2. 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 Multiple Dose, Double-Blind, Double-Dummy, 3 PeriBod Cross-Over, Placebo Controlled Clinical Trial to Assess the Efficacy and Safety of Once Daily Inhaled Aclidinium Bromide 200 µg Given Either in the Morning or in the Evening in Patients with Stable Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD).		
Investigators:		
Study centre (s):		
Publication (reference): None		
Study period (years): Date study initiated (first screening): 20 November 2007 Date study finalised (last patient last visit): 13 March 2008	**Phase of development:** II	
Objectives: The objectives of this study were to assess whether the time of dosing (a.m. or p.m.) at steady state influences the bronchodilator response of aclidinium bromide compared with placebo in patients with moderate to severe COPD, and to evaluate the safety and tolerability of multiple doses of aclidinium bromide in moderate to severe COPD patients.		

Methodology:
This was a multicentre, multiple dose, randomised, double-blind, double-dummy, 3-period cross-over, placebo-controlled study.

The study consisted of a run-in period (minimum 5 days, maximum 9 days) and three 7-day treatment periods. Each treatment period was separated by a washout period of 7 (± 2) days. A minimum of 5 days between treatment periods was required. At each treatment period, patients received either aclidinium bromide 200 µg in the morning and placebo in the evening (aclidinium bromide 200 µg a.m.), placebo in the morning and aclidinium bromide 200 µg in the evening (aclidinium bromide 200 µg p.m.), or placebo morning and evening (placebo). Patients were randomly assigned to one of the six treatment sequences in a 1:1:1:1:1:1 randomisation ratio.

Number of subjects (planned and analysed):
Planned: 48 randomised
Screened: 86
Randomised: 69
Completed study: 67
Evaluated for safety: 69
Evaluated for efficacy (Intent-to-Treat [ITT] population): 69
Evaluated for efficacy (Per protocol [PP] population): 63

Diagnosis and main criteria for inclusion:
Males and non-pregnant, non-lactating females aged ≥40 years, with stable moderate to severe COPD with a post-salbutamol forced expiratory volume in 1 second (FEV_1) <80% and ≥30% of predicted normal value and post-salbutamol FEV_1/Forced Vital Capacity (FVC) <70%. Patients were current or ex-smokers with a smoking history of ≥10 pack-years, no history or current diagnosis of asthma, allergic rhinitis or atopy, an eosinophil count <600 cells/mm^3, and no signs of an exacerbation within 6 weeks prior to the screening visit.

Test product, dose and mode of administration, batch number, expiry date:
Name: Aclidinium bromide
Administration route: Oral inhalation by Almirall multidose dry powder inhaler (Almirall inhaler).
Dosage form: Dry powder for inhalation.
Dose and regimen: 200 µg (1 puff) either at 09:00 or 21:00 (± 1 hour), depending on the randomisation schedule
Batch number: 6B001 Expiry date: January 2009

Duration of treatment:
Three periods of 7 treatment days. Approximate study duration of 7 weeks for each patient.

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Placebo to aclidinium bromide
Administration route: Oral inhalation by Almirall multidose dry powder inhaler (Almirall inhaler).
Dosage form: Dry powder for inhalation.
Dose and regimen: 200 µg (1 puff) either at 09:00 or 21:00 (± 1 hour) or both time-points, depending on the randomisation schedule.
Batch number: K1-13 Expiry date: January 2009

Criteria for evaluation:
Efficacy:
Spirometric assessments were made over a period of approximately 25 hours prior to the first administration of study treatment in each treatment period and at the end of each treatment period, after 7 days of treatment.

The primary efficacy variable was the change from baseline in the trough FEV_1 after 6 days of treatment.

The secondary efficacy variables were the change from baseline in trough FVC and Inspiratory Capacity (IC) after 6 days of treatment, change from baseline in FEV_1, FVC and IC at all time-points after 7 days of treatment for the a.m. regimen and after 6-7 days for the p.m. regimen, change from baseline in normalised FEV_1 and FVC area under the curve over 24 hours (AUC_{0-24})

after 7 days of treatment for the a.m. regimen and 6-7 days for the p.m. regimen, change from baseline in normalised FEV_1 and FVC AUC_{0-12} after 7 days of treatment, change from baseline in normalised FEV_1 and FVC AUC_{12-24} after 7 days of treatment for the a.m. regimen and after 6 days of treatment for the p.m. regimen and use of "as needed" daily rescue medication (number of salbutamol puffs, as recorded by the patient).

Safety:
Adverse events (AEs), 12-lead electrocardiograms (ECGs), blood pressure measurements, clinical laboratory evaluations, pregnancy tests, and physical examination.

Statistical methods:
Analyses of the primary efficacy variable, the change from baseline in the trough FEV_1 after 6 days of treatment, were based on the ITT Population and this was considered the primary analysis. Analysis of the primary efficacy variable based on the PP Population was considered a sensitivity analysis. The change from baseline in the trough FEV_1 after 6 days of treatment was analysed descriptively and using an exploratory Analysis of Covariance (ANCOVA) model for crossover designs. Sequence, period, treatment and centre were included in the model as fixed effects, patient was a random effect and baseline FEV_1 was included as a covariate. The treatment comparisons were:
1) Aclidinium bromide 200 µg a.m. vs. placebo (time-matched trough at a.m.),
2) Aclidinium bromide 200 µg p.m. vs. placebo (time-matched trough at p.m.),
3) Aclidinium bromide 200 µg a.m. versus aclidinium bromide 200 µg p.m.
Due to the exploratory nature of this study, the type I error rate was not adjusted.
The variation between patients was assumed to be random and the sequence effects were tested using the estimated error of between patient (within sequence) mean square in the ANCOVA model. The treatment comparisons were carried out by means of the contrasts on the treatment factor. The treatment effect was estimated by means of the Least Square (LS) mean and its standard error (SE) and 95% confidence intervals (CI). The differences between treatments were estimated by differences between LS means and their SE and 95% CIs.
Analyses of secondary efficacy variables were based on the ITT and PP populations. Secondary efficacy variables were also analysed descriptively and using ANCOVA models for cross-over designs including sequence, patient, period, treatment and country as factors and baseline as a covariate. For the change from baseline in normalised FEV_1 and FVC AUC_{0-12} after 7 days of treatment and the change from baseline in normalised FEV_1 and FVC AUC_{12-24} after 7 days of treatment in the a.m. regimen and after 6 days of treatment in the p.m. regimen, only treatment comparisons of aclidinium bromide 200 µg a.m. vs. placebo and aclidinium bromide 200 µg p.m. vs. placebo were performed.

SUMMARY – CONCLUSIONS

Efficacy Results:
Primary Efficacy Variable
Mean trough FEV_1 values at baseline observed for morning regimens were slightly higher than those observed for evening regimens for both aclidinium bromide and placebo. Mean trough FEV_1 values at baseline were similar for placebo a.m. (1.440 L; SD=0.5290; 95% CI=1.313 to 1.567 L) and for aclidinium bromide 200 µg a.m. (1.424 L; SD= 0.4850; 95% CI=1.307 to 1.540 L) and they were almost identical for aclidinium bromide 200 µg p.m. (1.407; SD=0.5338; 95% CI=1.279 to 1.536 L) and placebo p.m. (1.408 L; SD=0.5389; 95% CI=1.278 to 1.537 L).
After 6 days of treatment, adjusted mean trough FEV_1 values were higher for both aclidinium bromide 200 µg a.m. and aclidinium bromide 200 µg p.m. (1.468 L and 1.440 L, respectively), compared to placebo (1.422 L for placebo a.m. and 1.403 L for placebo p.m.).
The adjusted mean trough FEV_1 increased from baseline for both aclidinium bromide 200 µg a.m. and aclidinium bromide 200 µg p.m. (0.048 and 0.020 L, respectively) after 6 days of treatment. After placebo administration the adjusted mean changes from baseline in trough FEV_1 were 0.003 L for placebo a.m. and -0.016 L for placebo p.m. There was a trend for a treatment difference between each of the aclidinium bromide treatments and placebo, favouring the active treatments. However, these differences were not statistically significant (0.045 L; p=0.0878 and 0.037 L; p=0.1691, respectively). Similarly, no statistically significant difference was observed between aclidinium bromide 200 µg given in the morning and evening (0.028 L; p=0.2904). Results of the analysis for the PP population for all comparisons were similar to those of the ITT population, confirming the robustness of the analysis.

Secondary Efficacy Variables

Change from baseline in the trough FVC after 6 days of treatment: Adjusted mean trough FVC increased from baseline for both aclidinium bromide 200 µg a.m. and aclidinium bromide 200 µg p.m. (0.054 and 0.034 L, respectively) after 6 days of treatment. After placebo administration, the changes from baseline in trough FVC were -0.005 L for placebo a.m. and 0.013 L for placebo p.m. However, there were no statistically significant differences between aclidinium bromide 200 µg a.m. and placebo a.m. in the change from baseline in trough FVC (0.059 L; p=0.1864). Likewise there was no statistically significant difference between aclidinium bromide 200 µg p.m. and placebo p.m. in the change from baseline in trough FVC (0.021 L, p=0.6460). Similarly, no statistically significant difference was observed between aclidinium bromide 200 µg given in the morning and evening (0.020 L; p=0.6521).

Change from baseline in trough IC after 6 days of treatment: There was no statistically significant difference between aclidinium bromide 200 µg a.m. and placebo a.m. in the change from baseline in trough IC (0.026 L; p=0.5930). However, there was a statistically significant difference between aclidinium bromide 200 µg p.m. and placebo p.m. in the change from baseline in IC (0.114 L; p=0.0202). There was no statistically significant difference between aclidinium bromide 200 µg given in the morning and evening (0.003 L; p=0.9537).

Change from baseline in the FEV_1 and FVC at all time-points: For FEV_1, statistically significant differences were found in the change from baseline in FEV_1 between aclidinium bromide 200 µg and placebo for time-points up to 12-15 hours after dosing whether the dose was administered in the morning or the evening. Some statistically significant differences were also observed between a.m. and p.m. dosing with aclidinium bromide 200 µg; these were in favour of a.m. dosing at 12:00, 15:00, 18:00 and 21:00 on Day 7 and in favour of p.m. dosing at 06:00 on Day 8. For FVC, statistically significant differences were seen between aclidinium bromide 200 µg a.m. and placebo at 12:00, 15:00, 18:00 and 21:00 on Day 7 and between aclidinium bromide 200 µg p.m. and placebo at 00:00 (midnight) on Day 8. Statistically significant differences were also observed between a.m. and p.m. dosing with aclidinium bromide 200 µg; these were observed at 12:00, 15:00, 18:00, and 21:00 on Day 7 and were in favour of a.m. dosing.

Change from baseline in the IC at all time-points: Overall, there was considerable variability in IC values between patients. This variability was due to the fact that several slow manoeuvres were not acceptable according to ATS/ERS criteria, however, all were included in the analysis. Statistically significant differences were seen between aclidinium bromide 200 µg a.m. and placebo at the 20:45 time-point and between aclidinium bromide 200 µg p.m. and placebo at the 20:45 and 23:45 time-points. A statistically significant difference was also observed between a.m. and p.m. dosing with aclidinium bromide 200 µg, in favour of p.m. dosing, at the 23:45 time-point.

Change from baseline in normalised FEV_1 and FVC AUC_{0-24}, AUC_{0-12} and AUC_{12-24}: For normalised FEV_1 AUC_{0-24} statistically significant differences between both aclidinium bromide regimens and placebo were observed; the adjusted mean treatment difference for aclidinium bromide 200 µg a.m. compared with placebo was 0.085 L (p<0.0001) and the adjusted mean treatment difference for aclidinium bromide 200 µg p.m. compared with placebo was 0.071 L (p=0.0003). No statistically significant difference was observed between aclidinium bromide 200 µg a.m. and p.m. Similar results were observed for normalised AUC_{0-12} FEV_1 and AUC_{12-24} FEV_1. However, due to the design of the trial, the comparison between aclidinium bromide 200 µg a.m. and p.m. for these two variables was not performed. For normalised FVC AUC_{0-24}, a statistically significant difference between aclidinium bromide 200 µg a.m. and placebo was observed; the adjusted mean treatment difference for aclidinium bromide 200 µg compared with placebo was 0.118 L (p=0.0006). The adjusted mean difference between aclidinium bromide 200 µg p.m. and placebo (0.066 L) approached significance (p=0.0508). There was no statistically significant difference observed between aclidinium bromide 200 µg a.m. and p.m. Both aclidinium bromide treatment regimens were superior to placebo for normalised AUC_{0-12} FVC, although a statistically significant difference was only observed between aclidinium bromide 200 µg a.m. and placebo for normalised AUC_{12-24} FVC. As for FEV_1, the comparison between aclidinium bromide 200 µg a.m. and p.m. for these two variables was not performed.

For all secondary pulmonary function variables, results of analyses for the PP population for all comparisons were similar to those of the ITT population, confirming the robustness of the analyses.

Use of “as needed” daily rescue medication: No analysis of this variable was performed since patients did not record the total number of puffs of salbutamol per day properly in the patient diary card and therefore these data were not considered to be clinically reliable.

Safety Results:
Inhaled treatment with aclidinium bromide 200 µg administered either in the morning or in the evening for 7 days was well-tolerated with a safety profile similar to that observed with placebo.
Treatment-emergent AEs were reported in 12 patients (17.4%) treated with aclidinium bromide 200 µg a.m., 13 patients (18.8%) treated with aclidinium bromide 200 µg p.m. and six patients (8.7%) treated with placebo. Only one TEAE, an episode of moderate dry mouth experienced by a patient during treatment with aclidinium bromide 200 µg p.m., was considered by the Investigator to be treatment-related. This was the only pharmacologically predictable anticholinergic adverse drug reaction reported during study treatment. The majority of TEAEs were of mild or moderate intensity. During each treatment, only two patients experienced TEAEs that were of severe intensity.
Headache was the most commonly reported TEAE during treatment, reported in 5 patients (7.2%) during treatment with aclidinium bromide 200 µg a.m., 4 patients (5.8%) during treatment with aclidinium bromide 200 µg p.m. and 3 patients (4.3%) during treatment with placebo. This AE was also the most commonly reported (7 patients [10.1%]) prior to administration of any study medication. No other TEAE was reported by more than two patients during any treatment.
One SAE (suspected pulmonary embolism) was reported during treatment with aclidinium bromide 200 µg p.m. and this SAE had a fatal outcome. It was not considered to be related to study treatment. One further patient was withdrawn prematurely because of a severe respiratory tract infection during treatment with aclidinium bromide 200 µg a.m.
There were no clinically significant findings on physical examination, vital signs, 12-lead ECG, and clinical laboratory data.

CONCLUSIONS:

DATE OF REPORT:
26 September 2008