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, PLACEBO CONTROLLED, PARALLEL CLINICAL TRIAL TO ASSESS THE EFFICACY AND SAFETY OF TWICE DAILY INHALED ACLIDINIUM BROMIDE 400 µg COMPARED TO PLACEBO AND TO TIOTROPIUM BROMIDE 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): 17 October 2011 Date study finalised (last patient last visit): 14 March 2012	**Phase of development:** IIIb	

Objectives:

- To evaluate the 24-hour (h) bronchodilatory efficacy of inhaled aclidinium bromide 400 µg twice daily (BID) versus placebo in moderate to severe COPD patients.
- To evaluate the night-time bronchodilation of inhaled aclidinium bromide 400 µg BID versus tiotropium bromide in moderate to severe COPD patients.
- To assess the safety and tolerability of inhaled aclidinium bromide 400 µg BID in the same target population.

Methodology:

This was a 6-week prospective, randomised, double-blind, double-dummy, placebo and active comparator controlled, parallel multicentre clinical study.

The study consisted of a Screening Visit (Visit -1) 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) were assessed. 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 and during this period, patients recorded their COPD symptoms daily. Patients who still met entry criteria at Visit 1 were assigned to one of the 3 treatment arms (aclidinium bromide 400 µg BID, tiotropium bromide 18 µg once daily [QD] or placebo) according to a 2:2:1 randomisation ratio.

During the 6-week double-blind treatment period, patients visited the site to assess clinical efficacy and safety on two occasions (Day 1 [Visit 1] and Day 42 [Visit 2]). A phone contact was performed after 3 weeks of treatment and a follow-up contact was performed 2 weeks after treatment completion to monitor the safety of the patients. Patients were considered to have completed the study if they had undergone treatment up through Visit 2, even if they did not complete the follow-up contact.

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Number of patients (planned and analysed):
Planned: Approximately 625 patients were planned to be screened to achieve a total number of 405 randomised patients; that is 162 patients to aclidinium bromide 400 µg, 162 to tiotropium bromide 18 µg and 81 to placebo.
Screened: 485 patients
Randomised: 414 patients
Completed treatment: 400 patients
Completed study: 400 patients
Evaluated for safety: 414 patients
Evaluated for efficacy (Intention-to-Treat [ITT] analysis): 414 patients
Evaluated for efficacy (Per-Protocol [PP] analysis): 391 patients

Diagnosis and main criteria for inclusion:

- Adult male and female patients aged ≥40 years with stable moderate to severe COPD (as defined by the GOLD guidelines).
- Post-salbutamol FEV_1 ≥30% and <80% 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 respiratory tract infection or COPD exacerbation within 6 weeks prior to the Screening Visit.
- No evidence of clinically significant respiratory and/or cardiovascular conditions or laboratory abnormalities.
- No conditions which are contraindicated to use of anticholinergic drugs such as known symptomatic prostatic hypertrophy, bladder neck obstruction or narrow-angle glaucoma.

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

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 2013.

Duration of treatment:
The planned treatment duration for this study was 6 weeks.

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Tiotropium bromide
Administration route: Oral inhalation by HandiHaler® single-dose dry powder inhaler
Dosage form: Dry powder in a hard gelatin capsule
Dose and regimen: 1 capsule (tiotropium bromide 18 µg) in the morning (09:00 ± 1h).
Batch number: 060559 Expiry date: August 2012.

Name: Placebo to aclidinium bromide
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: December 2013.

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Reference therapy, dose and mode of administration, batch number, expiry date (continued):
Name: Placebo to tiotropium bromide
Administration route: Oral inhalation by HandiHaler® single-dose dry powder inhaler
Dosage form: Dry powder in a hard gelatin capsule
Dose and regimen: 1 capsule of placebo in the morning (09:00 ± 1h).
Batch number: 111F0255 Expiry date: August 2012.

Criteria for evaluation:

Efficacy:

Primary Efficacy Variable:

- Change from baseline in normalised FEV_1 area under the curve over the 24-h period immediately after morning investigational medicinal product (IMP) administration (AUC_{0-24}) after 6 weeks of treatment.

Secondary Efficacy Variable:

- Change from baseline in normalised FEV_1 area under the curve over the 12-h night-time period (AUC_{12-24}) after 6 weeks of treatment.

Additional Efficacy Variables:

- Pulmonary function (FEV_1 and FVC) at Day 1 and after 6 weeks of treatment.
- The use of relief medication and any change in the percentage of relief medication-free days.
- Daily COPD symptoms and any change in the percentage of days without daily COPD symptoms.
- Percentage of patients who preferred one of the 2 devices and percentage of patients who were willing to continue on each device.

Safety:
Safety assessments included eliciting of adverse events (AEs) and serious AEs (SAE), blood pressure (BP) and heart rate (HR) measurements and physical examinations. Pregnancy tests were performed in females of childbearing potential (results not presented in this report).

Statistical methods:
The analysis of the primary and secondary efficacy variables were performed using the ITT population (i.e., patients who took at least 1 dose of IMP and had at least a baseline FEV_1 assessment and at least one post-baseline FEV_1 value were included in the analysis). In addition, the primary and secondary efficacy variables were also analysed using the PP population to assess the robustness of the findings from the ITT population.

Efficacy variables, except for time to peak FEV_1 and percentage of patients preferring each device and willing to continue to use them, were analysed by means of an analysis of covariance (ANCOVA) with treatment and sex as factors and corresponding baseline and age as covariates. All between-group comparisons were tested using the appropriate contrast in the ANCOVA model. Between-groups least squares (LS) means (adjusted means) and 95% confidence intervals (CI) were given for all pairwise comparisons.

Time to peak FEV_1 was analysed descriptively. The percentage of patients preferring each device was described and the percentage of patients preferring Genuair® was compared to 50% using an exact binomial test. The mean difference in scores corresponding to "willingness to continue" for the two devices was tested to be different from zero using a t-test.

A sensitivity analysis for the primary and secondary efficacy variables was also carried out by using a mixed model for repeated measures.

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Statistical methods (continued):
All statistical comparisons were 2-sided hypothesis tests and the significance level was set at 0.05. All CI were 2-sided at the 95% confidence level. The primary and the 2 secondary comparisons were tested in a stepwise manner to control for multiplicity.

The primary comparison for AUC_{0-24} was between aclidinium bromide 400 µg BID and placebo. Other treatment comparisons (tiotropium bromide 18 µg QD vs. placebo and aclidinium bromide 400 µg BID vs. tiotropium bromide 18 µg QD) were considered additional. For AUC_{12-24}, a hierarchical testing approach was carried out with the comparison between aclidinium bromide 400 µg BID and placebo in the first step and the comparison between aclidinium bromide 400 µg BID and tiotropium bromide 18 µg QD in the second step. The other treatment comparison (tiotropium bromide 18 µg QD vs. placebo) for AUC_{12-24} was considered additional. No control for multiplicity was implemented.

All demographic and baseline characteristics, safety outcomes and other variables were analysed using summary statistics for the Safety population.

SUMMARY – CONCLUSIONS

Disposition:

A total of 485 patients were screened, of whom 414 patients were assessed as eligible and were randomised into the study. Overall, 400 (96.6%) of the randomised patients completed the study. A total of 14 (3.4%) patients were discontinued from the study, mainly due to AEs (10 [2.4%] patients overall: 4 in the placebo group and 3 in each active treatment group).

Demographic and Baseline Characteristics:

Overall, the treatment groups were similar with respect to demographic and baseline characteristics, with the exception of a higher percentage of male patients compared to female patients in the aclidinium bromide (66.7%) and tiotropium bromide (73.4%) groups than in the placebo group (56.5%). The mean baseline FEV_1 value at Visit 1 was slightly numerically higher in the tiotropium bromide group (1.543 L) compared to the aclidinium bromide (1.462 L) and placebo (1.422 L) groups, however the mean baseline percentages of predicted FEV_1, which account for differences related to gender, were similar across the treatment groups (50.3% to 51.8%).

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Efficacy Results:

The results of the statistical analyses of the changes from baseline in FEV_1 parameters are summarised in the following table:

Variable	Comparison	Differences in Adjusted Mean Changes from Baseline			
		Day 1		Week 6	
		AB 400 µg BID (N=171)	TB 18 µg QD (N=158)	AB 400 µg BID (N=171)	TB 18 µg QD (N=158)
FEV_1 (L)					
Normalised AUC_{0-24}	versus Placebo	0.156*	0.117*	0.150*	0.140*
	versus TB	0.040**		0.010	
Normalised AUC_{12-24}	versus Placebo	0.168*	0.100*	0.160*	0.123*
	versus TB	0.067**		0.037	
Normalised AUC_{0-12}	versus Placebo	0.149*	0.136*	0.138*	0.156*
	versus TB	0.013		-0.018	
Morning Pre-dose (trough)	versus Placebo	0.141*	0.093*	0.141*	0.102*
	versus TB	0.048**		0.038	
Evening Pre-dose (trough)	versus Placebo	0.147*	0.126*	0.125*	0.165*
	versus TB	0.020		-0.040	
Morning Peak	versus Placebo	0.154*	0.139*	0.180*	0.172*
	versus TB	0.014		0.008	
Evening Peak	versus Placebo	0.193*	0.112*	0.180*	0.155*
	versus TB	0.082**		0.025	

Study M/34273/39
AB=aclidinium bromide; AUC_{0-12}=area under the curve over the 12-h period immediately after morning IMP administration; AUC_{0-24}=area under the curve over the 24-h period immediately after morning IMP administration; AUC_{12-24}=area under the curve over the 12-h night-time period; BID=twice daily; FEV_1=forced expiratory volume in 1 second; ITT=Intention-to-Treat; N=ITT population size; QD=once daily; TB=tiotropium bromide.
* Statistically significant versus placebo. ** Statistically significant versus TB. Statistical significance was declared if the p-value for the comparison was <0.05. For placebo, N=85.
Adjusted mean differences and p-values obtained from an analysis of covariance model with change from baseline in FEV_1 variable as response, with treatment group and sex as factors and corresponding baseline and age as covariates.

Primary efficacy variable: Change from baseline in normalised FEV_1 AUC_{0-24} at Week 6

After 6 weeks of treatment, aclidinium bromide 400 µg BID showed a statistically significantly greater increase in the adjusted mean change from baseline in normalised FEV_1 AUC_{0-24} compared to placebo (0.150 L; $p<0.0001$) and a numerically greater increase in adjusted mean change from baseline in normalised FEV_1 AUC_{0-24} compared to tiotropium bromide (0.010 L; $p>0.05$).

Secondary efficacy variable: Change from baseline in normalised FEV_1 AUC_{12-24} at Week 6

After 6 weeks of treatment, aclidinium bromide 400 µg BID showed a statistically significantly greater increase in adjusted mean change from baseline in normalised FEV_1 AUC_{12-24} compared to placebo (0.160 L; $p<0.0001$) and a numerically greater increase in adjusted mean change from baseline in normalised FEV_1 AUC_{12-24} compared to tiotropium bromide (0.037 L; $p>0.05$).

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Efficacy Results (continued):

Additional efficacy variables: Endpoints based on FEV_1 and FVC

At Day 1 and after 6 weeks of treatment, aclidinium bromide showed statistically significantly greater increases compared to placebo in the adjusted mean changes from baseline in all additional FEV_1 variables (AUC_{0-12} at Week 6, AUCs at Day 1, morning and evening peak and pre-dose [trough] FEV_1 at both time points) and all FVC variables (AUCs, peak FVCs and pre-dose FVCs at both time points). Aclidinium bromide also showed numerically greater increases from baseline in most of the FEV_1 and FVC variables compared to tiotropium bromide, with statistically significant improvements in favour of aclidinium bromide in AUC_{0-12}, AUC_{12-24}, morning pre-dose values and evening peak values at Day 1 for both FEV_1 and FVC.

At all time points during the 24-hour observation period, aclidinium bromide showed statistically significantly greater increases in the adjusted mean change from baseline in FEV_1 values compared to placebo both at Day 1 and Week 6 (0.070 L to 0.202 L; p<0.0001 to p=0.0046). At Day 1, aclidinium bromide generally showed numerically greater increases from baseline in FEV_1 compared to tiotropium bromide throughout the 24-hour observation period, with statistical significance at 13 to 23 hours post-dose (0.042 L to 0.092 L; p<0.0001 to p=0.0238). At Week 6, aclidinium bromide showed numerically greater increases from baseline in FEV_1 compared to tiotropium bromide at 0 to 2 hours and 13 to 24 hours post-dose (0.007 L to 0.047 L; p>0.05), while increases between 3 and 12 hours post-dose were numerically lower than tiotropium bromide (-0.005 L to -0.046 L; p>0.05).

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

Over 6 weeks of treatment, both aclidinium bromide and tiotropium bromide showed a statistically significantly greater increase from baseline in the percentage of relief medication-free days (24 hours without relief medication use) compared to placebo (9.6%; p=0.0229 and 8.9%; p=0.0366, respectively) and a numerically greater reduction from baseline in the use of daily relief medication compared to placebo (-0.4 puffs; p>0.05 for both active treatments).

Additional efficacy variables: Incidence and severity of COPD symptoms

Aclidinium bromide provided a consistent and greater improvement in COPD symptoms compared to placebo in most of the symptomatic variables over 6 weeks of treatment, with statistically significantly greater improvements from baseline in daily E-RS scores (total score, Breathlessness, Cough & Sputum and Chest domains: -0.4 to -2.0; p<0.0001 to p=0.0026), the severity of morning symptoms (overall and by symptom: -0.14 to -0.22; p=0.0001 to 0.0356), the limitation of activity due to COPD symptoms (-0.18; p=0.0016) and the severity of night-time symptoms (-0.14; p=0.0099). Moreover, aclidinium bromide also showed a statistically significant increase in the percentage of days without morning symptoms compared to placebo (any symptoms, cough, wheeze and shortness of breath: 7.2% to 8.9%; p=0.0004 to 0.0213). The improvements in COPD symptoms observed in the tiotropium bromide group were numerically inferior to those observed for aclidinium bromide and were only statistically significantly greater than placebo for E-RS total, Breathlessness and Chest scores (-0.3 to -1.2; p=0.0094 to 0.0432), severity of any morning symptoms (-0.12; p=0.0320) and percentage of days without morning symptoms (5.6%; p-0.0291).

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Efficacy Results (continued):

Additional efficacy variables: Device preference and willingness to continue

Over 6 weeks of treatment, the majority of patients (80.1%) preferred the Genuair® inhaler to the HandiHaler® device. The overall mean "willingness to continue" score (based on a scale from 0 to 100) was higher for the Genuair® inhaler (88.8) than the Handi Haler® device (45.4), with statistical significance ($p<0.0001$) in favour of the Genuair® device.

Safety and Tolerability Results:

Overall, 28.0% of the patients reported at least one treatment-emergent AE (TEAE), with the lowest incidence in the placebo group (25.9%) and the highest in the tiotropium bromide group (29.7%). The majority of TEAEs were mild or moderate in intensity. The percentage of patients who experienced severe TEAEs was low (<2.5%) and similar between all treatment groups, including placebo. None of the severe TEAEs reported during this study were considered related to the IMPs.

The most common TEAEs by PT were headache (5.1% of patients overall), nasopharyngitis (5.1%), COPD (exacerbation) (2.4%) and cough (2.2%). Headache was reported more frequently in the aclidinium bromide group than the placebo group, while nasopharyngitis was similarly reported across the active treatment groups and at a higher incidence than in the placebo group.

Of the patients with TEAEs, the majority (25.8%) had TEAEs which were considered not related to the IMP; 2.7% of patients had at least one IMP-related TEAE. The most common IMP-related TEAE was dry mouth, being reported in 3 patients (0.7%) overall (1 [0.6%] and 2 [1.3%] for the aclidinium bromide and tiotropium bromide groups, respectively). All other IMP-related TEAEs were reported in individual patients across all treatment groups.

No deaths occurred during this study and the percentage of patients experiencing treatment-emergent serious TEAEs was low (≤2.5% of patients) and was similar between the active treatments (aclidinium bromide and tiotropium bromide; no SAEs were reported for the placebo group). Overall, there were no trends in the type of SAEs reported during the study and none of the SAEs were considered related to the IMP.

The percentage of patients experiencing TEAEs leading to discontinuation was low (≤3.5% of patients) and was similar between all treatments, including placebo. Overall, the most common TEAE leading to discontinuation was exacerbation of COPD (6 patients [1.4%]), as per protocol requirement. None of the TEAEs leading to discontinuation were considered related to the IMP.

The incidence of cardiac, cerebrovascular and potential anticholinergic events was low (≤2 patients in any treatment group).

No clinically significant changes from baseline in BP and HR were observed after 6 weeks of treatment.

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CONCLUSIONS:

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DATE OF REPORT:
31 August 2012