followed a similar pattern, with mean increases of 0.257 L and 0.506 L, respectively, in the FDC + placebo treatment group compared with 0.200 L and 0.374 L in the formoterol only treatment group.

Changes in normalized $AUC_{12\text{-}24\ h}$ FEV_1 and FVC, on the other hand, were slightly greater in treatment groups including formoterol Q_{PM}, with mean increases of 0.241 L and 0.353 L (formoterol only group), respectively, compared with 0.097 L and 0.188 L in the FDC + placebo treatment group. Changes in normalized $AUC_{12\text{-}24\ h}$ IC were smaller in magnitude. All these changes in $AUC_{12\text{-}24h}$ were observed in the spirometry/PK subgroup only. Given the very small sample size ($n \leq 10$ per arm) and the wide variation, these changes are difficult to interpret.

Changes in FEV_1 30, 60, 120, and 180 minutes post morning dose of study drug were slightly greater in both FDC-containing treatment groups, with maximum increases of 0.320 L and 0.262 L at 180 minutes post-dose, compared with 0.206 L in the formoterol only treatment group. Changes in FVC at these timepoints followed the same profile. In both cases, these changes were consistent with the changes in normalized $AUC_{0\text{-}3\ h}$.

Changes in FEV_1 pre evening dose and 3, 9, and 12 hours post evening dose of study drug reached maximum values at 3 hours post dose in treatment groups including formoterol Q_{PM}, ranging from 0.298 L to 0.344 L, compared with 0.125 L in the FDC only treatment group. Changes in FVC and IC at these timepoints followed the same profile. For both FEV_1 and FVC, these changes, which were examined in the spirometry/PK subgroup only, were consistent with the changes in normalized $AUC_{12\text{-}24\ h}$. Again, given the very small sample size ($n \leq 10$ per arm) and the wide variation, these observations are difficult to interpret.

Changes in IC at 180 minutes post morning dose ranged from 0.203 L to 0.307 L across all treatment groups. Like trough IC, changes in IC 180 minutes post morning dose were more pronounced in treatment groups including the FDC 12 µg combination.

COPD symptom scores
There were minor differences observed among treatment groups, however, none of these differences were considered to be clinically significant.

Nocturnal symptom scores improved (decreased) by 0.09 to 0.35 point. The improvement observed in the formoterol only treatment group was slightly greater than that seen in both FDC-containing treatment groups.

Daily sputum volume scores improved (decreased) by 0.17 point in the FDC + placebo treatment group but did not change or worsen slightly (0.13 point) in the other groups.

Night time sputum volume scores improved (decreased) slightly and to the same extent in both the FDC-containing treatment groups and formoterol only treatment groups (0.13 point).

Night time use of rescue medication decreased across all treatment groups; particularly in the formoterol only treatment group (-1.28 puffs vs. -0.63 puffs in the FDC + placebo treatment group). Night time use of rescue medication at baseline was slightly higher in the formoterol only treatment group.

Morning cough symptom scores improved (decreased) from 0.08 to 0.32 point across treatment groups, and evening cough symptom scores improved (decreased) from 0.26 to 0.46 point across treatment groups. The changes observed were comparable across all treatment groups.

Morning breathlessness symptom scores improved (decreased) from 0.16 to 0.39 point across all treatment groups, and evening breathlessness symptom scores improved (decreased) from 0.15 to 0.54 point, across all treatment groups. The changes in morning scores were comparable in all treatment groups. Changes in evening scores observed in the FDC + placebo treatment group were slightly greater than those observed in the formoterol only group (-0.54 point vs. -0.38 point).

Morning use of rescue medication decreased from 0.44 to 1.28 puffs while evening use of rescue medication was more pronounced, decreasing from 1.25 to 1.91 puffs, across treatment groups. In both cases, the changes observed in the FDC-containing treatment groups were slightly greater than those observed in the formoterol only group.

Changes in COPD symptoms observed at Weeks 2, 3 and 4 followed a similar pattern.

Changes observed in the Randomized population using OC were similar to those observed in the Randomized population using last observation carried forward (LOCF), and results of the analysis using the PP population with LOCF or OC followed a similar pattern.

Summary:
All treatments resulted in various degree of improvement in lung function and COPD symptom scores. The clinical significance of the small differences observed among treatment groups are difficult to evaluate, given the small sample size and the variability of the responses.

Treatments involving FDC in the morning, alone or together with an evening dose of formoterol (FDC + placebo and FDC + formoterol), had a slightly better outcome on peak and normalized $AUC_{0\text{-}3\ h}$ FEV_1 and FVC. Changes observed at 30, 90, 120, and 180 minutes post morning dose in FEV_1 and FVC were consistent also with these observations.

Treatments involving formoterol Q_{PM} (FDC + formoterol, and formoterol + formoterol) had a slightly better outcome on normalized $AUC_{12\text{-}24\ h}$ FEV_1 and FVC (as only observed in the spirometry/PK subgroup). Changes observed 3, 9, and 12 hours post evening dose in FEV_1 and FVC were consistent with these observations.

Improvements in COPD symptoms are more difficult to interpret when comparing day and night scores, most likely due to the high variability of the response and the baseline scores. Night time sputum volume scores, cough scores (morning and evening) and breathlessness (morning score) improved to a similar magnitude in all treatment groups. Treatment with FDC + placebo led to a slightly greater improvement in daily sputum volume scores and evening breathlessness scores, and both FDC treatment arms led to a slightly greater reduction in the use of rescue medication (morning and evening). This could potentially be explained by the additive effect of two bronchodilators.

Safety Results:
When reviewing the number of patients experiencing AEs and the number of AEs reported, the 2:2:1 randomization ratio among the different treatment groups: FDC + placebo; FDC + formoterol; and formoterol + formoterol, should be considered.

Inhaled treatment with FDC + placebo, FDC + formoterol, and formoterol + formoterol, was well-tolerated with a similar safety profile observed across all three treatment groups. Adverse events observed in each treatment group were generally events expected in COPD patients.

Overall, the proportion of patients who experienced at least one treatment emergent adverse event (TEAE) was higher in the formoterol + formoterol (38.7%) treatment group compared with the remaining two treatment groups, in which the distribution was comparable and reported as 29.0% in the FDC + formoterol treatment group, and 25.4% in the FDC + placebo treatment group.

The TEAEs that were reported by two or more patients in any treatment group were: COPD exacerbation, headache, cough, oxygen saturation decreased, edema peripheral, productive cough, dry mouth, nausea, upper respiratory tract infection, and urinary tract infection. All other TEAEs were reported by no more than one patient. Treatment-emergent AEs of COPD exacerbation, which were observed in all treatment groups except the formoterol + formoterol treatment group, and headache, reported in all treatment groups, were the two most commonly reported TEAEs and were each reported in five patients overall.

Headache was the treatment-related TEAE reported with the highest incidence, being reported by a total of four patients. The following treatment-related events were also experienced by at least two patients overall: productive cough, edema peripheral; blood urea increased; and cough. All other treatment-related events were reported by no more than one patient overall.

The majority of TEAEs reported by patients were considered mild or moderate in severity in all treatment groups. The formoterol + formoterol treatment group had the highest incidence of patients reporting moderate TEAEs: five patients (16.1%) compared with the other two treatment groups, in which only four patients in the FDC + placebo (6.3%); and four patients in the FDC + formoterol (6.5%) treatment groups reported moderate TEAEs. The incidence of patients reporting severe TEAEs was low, with two patients in the FDC + placebo treatment group and one patient in the FDC + formoterol treatment group experiencing such events.

With the exception of the formoterol + formoterol treatment group, the majority of TEAEs that occurred within any treatment group were considered to be not related to study drug rather than related. Within the formoterol + formoterol treatment group half of all TEAEs reported were considered by the Investigator to be related to study drug (six patients [19.4%]). By comparison, six patients (9.5%) in the FDC + placebo treatment group experienced related TEAEs compared with ten patients (15.9%) who experienced non-related TEAEs; and in the FDC + formoterol treatment group, five patients (8.1%) experienced related TEAEs compared with 13 patients (21.0%) who experienced non-related TEAEs.

No randomized patients died during the study.

In total, one [1.6%] patient each in the FDC + placebo and FDC + formoterol treatment groups experienced an SAE: drug withdrawal convulsions in the FDC + placebo treatment group, and COPD exacerbation in the FDC + formoterol treatment group. Both SAEs were treatment-emergent and not considered related to study drug. An additional two patients reported three SAEs (myocardial infarction, chest pain, and hypertension) that were non–treatment-emergent. Of the three non–treatment-emergent SAEs, the myocardial infarction was fatal and occurred during the screening period; the remaining two events occurred in a patient who was a screen failure and therefore was ineligible for entry into the study. Due to the low incidence of SAEs within this study, it is not possible to establish whether or not SAEs occurred most frequently in one treatment group more than another.

Four patients experienced at least one AE that led to their premature discontinuation from the study. Of these patients one patient experienced a non-treatment-emergent rash. The remaining three patients experienced treatment-emergent episodes of COPD related events (two [3.2%] events in the FDC + placebo, and one [1.6%] in the FDC + formoterol treatment groups). Of these three events, only one event of COPD exacerbation experienced by a patient in the FDC + placebo treatment group was considered by the Investigator to be related to study drug. In addition, one other patient experienced an episode of COPD exacerbation which occurred prior to randomization and led to the patient's premature discontinuation from the study.

Few patients in any treatment group reported potential anticholinergic and/or β-adrenergic TEAEs. In fact, no such events were reported in the FDC + placebo treatment group, and only two events were reported in the formoterol + formoterol treatment group. The remaining events were all observed in the FDC + formoterol treatment group, with a total of eight events. The only TEAEs that were reported by at least two patients in any treatment group were: dry mouth (two patients [3.2%]) and urinary tract infection (two patients [3.2%]), both in the FDC + formoterol treatment group. All other potential anticholinergic and/or β-adrenergic TEAEs were reported in only one patient. Hypertension was the only event reported in more than one treatment group.

Laboratory tests and vital signs data were in general similar across all treatment groups. The changes observed were small and none were considered to be clinically relevant.

Overall, relatively small mean changes from baseline in all the ECG parameters were observed. These changes were comparable across all three treatment groups and none were considered to be clinically relevant.

Thirty-five patients underwent Holter monitoring: 14 each in the FDC + placebo, and FDC + formoterol treatment groups, and seven in the formoterol + formoterol treatment group.

The number of patients with at least one non-sustained supraventricular tachycardia (NSVT) increased from Baseline to Week 5 by one in the FDC + placebo treatment group (from two [14.3%] to three [21.4%]) and in the formoterol + formoterol treatment group (from none to one [14.3%]); and remained the same in the FDC + formoterol treatment group (two [14.3%]).

The number of episodes of VPCs remained similar after five weeks of treatment compared with baseline and was >71% in any treatment group throughout the study. The majority of episodes in each treatment group were within the 1–50 VPCs per hour range, both at Baseline and after five weeks of treatment. No more than two episodes in any treatment group were in the 51–100 VPCs per hour range at Baseline and after five weeks of treatment. No more than one episode in any treatment group was in the 101-300 VPCs per hour range, and there were no episodes in the > 300 VPCs per hour range.

No episodes of SVT were observed over the course of the study.

At Baseline, the proportion of patients with results that were interpreted by the cardiologist as abnormal ranged from 28.6% (in both the FDC + formoterol and the formoterol + formoterol treatment groups), to 64.3% (in the FDC + placebo treatment group). The FDC + placebo treatment group showed a decrease in the number of patients with abnormal Holter interpretations at Week 5. The numbers remained the same in the FDC + formoterol treatment group, and increased in the formoterol + formoterol treatment group. The FDC + placebo treatment group exhibited the largest change, from a Baseline of 64.3% to 35.7% at Week 5.

The most common abnormal finding across all treatment groups was frequent VPCs. The formoterol + formoterol treatment group showed a higher proportion of patients with this finding compared with the other two treatment groups. At Baseline, the FDC + placebo treatment group had the highest proportion of patients with this finding: 35.7%, compared with 14.3% and 28.6% in the FDC + formoterol, and formoterol + formoterol treatment groups, respectively. At Week 5, the formoterol + formoterol treatment group had the highest proportion of patients with this finding: 42.9%, compared with 28.6% and 21.4% in the FDC + placebo and the FDC + formoterol treatment groups, respectively.

CONCLUSIONS:

[redacted]

DATE OF REPORT:
05 November 2009