## 2. SYNOPSIS

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

**Title of Study:** A RANDOMISED, 4-WEEK, PLACEBO-CONTROLLED, DOUBLE-BLIND, 6 ARM PARALLEL GROUP, DOSE-FINDING CLINICAL TRIAL, TO ASSESS THE EFFICACY AND SAFETY OF THREE DIFFERENT DOSES OF FORMOTEROL (6, 12 & 18 µg) COMBINED WITH THE INHALED ANTICHOLINERGIC ACLIDINIUM BROMIDE 200 µG, ACLIDINIUM BROMIDE 200 µg MONOTHERAPY AND FORMOTEROL 12 µg MONOTHERAPY ALL ADMINISTERED ONCE DAILY BY INHALATION VIA INHALER IN PATIENTS WITH STABLE MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

**Investigators:**

**Study centres:**

**Publication (reference):**
None

| | |
|---|---|
| **Studied period (years):**<br>Date study initiated (first screening): 28 February 2008<br>Date study finalised (last patient last visit ): 10 November 2008 | **Phase of development:** IIb |

**Objectives:**
The objectives of this study were:

1. to assess the efficacy and safety of three combinations of aclidinium bromide 200 µg with formoterol (6, 12 or 18 µg) compared to placebo, monotherapy treatment formoterol 12 µg and monotherapy treatment aclidinium bromide 200 µg in patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD).
2. to determine the optimal formoterol dose combined with aclidinium bromide 200 µg to be investigated in subsequent clinical trials.

**Methodology:**
This was a double-blind, randomised, 6 arm parallel-group, placebo-controlled, dose-finding study of 4 weeks' treatment with: aclidinium bromide 200 µg + formoterol 6, 12 or 18 µg; aclidinium bromide 200 µg only; formoterol 12 µg only or placebo, all given once daily to male or female patients with moderate to severe stable COPD.

Before starting the 4-week treatment period, patients had to discontinue most of their COPD medications for one week to ten days before the screening evaluations. Patients were randomised as soon as possible within the week following the screening evaluations. During the 4-week treatment period, patients were treated once daily with inhalers containing aclidinium bromide + formoterol, aclidinium bromide only, formoterol only or placebo of the same external appearance to ensure the double-blind nature of the trial. During the treatment phase, patients attended the clinic visit after 14 ±2 days and 28 ±2 days. Substudy patients were also seen on Day 2. At the end of the 4-week double-blind treatment period, there was a 7-day (+3) follow-up period. The total duration of the study for each patient was approximately 8 weeks including the screening and follow-up visit.

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

**Number of subjects (planned and analysed):**

Planned: 513 randomised (the trial randomisation ratio was 2:2:2 (the 3 fixed dose combination [FDC] arms):1:1:1 (the aclidinium bromide alone, formoterol alone and placebo arms).
Screened: 808
Randomised: 566
Completed study: 534
Evaluated for safety: 566
Evaluated for efficacy (Intent-to-treat [ITT] analysis): 563
Evaluated for efficacy (Per Protocol [PP] analysis): 459

**Diagnosis and main criteria for inclusion**:

Males and non-pregnant, non-lactating females aged ≥40 and ≤80 years old, who were current or former cigarette smokers with a smoking history of at least 10 pack-years, with a clinical diagnosis of stable moderate to severe COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2006 Classification guidelines and who consented to participate were eligible for the study. The patient's forced expiratory volume in one second ($FEV_1$) at the Screening Visit measured between 30-45 min post inhalation of 400 µg of salbutamol had to be ≥30% and <80% of the predicted normal value, and the post-salbutamol $FEV_1$/forced vital capacity (FVC) at the Screening Visit 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 the screening visit (or 3 months if requiring hospitalisation).

**Test product, dose and mode of administration, batch number, expiry date:**

Name: Aclidinium bromide + formoterol
Administration route: Oral inhalation by multidose dry powder inhaler (inhaler)
Dosage form: Dry powder for inhalation
Dose and regimen: 200 µg aclidinium bromide + 6 µg formoterol (1 inhalation) once daily
Batch number: K16-76 Expiry date: June 2009

Dose and regimen: 200 µg aclidinium bromide + 12 µg formoterol (1 inhalation) once daily
Batch number: K16-69 Expiry date: June 2009

Dose and regimen: 200 µg aclidinium bromide + 18 µg formoterol (1 inhalation) once daily
Batch number: K16-77 Expiry date: June 2009

Name: Aclidinium bromide
Administration route: Oral inhalation by multidose dry powder inhaler (inhaler)
Dosage form: Dry powder for inhalation
Dose and regimen: 200 µg aclidinium bromide (1 inhalation) once daily
Batch number: 6F003 Expiry date: June 2009

Name: Formoterol
Administration route: Oral inhalation by multidose dry powder inhaler (inhaler)
Dosage form: Dry powder for inhalation
Dose and regimen: 12 µg formoterol (1 inhalation) once daily
Batch number: K16-68 Expiry date: June 2009

**Duration of treatment:**

4-week treatment period. The total duration of the study for each patient was approximately 8 weeks including the screening and follow-up visit.

**Reference therapy, dose and mode of administration, batch number, expiry date:**

Name: Placebo
Administration route: Oral inhalation by multidose dry powder inhaler (inhaler).

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

Dosage form: Dry powder for inhalation.
Dose and regimen: 1 inhalation once daily
Batch number: K16-65 Expiry date: June 2009

**Criteria for evaluation:**

**Efficacy:**
Efficacy was assessed by pulmonary function tests ($FEV_1$, FVC and inspiratory capacity [IC]), daily assessment by the patient of COPD symptoms (breathlessness, nighttime symptoms, cough, and sputum production) and rescue medication usage.

**Safety:**
Safety assessments included eliciting of adverse events (AEs) (including COPD exacerbations) and serious AEs (SAE), the monitoring of haematology, blood biochemistry and urine values, physical examination, blood pressure and recording of 12-lead electrocardiograms (ECGs). Pregnancy tests were performed in females of child-bearing potential.
Additionally, substudy patients had 12-lead 24-hour Holter monitoring performed.

**Statistical methods:**

Analysis of the primary efficacy variable, the change from baseline in the normalised $FEV_1$ Area Under the Curve $(AUC)_{(0\text{-}12\ h)}$ after 4 weeks of treatment was analysed using an Analysis of Covariance (ANCOVA) model.

Treatment effects were estimated by Least Square (LS) means and their standard error (SE) and 95% confidence intervals (CI). Primary treatment comparisons between the FDC groups and placebo were carried out by means of the contrasts on the treatment factor. Differences between treatments were estimated by differences between LS Means and their SE and 95% CI.

There were four secondary efficacy variables defined in the study: the change from baseline after 4 weeks of treatment in the trough $FEV_1$, in the peak $FEV_1$, in the normalised $FEV_1$ $AUC_{(0\text{-}3\ h)}$ and in the normalised $FEV_1$ $AUC_{(0\text{-}6\ h)}$. All secondary variables were analysed using ANCOVA models.

There were also many spirometry-based additional efficacy variables, and all of them were analysed using the ANCOVA model.

In all statistical analyses, the significance level was set at 0.05 two-tailed for all treatment comparisons. All CIs were two-sided at 95%.

**SUMMARY – CONCLUSIONS**

**Efficacy Results:**

The results from this study show that following 4 weeks of treatment, normalised FEV1 AUC(0-12 h), the primary efficacy variable, increased gradually with the three FDCs, from 0.170 L (FDC 6 µg) to 0.230 L (FDC 18 µg); increased at lower magnitude (0.075 L and 0.099 L) with monotherapies, aclidinium bromide 200 µg and formoterol 12 µg, while decreasing slightly (0.036 L) in the placebo group.

The primary treatment comparison showed that all three FDC groups were statistically significantly superior to placebo ($p<0.0001$), with mean treatment differences (active – placebo) in normalised $FEV_1$ $AUC_{(0\text{-}12\ h)}$ of 0.206 L in the FDC 6 µg group, 0.254 L in the FDC 12 µg group and 0.265 L in the FDC 18 µg group.

Secondary treatment comparisons of the primary variable entailed comparisons first between the three FDC

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

groups, then between each of the FDC groups and each of the monotherapy groups (formoterol 12 µg and aclidinium bromide 200 µg), and finally between each of these monotherapy groups and placebo. These comparisons (change from baseline on normalised $FEV_1$ $AUC_{(0\text{-}12\ h)}$ after 4 weeks of treatment) showed the following:

There was no statistically significant difference between FDC 18 µg and FDC 12 µg.

Treatment differences between both higher fixed dose combination groups (FDC 12 µg and FDC 18 µg) and FDC 6 µg were pronounced and within the same range (0.048 L to 0.059 L, respectively), but did not however reach statistical significance.

Treatment differences between the three FDC groups and either of the monotherapy groups followed a similar pattern, the smallest differences being observed between FDC 6 µg and the monotherapies (particularly formoterol 12 µg), and the largest differences between FDC 18 µg and formoterol 12 µg or aclidinium bromide 200 µg. All fixed dose combinations were statistically significantly superior to both monotherapies ($p<0.001$) except for the comparison FDC 6 µg and formoterol 12 µg.

Both formoterol 12 µg and aclidinium bromide 200 µg monotherapies were statistically superior to placebo ($p<0.0078$).

| **Analysis of mean change from baseline in normalised $FEV_1$ $AUC_{(0\text{-}12\ h)}$ (L) after 4 weeks: ITT population** | **Treatment difference in LS Mean (SE) change from Baseline** | **p-value** |
|---|---|---|
| **Primary treatment comparison** | | |
| FDC 6 µg vs Placebo | 0.206 (0.038) | <0.0001 |
| FDC 12 µg vs Placebo | 0.254 (0.038) | <0.0001 |
| FDC 18 µg vs Placebo | 0.265 (0.038) | <0.0001 |
| **Secondary treatment comparison** | | |
| FDC 12 µg vs FDC 6 µg | 0.048 (0.031) | 0.117 |
| FDC 18 µg vs FDC 6 µg | 0.059 (0.031) | 0.0555 |
| FDC 18 µg vs FDC 12 µg | 0.011 (0.031) | 0.7263 |
| FDC 6 µg vs Formoterol 12 µg | 0.071 (0.038) | 0.0622 |
| FDC 12 µg vs Formoterol 12 µg | 0.120 (0.038) | 0.0018 |
| FDC 18 µg vs Formoterol 12 µg | 0.131 (0.038) | 0.0007 |
| FDC 6 µg vs Aclidinium | 0.095 (0.035) | 0.0066 |
| FDC 12 µg vs Aclidinium | 0.144 (0.035) | <0.0001 |
| FDC 18 µg vs Aclidinium | 0.155 (0.035) | <0.0001 |
| Formoterol 12 µg vs Placebo | 0.135 (0.044) | 0.0024 |
| Aclidinium vs Placebo | 0.111 (0.041) | 0.0078 |

AUC= area under the curve; LS mean= least square mean for change from baseline in the normalized $AUC_{(0\text{-}12\ h)}$ $FEV_1$ in the ANCOVA model. SE= standard error; L= litres.

These results were similar when considering normalised $FEV_1$ AUC at (0-3 h), (0-6 h), (0-24 h) and (12-24 h) as well as trough and peak $FEV_1$.

Results of the sensitivity analysis with the PP population or with the ITT population using the Observed Cases (OC) approach confirmed the results of the primary analysis.

Changes observed after 2 weeks of treatment followed essentially the same pattern as that described following

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

4 weeks of treatment.

Results for FVC and IC followed the same pattern to those described for $FEV_1$ in all respects, both after 2 and 4 weeks of treatment.

Changes observed after 4 weeks of treatment in the group of patients within the ITT population who participated in the substudy were similar to those observed in the entire ITT population.

There was a small improvement in COPD symptom scores (mainly breathlessness and cough scores) after 4 weeks in all treatment groups, including placebo. No difference was observed between any of the treatment groups in this regard.

Similarly, a small reduction in day and night use of rescue medication was observed after 4 weeks in all treatment groups, including placebo. No difference was observed between any of the treatment groups in this regard.

Conclusion

The primary treatment comparison showed that all three FDC groups were statistically significantly superior to placebo.

For most lung function variables examined all three FDC combination groups showed superiority versus placebo, although statistical significance was not consistently observed.

For all lung function variables examined, in most cases, the changes observed in both FDC 12 µg or FDC 18 µg groups were within the same range, and consistently greater than those seen in the lowest FDC group (FDC 6 µg). While FDC 12 µg and FDC 18 µg showed systematically superior mean bronchodilation values to FDC 6 µg, statistical significance was not reached as the study was not powered for this comparison.

Pairwise comparison between the FDC groups and either of the two monotherapy groups supported this trend. In fact, treatment differences (in favour of the fixed dose combination) between the FDC 6 µg group and either formoterol 12 µg or aclidinium bromide 200 µg, failed to reach statistical significance in most of the variables and were smaller than those observed between the two higher FDC groups and the monotherapy groups

**Safety Results:**

Inhaled treatment with FDC 6 µg, 12 µg and 18 µg for 4 weeks was well-tolerated with a safety profile similar to that observed with either of the monotherapy groups or placebo. No dose relationship between the three FDC treatment groups was observed for any safety outcome.

Adverse events observed in each treatment group were generally events expected in COPD patients. The types of AEs reported were generally similar across all treatment groups.

In total, treatment-emergent AEs (TEAEs) were reported in 126 patients (22.3%): 32 patients (26.4%) treated with FDC 6 µg, 25 patients (20.8%) treated with FDC 12 µg, 25 patients (20.0%) treated with FDC 18 µg, 14 patients (18.4%) treated with aclidinium bromide 200 µg, 17 patients (26.2%) treated with formoterol 12 µg and 13 patients (22.0%) treated with placebo.

The TEAEs that were reported by at least three patients in any treatment group were: COPD exacerbation, headache, ventricular extrasystoles, and blood pressure increased.

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

COPD exacerbations were the most frequently reported TEAE with 18 episodes (including one of infective nature) in 18 patients, followed by headache with 10 episodes in nine patients, nasopharyngitis with seven episodes in seven patients, ventricular extrasystoles with seven episodes in six patients, and ECG QT interval prolonged and upper respiratory tract infection with six episodes in six patients each. TEAEs of COPD exacerbation were observed more commonly with the monotherapy groups than with the fixed dose combination groups.

The majority of TEAEs were of mild or moderate intensity in all treatment groups. The fixed dose combination groups had a higher incidence of moderate AEs compared with the monotherapy groups or placebo. The FDC 6 µg group had the highest number of patients (13 patients [10.7%]) with moderate events compared to all the other active treatment groups (from one patient [1.5%] in the formoterol 12 µg group to seven patients [5.8%] in the FDC 12 µg group). The number of patients reporting severe TEAEs was low with no more than one case in each of the FDC 18 µg group, formoterol 12 µg group and placebo group and three in the FDC 12 µg group.

The majority of TEAEs were considered by the Investigator to be not related to IMP for all active treatment groups, although within the placebo group, TEAEs were considered related to IMP more often than not. The three most common treatment-related TEAEs were ECG QT prolonged (five episodes in five patients), ECG QT corrected interval prolonged (five episodes in four patients) and ventricular extrasystoles (four episodes in four patients).

There were no treatment-emergent deaths in this study.

Overall, six patients experienced a total of six SAEs, five of which were treatment-emergent. None were fatal. Five SAEs were observed in the fixed dose combination groups, the remaining SAE was reported in the formoterol 12 µg monotherapy group. The FDC 18 µg group had most SAEs, three in total (overdose, acute myocardial infarction and iron deficiency anaemia, this last event was non-treatment emergent), all of them were considered not related to IMP. One SAE (infective exacerbation of chronic obstructive airways disease) occurred in the FDC 12 µg group and one (ECG abnormal) in the FDC 6 µg group; both were reported to be related to IMP. One SAE (COPD exacerbation) occurred in the formoterol 12 µg group, and was considered not to be related to IMP. All patients who experienced the SAEs recovered.

No AE was reported as a consequence of a patient's overdose.

Among the six SAEs only four of them (ECG abnormal, infective exacerbation of chronic obstructive airways disease, COPD exacerbation and acute myocardial infarction) led to patient discontinuation from the study.

Overall, nine patients had a TEAE that led to premature discontinuation from the study. The number of patients who experienced a TEAE that led to discontinuation was comparable across all treatment groups. No TEAE led to the discontinuation of more than two patients in any group.

Few patients (≤four patients per preferred term) in any treatment group reported possible anticholinergic and/or beta-adrenergic TEAEs. Four patients had possible anticholinergic and/or beta-adrenergic TEAEs that led to discontinuation from the study: two patients in the FDC 6 µg group (ventricular extrasystoles and ECG abnormal) and two patients in the 18 µg group (acute myocardial infarction and dry mouth).

Laboratory tests (including serum potassium and glucose) and vital signs data in the active treatment groups were in general similar to placebo and did not reveal any safety signals.

ECGs were evaluated by the Investigator and by an independent cardiologist. The proportion of patients with ECGs evaluated as abnormal and possibly significant by the independent cardiologist was higher than by the

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

Investigator. However, the overall incidence of ECGs evaluated as abnormal with clinical relevance by the Investigator was very low (≤1.7%). Overall, there were no notable differences between any of the FDC groups and the formoterol 12 µg group in any of the evaluations made..

The following table shows the number and percentage of patients with ECGs evaluated by the cardiologist as abnormal and possibly significant.

| | FDC 6 µg | FDC 12 µg | FDC 18 µg | Aclidinium 200 µg | Formoterol 12 µg | Placebo |
|---|---|---|---|---|---|---|
| | (N=121) n (%) | (N=120) n (%) | (N=125) n (%) | (N=76) n (%) | (N=65) n (%) | (N=59) n (%) |
| Screening | 34 (28.1) | 38 (31.7) | 35 (28.0) | 35 (46.1) | 20 (30.8) | 13 (22.0) |
| Day 1, baseline | 32 (26.4) | 43 (35.8) | 44 (35.2) | 36 (47.4) | 21 (32.3) | 13 (22.0) |
| Day 1, + 2 hours | 38 (31.4) | 43 (35.8) | 41 (32.8) | 39 (51.3) | 20 (30.8) | 15 (25.4) |
| Week 2, +2 hours | 40 (33.1) | 44 (36.7) | 43 (34.4) | 37 (48.7) | 16 (24.6) | 16 (27.1) |
| Week 4, + 2 hours | 37 (30.6) | 41 (34.2) | 45 (36.0) | 42 (55.3) | 24 (36.9) | 20 (33.9) |

Source: Table 14.5.5.4.2

N= Number of patients in each treatment group.

n= number of patients in each category; percentage calculated as 100 x (n/N).

Aclidinium bromide shower a higher incidence of possibly significant abnormalities than the rest of the treatments, but this difference across groups was already present at screening and baseline.

There were no clinically relevant changes in heart rate (HR) or QT interval corrected using Bazett's formula ($QT/RR^{1/2}$) (QTcB) or QT interval corrected using Fredericia's formula ($QT/RR^{1/3}$) (QTcF) interval over time at Week 4.

No patients showed QTcF values >500 msec. The number of patients with a change of ≥60 msec at any visit was low: one patient (1.3%) in the aclidinium bromide 200 µg group at Day 1 (30 minutes post-dose); one patient each in the FDC 18 µg group and aclidinium bromide 200 µg group at Week 2 (30 minutes post-dose), one patient in the aclidinium bromide 200 µg group at Week 4 (3 and 12 hours post-dose) and another patient in the FDC 18 µg group at Week 4 (24 hours post-dose).

The FDC 12 µg and placebo groups both showed an increase in the number of patients with abnormal Holter interpretations at Week 4 (Day 29) compared to baseline, but the FDC 6 µg, FDC 18 µg and aclidinium bromide 200 µg groups all showed a decrease in the number of patients with abnormal Holter interpretations which suggest no dose-related effect. The formoterol 12 µg group remained the same. The placebo group exhibited the largest change from baseline (from 13.3% to 42.9% at Week 4 (Day 29)).

The following table shows the number and percentage of patients with a 12-lead 24-hour Holter monitoring cardiologist review finding of overall interpretation abnormal.

**Name of Sponsor / Company:**
AstraZeneca

**Name of Finished Product:**
N.A.

**Name of Active Ingredients:**
Aclidinium bromide, Formoterol

**Individual Study Table Referring to Part of the Dossier**

**(For National Authority Use only)**

**Volume:**

**Page:**

| | FDC 6 µg (N=33) n (%) | FDC 12 µg (N=32) n (%) | FDC 18 µg (N=35) n (%) | Aclidinium 200 µg (N=32) n (%) | Formoterol 12 µg (N=18) n (%) | Placebo (N=15) n (%) |
|---|---|---|---|---|---|---|
| Baseline | 14 (45.2) | 18 (56.3) | 15 (42.9) | 15 (48.4) | 7 (38.9) | 2 (13.3) |
| Day 1 | 11 (35.5) | 14 (43.8) | 13 (39.4) | 10 (32.3) | 8 (44.4) | 3 (21.4) |
| Week 4 | 12 (40.0) | 19 (63.3) | 10 (31.3) | 14 (46.7) | 7 (46.7) | 6 (42.9) |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Source: Table 14.6.2.2.1

N= Number of patients in each treatment group.

n= number of patients in each category; percentage calculated as 100 x (n/N).

The most common abnormal findings across all treatment groups were frequent ventricular premature complexes (VPCs) and ≥30 VPCs in one hour. The active treatment groups showed a higher proportion of patients with these findings compared to placebo, also at baseline. At this timepoint, the FDC groups had a similar proportion of patients, with these abnormal findings. For frequent VPCs at Week 4 there was no indication of dose response effect between the FDC arms.

The overall incidence of non-sustained ventricular tachycardia (NSVT) was low, ≤five patients in any group at any timepoint, with NSVT occurring slightly more frequently in the FDC 6 µg and 12 µg groups after 4 weeks of treatment than in the other treatment groups.

None of these findings were considered clinically relevant.

**CONCLUSIONS:**

**DATE OF REPORT:**
18 August 2009