2 SYNOPSIS

<table>
<tr><td>Name of Sponsor / Company:
AstraZeneca

Name of Finished Product:
N.A.

Name of Active Ingredients:
Aclidinium bromide</td><td>Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="3">Title of Study: EFFICACY AND SAFETY O F THREE DOSES OF ACLIDINIUM BROMIDE COMPARED TO PLACEBO AND TO AN ACTIVE COMPARATOR ALL A DMINISTERED TWICE DAILY BY INHALATION IN PATIENTS WITH STABLE MO DERATE AND SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD).</td></tr>
<tr><td colspan="3">Investigators:</td></tr>
<tr><td colspan="3">Study centre (s):</td></tr>
<tr><td colspan="3">Publication (reference):
None</td></tr>
<tr><td colspan="2">Studied period (years):
Date study initiated (first screening): 21 April 2010
Date study finalised (last patient last visit): 19 August 2010</td><td>Phase of development: IIb</td></tr>
<tr><td colspan="3">Objectives:
• To assess the efficacy of three doses of aclidinium bromide (100 µg, 200 µg or 400 µg) twice a day (BID) compared to formoterol 12 µg BID and placebo in patients with moderate to severe COPD
• To evaluate the safety and tolerability of aclidinium bromide (100 µg, 200 µg or 400 µg) BID in the same target population.</td></tr>
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Methodology:
This was a prospective, double-blind, double-dummy, randomised, 5x5 Latin square cross-over, placebo and active controlled multinational, multicentre study.
The study consisted of a Screening Visit (Visit 1) conducted after signature of the informed consent form, where medical history, COPD severity stage, physical examination, and baseline laboratory and electrocardiogram (ECG) assessments were conducted. Patients fulfilling inclusion/exclusion criteria at the time of the Screening Visit were entered into a run-in period of 14 ± 3 days to assess patient's disease stability. Patients who met the entry criteria were assigned to 1 of the 5 treatment sequences using a balanced randomisation ratio (1:1:1:1:1). The treatment period consisted of 5 periods of 7 treatment days each separated by a washout period of 7 (±2) days. During the double-blind treatment period, patients visited the centre for assessment of clinical efficacy and safety on 10 occasions (from Visit 2 to Visit 11) and, after treatment completion, a follow-up contact was performed 2 weeks later.

Number of patients (planned and analysed):
Planned: 65
Screened: 99
Randomised: 79
Completed study: 68
Evaluated for safety: 79
Evaluated for efficacy (Intention-to-Treat [ITT] analysis): 79
Evaluated for efficacy (Per-Protocol [PP] analysis): 73

Diagnosis and main criteria for inclusion:
- Adult male and female patients aged ≥40 years with stable moderate to severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines).
- Post-salbutamol forced expiratory volume in 1 second (FEV_1) <80% and ≥30% of predicted normal value and FEV_1/forced vital capacity (FVC) <70%.
- Current or ex−smokers of ≥10 pack-years.
- Patients with no history or current diagnosis of asthma.
- 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 contraindication to use of anticholinergic drugs such as known symptomatic prostatic hypertrophy, bladder neck obstruction, acute urinary retention or narrow-angle glaucoma.

Test product, dose and mode of administration, batch number, expiry date:
Name: Aclidinium bromide
Administration route: Oral inhalation using the Genuair® multi-dose dry powder inhaler
Dosage form: Inhalation powder
Dose and regimen: 1 puff of 100 µg, 200 µg or 400 µg in the morning (09:00 ± 30 minutes) and 1 puff in the evening (21:00 ± 30 minutes)
Batch number: K1-97-L20 (100 µg), DPI038-L18 (200 µg), DPI047-L19 (400 µg)
Expiry date: May 2011

Duration of treatment:
There were 5 periods of 7 treatment days, with 7 (±2) days washout between periods. The total duration of the study for each patient was approximately 13 weeks (including screening and follow-up contact).

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Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Formoterol
Administration route: Oral inhalation using the Aerolizer® dry powder inhaler (Foradil® [formoterol] via Aerolizer®)
Dosage form: Capsules for inhalation
Dose and regimen: 1 capsule (formoterol 12 µg) in the morning (09:00 ± 30 minutes) and 1 capsule in the evening (21:00 ± 30 minutes)
Batch number: 00002138-L21
Expiry date: July 2011

Name: Placebo to aclidinium bromide
Administration route: Oral inhalation using the Genuair® multi-dose dry powder inhaler
Dosage form: Inhalation powder
Dose and regimen: 1 puff of placebo in the morning (09:00 ± 30 minutes) and 1 puff of placebo in the evening (21:00 ± 30 minutes)
Batch number: DP-I031-L17
Expiry date: May 2011

Name: Placebo to formoterol
Administration route: Oral inhalation using the Aerolizer® dry powder inhaler (Foradil® [formoterol] via Aerolizer®)
Dosage form: Capsules for inhalation
Dose and regimen: 1 capsule of placebo in the morning (09:00 ± 30 minutes) and 1 capsule of placebo in the evening (21:00 ± 30 minutes)
Batch number: 093F0170-L22
Expiry date: July 2011

Criteria for evaluation:

Efficacy:

Primary efficacy variable:

- Change from baseline in normalised FEV_1 area under the curve (AUC) over the 12 hour (h) period immediately after morning investigational medicinal product (IMP) administration, (AUC_{0-12}) at Day 7 on treatment.

Secondary efficacy variables:

- Change from baseline in normalised FEV_1 AUC_{12-24} and AUC_{0-24} at Day 7 on treatment.
- Change from baseline in morning pre-dose (trough) FEV_1 at Day 7 on treatment.

Additional efficacy variables:

- Change from baseline in normalised FVC AUC_{0-12}, AUC_{12-24} and AUC_{0-24} at Day 7 on treatment.
- Change from baseline in normalised FEV_1 and FVC AUC over the 6 h period immediately after morning IMP administration (AUC_{0-6}) at Days 1 and 7 on treatment.
- Change from baseline in morning pre-dose (trough) FVC at Day 7 on treatment.
- Absolute values of morning pre-dose (trough) FEV_1 and FVC at Day 7.
- Change from baseline in the morning and evening peak FEV_1 and FVC at Day 7 on treatment.
- Change from baseline in the morning peak FEV_1 and FVC at Day 1 on treatment.
- Time to morning peak FEV_1 at Days 1 and 7.

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- Time to evening peak FEV_1 at Day 7.
- Change from baseline in FEV_1 and FVC at each specific time-point at Day 1 and Day 7 on treatment.
- Absolute values of FEV_1 and FVC by day and time-point.
- Number (and percentage) of patients using relief medication after 7 days of treatment.
- Change from baseline in the use of relief medication (number of puffs) after 7 days on treatment.

Safety:
Adverse events (AEs), serious adverse events (SAEs), blood pressure (BP), 12-lead ECG parameters, clinical laboratory parameter (haematology, biochemistry, urinalysis, and pregnancy tests).

Other variables:
Exposure to study drug, prior and concomitant medication, number of withdrawals and reason for withdrawal, convenience of device.

Statistical methods:
The analysis of all the efficacy variables was performed on the ITT population. In addition, the primary efficacy variable was also analysed using the PP population to assess the robustness of the findings from the ITT Population. All demographic and baseline characteristics, safety outcomes and other variables were analysed using the Safety population.
All statistical comparisons were two-sided hypothesis tests, and the significance level was set at 0.05.
The primary, secondary and additional efficacy variables except for "Time to peak FEV_1" and "Number (and percentage) of patients using relief medication after 7 days of treatment" were analysed by means of an analysis of covariance (ANCOVA) for cross-over designs with sequence, treatment and period as fixed effect factors, subject within sequence as random effect, and baseline value at each period as covariate.
"Time to peak F EV_1" and "Number (and percentage) of patients using relief medication after 7 days of treatment" were analysed descriptively.
Safety and tolerability outcomes, convenience of device assessment and other variables were summarised by means of descriptive statistics.

SUMMARY – CONCLUSIONS

Efficacy Results:

- Administration of aclidinium bromide BID induced statistically significant improvements in pulmonary lung function compared to placebo which was evident from post-morning administration on Day 1, was sustained over time and maintained until the end of the treatment period at Day 7.
- At the end of 7 days on treatment all aclidinium bromide BID doses (100 µg, 200 µg and 400 µg) provided a dose- dependent and statistically significant bronchodilation 12 h after morning and evening administration ($p<0.0001$) with aclidinium bromide 400 µg BID showing statistically significantly greater improvements compared to aclidinium bromide 100 µg BID for all values.
- The magnitude of the improvement in FEV_1 provided by aclidinium bromide 400 µg BID during the first 12 h was comparable to formoterol 12 µg BID, although significantly lower after the evening administration (0.056, $p=0.0065$).

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Summary of change from baseline in FEV_1 AUC_{0-12}, AUC_{12-24} and AUC_{0-24}: Analysis based on the ANCOVA model.

Day 7	Aclidinium bromide 100 µg BID	Aclidinium bromide 200 µg BID	Aclidinium bromide 400 µg BID	Formoterol 12 µg BID
	Adjusted mean difference*	Adjusted mean difference*	Adjusted mean difference*	Adjusted mean difference*
AUC_{0-12}	0.154	0.176	0.208	0.210
AUC_{12-24}	0.147	0.150	0.189	0.244
AUC_{0-24}	0.150	0.162	0.195	0.225

*p<0.0001 for all treatment comparisons versus placebo

- In addition, all aclidinium bromide BID doses provided a clinically and statistically significantly greater improvement in morning pre-dose (trough) FEV_1 after 7 days on treatment compared with placebo. The bronchodilation provided by aclidinium bromide 400 µg BID at the end of the dosing interval (trough) was comparable to that of formoterol 12 µg BID and statistically significantly greater than aclidinium bromide 100 µg BID (0.048L, p=0.0278).

Summary of change from baseline in trough FEV_1: analysis based on the ANCOVA model.

Day 7	Aclidinium bromide 100 µg BID	Aclidinium bromide 200 µg BID	Aclidinium bromide 400 µg BID	Formoterol 12 µg BID
	Adjusted mean difference*	Adjusted mean difference*	Adjusted mean difference*	Adjusted mean difference*
Trough FEV_1	0.106	0.114	0.154	0.148

*p<0.0001 for all treatment comparisons versus placebo

- All doses of aclidinium bromide BID provided a statistically significant higher morning peak FEV_1 when compared to placebo at Day 1 and this effect continued to be demonstrated and increased at Day 7 (p<0.0001). The difference between the highest (400 µg BID) and the lowest (100 µg BID) doses of aclidinium bromide was statistically significant at both Day 1 and Day 7. Peak FEV_1 values for aclidinium bromide 400 µg BID were comparable to those of formoterol 12 µg BID at Day 1 and Day 7.

Summary of change from baseline morning peak FEV_1: analysis based on the ANCOVA model.

	Aclidinium bromide 100 µg BID	Aclidinium bromide 200 µg BID	Aclidinium bromide 400 µg BID	Formoterol 12 µg BID
	Adjusted mean difference*	Adjusted mean difference*	Adjusted mean difference*	Adjusted mean difference*
Morning peak FEV_1 (Day 1)	0.140	0.176	0.223	0.221
Morning peak FEV_1 (Day 7)	0.189	0.201	0.242	0.246

*p<0.0001 for all treatment comparisons versus placebo

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- The slope of the FEV_1 curve of aclidinium bromide BID was comparable to the slope of an approved BID drug (formoterol 12 µg in Aerolizer®) at both 12 h and 24 h, thus supporting the BID dose regimen of aclidinium bromide. All doses of aclidinium bromide BID were statistically significantly different from placebo at the majority of timepoints throughout the 24 h period. Treatment with aclidinium bromide 400 µg BID resulted in significantly greater changes than the 100 µg BID dose throughout the 24 h period at all timepoints, except for the 30 minutes, 1, 10, 13, 22 and 23 h time points, with significance being achieved again at 24 h post dose.
- A dose response was observed for aclidinium bromide BID for daily use of relief medication, with more patients receiving 100 µg BID requiring relief medication than patients receiving 200 µg or 400 µg BID. There was a statistically significant reduction compared to placebo in the use of daily relief medication with aclidinium bromide 200 µg BID (p=0.0243) and aclidinium bromide 400 µg BID (p=0.0051).
- Most patients (62.8%) definitely preferred the Genuair®, with only 6.4% preferring the Aerolizer®, and found the Genuair® "very easy" to use (65.4%) compared to the Aerolizer® (24.4%). Similarly, more patients found the dose "very easy" to prepare with the Genuair® (73.1%) than the Aerolizer® (19.2%).

Safety Results:

- Administration of all doses of aclidinium bromide BID for 7 days was safe and well tolerated in patients with moderate to severe COPD. The safety profile of all doses of aclidinium bromide BID was, in general, comparable to those of the active comparator and placebo.
- The overall incidence of treatment emergent AEs (TEAEs) was highest with placebo BID (21.1%) and lowest with formoterol 12 µg BID (14.9%). The overall incidence of TEAEs was 15.1%, 17.8% and 18.9% for aclidinium bromide 100 µg BID, 200 µg BID and 400 µg BID, respectively. The most commonly reported TEAEs (reported by at least 2 patients with any treatment) were headache, nasopharyngitis, toothache, diarrhoea, cough and pruritus.
- No deaths occurred during the treatment phase. One patient died before he was randomised.
- Four patients experienced SAEs: 2 patients receiving placebo BID (COPD exacerbation and thermal burn), 1 patient receiving aclidinium bromide 200 µg BID (myocardial infarction) and 1 patient receiving aclidinium bromide 400 µg BID (infective exacerbation of COPD). All except thermal burn (placebo) led to discontinuation.
- An additional 4 patients were discontinued due to non-serious TEAEs: 2 patients receiving placebo BID (hypertension and atrial fibrillation), 1 patient receiving aclidinium bromide 400 µg BID (exacerbation of chronic obstructive pulmonary disease) and 1 patient receiving formoterol BID 12 µg (migraine).
- The majority of TEAEs were of mild or moderate intensity and severe TEAEs were reported in no more than 2 patients with any treatment.
- Study drug-related TEAEs were more commonly reported with placebo BID (10 events in 7 patients [9.2%]: atrial fibrillation, supraventricular extrasystoles, ventricular extrasystoles, headache [3 events], cough, dyspnoea, nasal dryness and hypertension). Three patients (4.1%) receiving

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aclidinium bromide 100 µg BID experienced 3 drug-related TEAEs (bundle branch block right, headache and cough). Two patients (2.7%) receiving aclidinium bromide 200 µg BID experienced 2 drug-related TEAEs (electrocardiogram t wave abnormal and throat irritation). No drug-related TEAEs were reported in patients receiving aclidinium bromide 400 µg BID. One patient (1.4%) receiving formoterol BID experienced 2 drug-related TEAEs (dry mouth and nasal dryness).

- There were no clinically relevant abnormalities in any ECG or laboratory safety parameter.

CONCLUSIONS:

DATE OF REPORT:
Final, 31 January 2011.