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, RANDOMISED, DOUBLE-BLIND, PLACEBO CONTROLLED, 2 PERIOD CROSSOVER CLINICAL TRIAL TO ASSESS THE EFFECT OF ACLIDINIUM BROMIDE 400 µg BID ON EXERCISE ENDURANCE IN PATIENTS WITH STABLE MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)		
Investigators:		
Study sites:		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 10 November 2011 Date study finalised (last patient last visit): 04 June 2012	**Phase of development:** IIIb	

Objectives:

- To evaluate the effect of aclidinium bromide 400 µg twice daily (BID) on exercise endurance compared with placebo in patients with moderate to severe COPD.
- To evaluate the effect of aclidinium bromide 400 µg BID on hyperinflation and dyspnoea at rest and during exercise compared with placebo in patients with moderate to severe COPD.
- To assess the safety and tolerability of inhaled aclidinium bromide 400 µg BID in the same target population.

Methodology:

This was a prospective, multiple dose, double-blind, randomised, 2 period crossover, placebo controlled, multinational, multicentre clinical study.

The study consisted of a Screening Visit conducted after signature of the informed consent form (ICF), where medical history and COPD severity stage (post-bronchodilator forced expiratory volume in 1 second [FEV_1] according to Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines), physical examination, laboratory tests, electrocardiogram (ECG) assessment, body plethysmography and incremental cycle ergometry were conducted. Patients fulfilling inclusion/exclusion criteria at the time of the Screening Visit were entered into a run-in period of 14 to 21 days to assess disease stability. During this period, one site visit (Run-in Visit) was performed to familiarise patients with study testing procedures (body plethysmography, spirometry and a constant work rate cycle exercise test). At the end of the run-in period, patients who met entry criteria at Visit 1 were randomised (1:1) to one of the 2 treatment sequences.

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Methodology (continued):
During the double-blind treatment period, patients visited the site for assessment of clinical efficacy and safety on 4 occasions (Day 1 [Visits 1 and 3] and Day 22 [Visits 2 and 4] of each treatment period). A follow-up contact was performed 2 weeks after treatment completion. Patients who remained on treatment and attended up to Visit 4 were considered to have completed the treatment, even if they did not complete the follow-up contact.

Number of patients (planned and analysed):
Planned: A total of 84 patients with moderate to severe COPD were required to complete the study. Approximately 170 patients were planned to be screened to achieve a total of 110 randomised patients. This takes into account a predicted 35% screening failure rate (prior to randomisation) and a predicted 20% drop-out rate after randomisation.
Screened: 149 patients
Randomised: 112 patients
Completed treatment: 106 patients
Completed study: 106 patients
Evaluated for safety: 112 patients
Evaluated for efficacy (Intention-to-Treat [ITT] analysis): 110 patients
Evaluated for efficacy (Per-Protocol [PP] analysis): 103 patients

Diagnosis and main criteria for inclusion:

- Males and non-pregnant, non-lactating females aged ≥40 years.
- Patients with a clinical diagnosis of stable moderate to severe COPD, according to the GOLD Guidelines and stable airway obstruction. Post-salbutamol FEV_1/forced vital capacity (FVC) <70% at the Screening Visit (i.e., 100 x post-salbutamol FEV_1/FVC <70%).
- Patients whose FEV_1 at the Screening Visit measured between 10-15 minutes post-inhalation of 400 µg salbutamol was ≥30% and <80% of the predicted normal value (i.e., 100 x observed post-salbutamol FEV_1/predicted FEV_1 <80% and ≥30%).
- Functional residual capacity (FRC) measured by body plethysmography at the Screening Visit ≥120% of predicted value.
- Current or former smokers with a smoking history of at least 10 pack-years.
- Patients with no history or current diagnosis of asthma.
- No signs of an exacerbation within 6 weeks (or 3 months if resulted in hospitalisation) prior to the Screening Visit or during the run-in period.
- No evidence of clinically significant respiratory (other than COPD) and/or cardiovascular conditions or laboratory abnormalities.
- No conditions where the use of anticholinergic drugs was contraindicated, such as known symptomatic prostatic hypertrophy, bladder neck obstruction or narrow-angle glaucoma.
- Patients with an oxygen saturation >85% during cycle exercise on room air at the Screening Visit, Run-in Visit and Visit 1.
- No contraindications of cardiopulmonary exercise testing (CPET).
- Patients who, in the investigator's opinion would not need to start a pulmonary rehabilitation program during the study and/or patients who had just started/finished pulmonary rehabilitation at least 3 months prior to the Screening Visit.

Patients previously included in prior studies with aclidinium bromide (administered as monotherapy or in combination) were allowed to be included in this study.

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Test product, dose and mode of administration, batch number, expiry date:
Name: Aclidinium bromide
Administration route: Oral inhalation by Genuair® multidose dry powder inhaler
Dosage form: Dry powder
Dose and regimen: 1 puff of 400 µg in the morning (09:00 ± 1h) and in the evening (21:00 ± 1h)
Batch number: D2 Expiry date: December 2012

Duration of treatment:
Two periods of 3 treatment weeks

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Placebo
Administration route: Oral inhalation by Genuair® multidose dry powder inhaler
Dosage form: Dry powder
Dose and regimen: 1 puff of placebo in the morning (09:00 ± 1h) and in the evening (21:00 ± 1h)
Batch number: E1 Expiry date: May 2014

Criteria for evaluation:

Efficacy:

Primary Efficacy Variable:

- Change from baseline in endurance time (ET) during constant work rate cycle ergometry to symptom limitation at 75% of the maximum work rate (Wmax) after 3 weeks of treatment, where ET is the time from the increase in work rate at 75% Wmax to the point of symptom limitation.

Secondary Efficacy Variables:

- Change from baseline in pre-dose (trough) inspiratory capacity (IC) after 3 weeks of treatment.
- Change from baseline in intensity of dyspnoea based on the Borg CR10 Scale® at isotime during constant work rate cycle ergometry after 3 weeks of treatment, where isotime is the duration of the shortest exercise test on Visit 1, 2, 3 and 4.

Additional Efficacy Variables:

- Percentage change from baseline in ET during constant work rate cycle ergometry after 3 weeks of treatment.
- Change from baseline in IC during constant work rate cycle ergometry after 3 weeks of treatment (at rest, every 2 minutes during exercise, at isotime and at end of exercise).
- Change from baseline in intensity of dyspnoea based on the Borg CR10 Scale® during constant work rate cycle ergometry after 3 weeks of treatment (at rest, every 2 minutes during exercise and at end of exercise).
- Change from baseline in intensity of leg discomfort based on the Borg CR10 Scale® during constant work rate cycle ergometry after 3 weeks of treatment (at rest, every 2 minutes during exercise, isotime and at end of exercise).
- Percentage of patients stopping exercise because of breathing discomfort, leg discomfort, breathing and leg discomfort, or other reasons during constant work rate cycle ergometry.
- Change from baseline in morning pre-dose (trough) FEV_1 and trough FVC after 3 weeks of treatment.
- Change from baseline in morning pre-dose (trough) specific airway conductance (sGaw), FRC, residual volume (RV), total lung capacity (TLC) and IC/TLC after 3 weeks of treatment.
- Change from baseline in morning post-dose sGaw, FRC, RV and TLC after 3 weeks of treatment.

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Criteria for evaluation (continued):

Additional Efficacy Variables (continued):

- Change from baseline in the daily average use of relief medication (day-time, night-time and daily) over 3 weeks of treatment.
- Change from baseline in the percentage of relief medication-free days (day-time, night-time and daily) over 3 weeks of treatment.
- Change from baseline of the physical activity parameters including: steps per day, minutes of at least moderate activity (defined as any physical activity >3 metabolic equivalents), mean physical activity level, mean daily active energy expenditure (>3 metabolic equivalents) and number of nocturnal awakenings due to COPD symptoms.

Safety:

Safety outcomes included recording of adverse events (AEs) and serious AEs (SAEs), blood pressure, 12-lead ECG and haematological and biochemical laboratory tests.

Statistical methods:

The analysis of all efficacy variables was performed on the ITT population comprising all randomised patients who took at least one dose of the investigational medicinal product (IMP), and had at least a baseline and one post-dose corresponding assessment value of the primary efficacy variable in one of the 2 treatment periods. 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 comprising all randomised patients who took at least one dose of IMP.

All statistical comparisons were two-sided hypothesis tests, and the significance level was set at 0.05. All confidence intervals (CIs) were two-sided at the 95% confidence level.

All efficacy endpoints, except the percentage of patients stopping exercise because of a specific reason, were analysed using a mixed model with treatment and period as fixed effects, patient as a random effect and baseline value prior to IMP intake of each period as a covariate. Between-treatment least squares (LS) means and 95% CIs were calculated.

The percentage of patients stopping exercise because of breathing discomfort, leg discomfort or both breathing and leg discomfort during constant work rate cycle ergometry was analysed using a binomial model, using patients stopping exercise as a response with baseline, treatment group and period as factors and Generalised Estimating Equations (GEE) to take into account the correlation between patients.

For the variables that were analysed every 2 minutes during exercise, analyses were performed provided at least 20 patients had data at the specific time point.

AEs, SAEs, ECG parameters, blood pressure, laboratory parameters and other variables were summarised by means of descriptive statistics.

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SUMMARY OF RESULTS

Disposition:
A total of 149 patients were screened, of whom 112 patients were assessed as eligible and were randomised into the study. Overall, 106 (94.6%) of the randomised patients completed the study and 6 (5.4%) patients were discontinued from the study due to AEs (4 and 2 following aclidinium bromide and placebo, respectively).

Demographic and Baseline Characteristics:
All patients were Caucasian (76 [67.9%] were males) with a mean age of 60.3 years and a mean smoking history of 48.0 pack-years. The majority of patients (71.4%) had moderate (GOLD Stage II) COPD with a mean duration of COPD at baseline of 8.8 years. At screening, the overall mean FRC (5.045 L) was 152.3% of the predicted value. The mean baseline FEV_1 value at Visit 1 was 1.480 L. The use of concomitant and relief medications was similar for both treatments.

Efficacy Results:

Primary efficacy variable: Change from baseline in ET at Week 3:

After 3 weeks of treatment, aclidinium bromide 400 µg BID showed a statistically significantly greater increase in the adjusted mean change from baseline in ET during constant work rate cycle ergometry compared to placebo, with an adjusted mean difference from placebo of 58.5 seconds (p=0.0210).

Secondary efficacy variables:

Change from baseline in pre-dose (trough) IC at Week 3: At Week 3, aclidinium bromide 400 µg BID showed a statistically significantly greater increase in the adjusted mean change from baseline in pre-dose (trough) IC compared to placebo (0.078 L; p=0.0248).

Change from baseline in intensity of dyspnoea at isotime at Week 3: Intensity of dyspnoea was based on the Borg CR10 Scale®, ranging from "nothing at all" (0) to "extremely strong/maximal" (10; the highest possible numerical value). After 3 weeks of treatment, aclidinium bromide 400 µg BID showed a statistically significantly greater decrease in the adjusted mean change from baseline in intensity of dyspnoea at isotime during constant work rate cycle ergometry compared to placebo (-0.63; p=0.0122).

Additional efficacy variables: Endpoints based on constant work rate cycle ergometry

Percentage change from baseline in ET at Week 3: After 3 weeks of treatment, aclidinium bromide 400 µg BID showed a numerically greater increase in the adjusted mean percentage change from baseline in ET during constant work rate cycle ergometry compared to placebo (8.9%; p=0.1196).

Changes from baseline in IC at rest, at isotime and end of exercise: After 3 weeks of treatment, aclidinium bromide 400 µg BID showed statistically significantly greater increases in the adjusted mean changes from baseline in IC at rest, isotime and end of exercise compared to placebo, with differences from placebo of 0.176 L (p<0.0001), 0.155 L (p=0.0002) and 0.161 L (p<0.0001), respectively.

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Efficacy Results (continued):

Changes from baseline in intensity of dyspnoea at rest and end of exercise: After 3 weeks of treatment, aclidinium bromide 400 µg BID showed a numerically greater decrease in the adjusted mean change from baseline in intensity of dyspnoea at rest compared to placebo (difference from placebo of -0.13, based on the Borg CR10 Scale®, range 0 to 10), but showed a numerically greater increase at end of exercise (difference of 0.39). Neither of these differences from placebo were statistically significant ($p>0.05$ in both cases).

Changes from baseline in intensity of leg discomfort at isotime: Intensity of leg discomfort was based on the Borg CR10 Scale®, ranging from "nothing at all" (0) to "extremely strong/maximal" (10; the highest possible numerical value). After 3 weeks of treatment, aclidinium bromide 400 µg BID showed numerically greater adjusted mean decreases from baseline in the intensity of leg discomfort compared to placebo at isotime (-0.28; $p>0.05$).

Patients stopping exercise for various reasons: After 3 weeks of treatment, there was no statistically significant difference between the treatments with respect to the percentage of patients stopping the exercise test for any of the specified reasons (breathing and leg discomfort, breathing discomfort alone and leg discomfort alone).

Additional efficacy variables: Changes from baseline in spirometry and body plethysmography parameters

After 3 weeks of treatment, aclidinium bromide provided statistically significantly greater increases from baseline in morning pre-dose (trough) and post-dose sGaw and morning pre-dose FEV_1, FVC and IC/TLC ratio, and statistically significantly greater decreases from baseline in morning pre-dose (trough) and post-dose FRC, RV and morning post-dose TLC versus placebo (see table below).

	Differences in Adjusted Mean Changes from Baseline vs. Placebo	
	AB 400 µg BID (N=109)	
Variable (unit)	Morning pre-dose (trough)	Morning post-dose
Spirometry		
FEV_1 (L)	0.132**	--
FVC (L)	0.243**	--
Body Plethysmography		
sGaw ($s^{-1}kPa^{-1}$)	0.094*	0.243**
FRC (L)	-0.197*	-0.318**
RV (L)	-0.238*	-0.443**
TLC (L)	-0.076	-0.150*
IC/TLC	0.014*	--

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AB=aclidinium bromide; BID=twice daily; FEV_1=forced expiratory volume in the first second; FRC=functional residual capacity; FVC=forced vital capacity; IC=inspiratory capacity; ITT=Intention-to-Treat; N=ITT population size of treatment; RV=residual volume; $s^{-1}kPa^{-1}$=amount of air reaching the alveoli per second per kilo-Pascal of pressure; sGaw=specific airway conductance; TLC=total lung capacity.

* $0.001<p<0.05$; ** $p<0.0001$. For placebo, N=108.

Adjusted mean differences and p-values obtained from an analysis of covariance model for crossover designs with change from baseline in trough or post-dose variable as the response, treatment and period as fixed effects, patient as a random effect and baseline value prior to investigational medicinal product intake of each period as a covariate.

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Efficacy Results (continued):

Additional efficacy variables: Changes from baseline in the use of relief medication

Over 3 weeks of treatment, aclidinium bromide 400 µg BID showed statistically significantly greater improvements from baseline in daily relief medication use (-0.9 puffs; $p<0.0001$) and in the percentage of days free from relief medication use (14.6%; $p<0.0001$) compared to placebo.

Additional efficacy variables: Changes from baseline in physical activity parameters

Over 3 weeks of treatment, aclidinium bromide 400 µg BID showed statistically significantly greater adjusted mean increases from baseline in the duration of at least moderate activity (10.1 minutes; $p=0.0156$) and daily active energy expenditure (54.5 kcal; $p=0.0103$) compared to placebo. Aclidinium bromide also showed numerically greater increases versus placebo in step count (459.0 steps per day; $p>0.05$) and physical activity level (0.024; $p>0.05$, physical activity level was a ratio calculated as the total daily energy expenditure divided by the whole night sleeping energy expenditure).

Safety and Tolerability Results:

Overall, 58.9% of the patients reported at least one treatment-emergent AE (TEAE), with a higher incidence reported following aclidinium bromide (44.1%) compared to placebo (30.6%). The majority of TEAEs were mild or moderate in intensity, only one TEAE of severe intensity reported during the study, which was considered to be not related to the IMP.

The most common TEAEs by Preferred Term (PT) were nasopharyngitis (9.8% of patients overall), headache (7.1%) and product taste abnormal (5.4%), all of which were reported at a slightly higher incidence following aclidinium bromide (6.3%, 4.5% and 3.6%, respectively) than following placebo (3.7%, 2.8% and 1.9%, respectively).

Of the patients with TEAEs, 54.5% had TEAEs which were considered not related to the IMP and 12.5% had at least one IMP-related TEAE. The most common IMP-related TEAE was 'product taste abnormal', being reported in 6 patients (5.4%) overall (4 [3.6%] following aclidinium bromide and 2 [1.9%] following placebo). The only other IMP-related TEAEs that were reported in more than one patient overall were dyspnoea (reported by 2 [1.9%] patients following placebo only) and dry mouth (2 [1.8%] patients following aclidinium bromide only).

No deaths occurred during the study and no SAEs were reported following aclidinium bromide (2 SAEs reported in 2 patients following placebo). TEAEs leading to discontinuation were reported in 6 patients (5.4%) overall. The percentage of patients with TEAEs leading to discontinuation was slightly higher following aclidinium bromide (4 [3.6%] patients) compared to placebo (2 [1.9%]). The most common TEAE leading to discontinuation was moderate COPD exacerbation (discontinuation required by the protocol), which was reported in 4 patients (3.6%) overall (2 patients following each treatment). None of the TEAEs leading to discontinuation were considered to be related to the IMPs.

Overall, the incidence of potential anticholinergic events and cardiac events was low (<2% of patients overall), and no cerebrovascular event were reported during the study.

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Safety and Tolerability Results (continued):

No clinically relevant changes versus screening were observed in haematology and biochemistry parameters, systolic and diastolic blood pressure, and ECG parameters (including heart rate) at the end of the study. No safety laboratory results constituted a TEAE. No QTcB (QT interval corrected, Bazett's formula [$QT/RR^{1/2}$]) and QTcF (QT interval corrected, Fridericia's formula [$QT/RR^{1/3}$]) changes from baseline >60 msec were observed during the study.

CONCLUSIONS:

DATE OF REPORT:

- **28 November 2012**