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 52-WEEK RANDOMISED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO CONTROLLED, MULTICENTRE CLINICAL TRIAL, TO ASSESS THE EFFICACY AND SAFETY OF 200 µg OF THE ANTICHOLINERGIC ACLIDINIUM BROMIDE (LAS 34273) COMPARED TO PLACEBO, BOTH ADMINISTERED ONCE-DAILY BY INHALATION, IN THE MAINTENANCE TREATMENT OF PATIENTS WITH MODERATE TO SEVERE, STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE		
Investigators:		
Study centre (s):		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 10 August 2006 Date clinical phase ended (last patient last visit): 6 May 2008	**Phase of development:** III	
Objectives: The objectives of the study were: (1) to assess the long term bronchodilator efficacy of aclidinium bromide 200 µg administered once daily by inhalation (via inhaler) for 12 weeks for the US filing and 28 weeks for the EU filing compared to placebo in moderate to severe, stable chronic obstructive pulmonary disease (COPD); (2) to assess the benefit in terms of exacerbation control and disease-related health status and additional outcomes for up to 52 weeks compared to placebo in the same target population; (3) to evaluate the long term safety and tolerability of aclidinium bromide 200 µg administered once daily for 52 weeks by inhalation (via inhaler) compared to placebo in the same target population.		

Methodology:
This was a prospective, double-blind, randomised, parallel-group, placebo-controlled, multinational, multicentre study of 52 weeks' treatment with aclidinium bromide 200 µg once daily or placebo in male or female patients with moderate to severe stable COPD.

Following a screening visit, patients entered a 14-day run-in period during which they used inhaled salbutamol administered via a pressurised metered dose inhaler (pMDI) as rescue medication on an "as needed" basis. During this period, patients also had to stop taking any other COPD medications, if any, prohibited by the study protocol. The 14-day run-in period was used to assess the stability of each patient's disease and established the patient's baseline characteristics. At the end of the run-in period, patients were randomised to treatment with either aclidinium bromide 200 µg once daily in the morning or placebo in a 3:1 randomisation ratio for 52 weeks. At the end of the 52-week double blind treatment period, there was a 2-week follow-up period. Patients were seen on an out-patient basis. During the active treatment phase, patients attended clinic visits after 1, 4, 8, 12, 16, 20, 28, 36, 44 and 52 weeks of treatment.

Number of subjects (planned and analysed):
Planned: 820 randomised (615 patients to aclidinium bromide 200 µg and 205 patients to placebo)
Screened: 1313 patients
Randomised: 843 (627 patients to aclidinium bromide 200 µg and 216 patients to placebo)
Completed study: 707 (83.9%) (aclidinium bromide 200 µg: 538 [85.8%]; placebo: 169 [78.2%])
Evaluated for safety: 843 (100%) (aclidinium bromide 200 µg: 627 [100%]; placebo: 216 [100%])
Evaluated for efficacy (Intention-to-Treat [ITT] population): 826 (98.0%) (aclidinium bromide 200 µg: 616 [98.2%]; placebo: 210 [97.2%])
Evaluated for efficacy (Per protocol [PP] population): 795 (94.3%) (aclidinium bromide 200 µg: 593 [94.6%]; placebo: 202 [93.5%])

Diagnosis and main criteria for inclusion:
Males and non-pregnant, non-lactating females aged ≥40 years, who were current or former cigarette smokers (with a ≥10 pack-year history), with a clinical diagnosis of COPD, according to the GOLD guidelines, stable airway obstruction and who consented to participate were eligible for the study. The patient's forced expiratory volume in one second (FEV_1) at Visit 1 measured between 30-45 minutes post inhalation of 400 µg of salbutamol had to be <80% of the predicted normal value, the pre-dose FEV_1 at Visit 2 had to be within the range of 80 to 120% of the FEV_1 measured at Visit 1 prior to salbutamol inhalation and the post-salbutamol FEV_1/forced vital capacity (FVC) at Visit 1 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.

Test product, dose and mode of administration, batch number, expiry date:
Name: Aclidinium bromide
Administration route: Oral inhalation by multidose dry powder inhaler.
Dosage form: Dry powder for inhalation.
Dose and regimen: 200 µg (1 inhalation) once daily in the morning
Batch number: 6B001, 6D002, 6F003
Expiry date: October 2008 for batches 6B001 and 6D002 and May 2009 for batch number 6F003.

Duration of treatment:
52-week treatment period. The total duration of the study for each patient was approximately 56 weeks including the screening and follow-up visits.

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Placebo to aclidinium bromide
Administration route: Oral inhalation by multidose dry powder inhaler.
Dosage form: Dry powder for inhalation.
Dose and regimen: 1 inhalation once daily in the morning
Batch number: 6A001 Expiry date: October 2008 extended to May 2009

Criteria for evaluation:
Efficacy:
Efficacy was assessed by pulmonary function tests (FEV_1, FVC and inspiratory capacity [IC]), evaluation of COPD exacerbations, measurement of disease-specific health status using the St George's Respiratory Questionnaire (SGRQ), evaluation of dyspnoea using the Baseline and Transition Dyspnea Indexes (BDI/TDI), measurement of health outcome using the EuroQol EQ-5D questionnaire, daily measurement by the patient of morning and evening peak expiratory flow (PEF), daily assessment by the patient of COPD symptoms (breathlessness, wheezing, cough and sputum production) and rescue medication usage, and a global assessment of efficacy made by

the patient.

Safety:
Safety assessments included eliciting of adverse events (AEs) and serious AEs (SAE), the monitoring of haematology, blood biochemistry and urine values, physical examinations including blood pressure measurement and recording of 12-lead electrocardiograms (ECGs). For some selected sites, 3-lead 24-hour Holter monitoring was done, in addition. Pregnancy tests were performed in females of child-bearing potential.

Statistical methods:
Analysis of the primary efficacy variable, the trough FEV_1 at 12 weeks of treatment for the US filing and 28 weeks of treatment for the EU filing was analysed using an Analysis of Covariance (ANCOVA) model. A last observation carried forward (LOCF) approach was used for the imputation of missing data. Sex and treatment group were factors in the model along with baseline trough FEV_1 and age as covariates. The treatment comparison between aclidinium bromide 200 µg and placebo was carried out by means of the contrasts on the treatment factor. The treatment effect was estimated by Least Square (LS) means and their standard error (SE) along with 95% confidence intervals (CI). The differences between treatments were estimated by differences between LS means and their SE and 95% CI. To confirm the robustness of the analysis, the analysis was repeated using the PP population and a sensitivity analysis was performed using a mixed model for repeated measures for which no data were imputed.

There were two secondary efficacy variables defined in the study: the time to first moderate or severe COPD exacerbation after the first intake of IMP and the number (%) of patients who achieved at least a 4-unit reduction from baseline in SGRQ total score at 52 weeks of treatment. For the time to first moderate or severe COPD exacerbation, the 95% CI of the hazard ratio between treatment groups (aclidinium bromide 200 µg / placebo) and p-value were estimated using a Cox Proportional Hazards model. Kaplan-Meier probability curves for each treatment were also provided. The number of patients who achieved at least a 4-unit reduction from baseline in SGRQ total score at 52 weeks of treatment were dichotomised into success (reduction from baseline in SGRQ total score ≥4 units) and failure (reduction from baseline in SGRQ total score <4 units). LOCF was used to impute missing SGRQ total scores. Analysis was performed using a Logistic Regression model including treatment and sex as factors and age and baseline SGRQ total score as covariates in the model. Statistical significance was tested using the Wald test. The treatment comparison was performed by estimating the odds ratio (OR) corresponding to the treatment effect and its 95% CI.

The remaining variables were analysed using statistical methods appropriate to the type of variable.

SUMMARY – CONCLUSIONS

Efficacy Results:
Primary Efficacy Variable
The primary efficacy variable in this study was the trough FEV_1 at the end of 12 weeks of treatment for the US filing and at the end of 28 weeks of treatment for the EU filing. The mean trough FEV_1 value at baseline in the aclidinium bromide 200 µg group was 1.410 L (SD=0.513; 95% CI=1.370 to 1.451 L) and in the placebo group was 1.388 L (SD=0.511; 95% CI=1.318 to 1.457 L). After both 12 and 28 weeks of treatment, adjusted mean trough FEV_1 values were higher for aclidinium bromide 200 µg than for placebo. The adjusted mean differences between treatments (0.061 L and 0.067 L, respectively) were statistically significant at both time points (p=0.0005 and p=0.0002, respectively). After 12 weeks the adjusted mean trough FEV_1 was 1.428 L for aclidinium bromide 200 µg and 1.366 L for placebo. After 28 weeks, the adjusted mean trough FEV_1 was 1.422 L for aclidinium bromide 200 µg and 1.356 L for placebo. A sensitivity analysis to investigate how handling of missing data affected the results was performed using a mixed model for repeated measures without LOCF. Results of this analysis and of an ANCOVA analysis for the PP population were similar to those of the primary analysis for the ITT population, confirming the robustness of the analyses.

Secondary Efficacy Variables
The secondary efficacy variables in this study were the time to first moderate or severe COPD exacerbation and the percentage of patients who achieved at least a 4-unit decrease from baseline in the SGRQ total score at 52 weeks.
For the ITT population, 164 patients (26.6%) in the aclidinium bromide 200 µg group and 54 patients (25.7%) in the placebo group experienced a moderate or severe exacerbation. The median time to first

moderate or severe COPD exacerbation could not be estimated for either group since fewer than 50% of the population had experienced a moderate or severe exacerbation. Analysis using a Cox's Proportional Hazard model showed that there was no statistically significant difference between treatments in the time to first moderate or severe exacerbation (HR=1.0; 95% CI=0.72 to 1.33; p=0.8870).
There were 284 patients (48.1%) in the aclidinium bromide 200 µg group and 79 patients (39.5%) in the placebo group who achieved at least 4-unit decrease in SGRQ total score after 52 weeks. Patients treated with aclidinium bromide 200 µg were approximately 1.5 times more likely to achieve at least a 4-unit decrease than patients treated with placebo and this difference was statistically significant (odds ratio 1.468; 95% CI=1.050 to 2.053; p=0.025).
Results of the analyses for the PP population were similar to those of the ITT population.

Other Efficacy Variables

Pulmonary Function Tests

Adjusted mean treatment differences in trough FEV_1 between active and placebo treatment were maintained at approximately 0.060 L at all visits up to Week 52 with the exception of Weeks 1 and 4 when differences of 0.044 L and 0.037 L were observed. Peak FEV_1 values were also significantly higher for aclidinium bromide 200 µg than for placebo throughout the study with adjusted treatment differences in the range of 0.147 L to 0.177 L throughout the study period. The median time to peak FEV_1 with aclidinium bromide 200 µg was 2 hours. FEV_1 values in the 3 hours after dosing were also significantly higher for aclidinium bromide 200 µg than for placebo from 30 minutes post-dose (the first time point assessed). At all visits from Day 1 to Week 52 of treatment, adjusted mean changes from baseline in normalised $AUC_{(0\text{-}3\ hours)}$ for FEV_1 were higher for aclidinium bromide 200 µg than for placebo with adjusted mean treatment differences of at least 0.168 L at all visits. The median time to onset of bronchodilation (defined as a 15% increase from baseline in FEV_1 on the first day of treatment) was 2 hours for aclidinium bromide 200 µg.
Results for FVC and IC were supportive of those obtained for FEV_1. Statistically significant differences between aclidinium bromide 200 µg and placebo were observed at all visits for trough and peak FVC and IC and for normalised $AUC_{(0\text{-}3\ hours)}$. Morning and evening PEF were also significantly higher following treatment with aclidinium bromide 200 µg than placebo.

Exacerbations

No significant difference was seen between treatments in exacerbation rate and the risk for a patient to experience at least one COPD exacerbation of any severity was similar in the two treatment groups; however, exacerbation rates during the study were low. The rate for exacerbations of any severity was 0.54 exacerbations per patient year (95% CI=0.46 to 0.63) in the aclidinium bromide 200 µg group and 0.56 exacerbations per patient year (95% CI=0.44 to 0.72) in the placebo group.

Health Status

Greater improvements in health status as measured by the SGRQ total score were observed for aclidinium bromide 200 µg than for placebo. Adjusted mean differences between treatments in SGRQ total score ranged from 1.53 to 2.71. Differences between treatments were statistically significant at Weeks 12 and 28 (p=0.0092 and p=0.0117, respectively), approached significance at Week 44 (p=0.0527) but were not significant at Week 52. As seen for the secondary endpoint at Week 52, patients treated with aclidinium bromide 200 µg were significantly more likely to achieve a decrease in SGRQ total score of at least 4 units than patients treated with placebo after 12, 28 and 44 weeks of treatment. The number needed to treat (NNT) to achieve a 4-unit reduction was approximately 12 at Week 52.
Small improvements in health status as measured by both the EuroQol weighted healthy state index and the VAS were seen during the study. Statistically significant differences between treatments in favour of aclidinium bromide 200 µg were seen at some time points.

Evaluation of Dyspnoea

Clinically and statistically significant improvements in dyspnoea, as measured by the TDI, were observed for aclidinium bromide 200 µg compared with placebo. All mean improvements in the aclidinium bromide group were clinically important (improvement in focal score ≥1 unit), whereas changes seen in the placebo group did not reach clinical relevance. Adjusted mean differences between treatments were statistically significant at all time points over 52 weeks in favour of aclidinium bromide 200 µg. After 52 weeks of treatment, 56.4% of patients in the aclidinium bromide 200 µg group and 38.0% in the placebo group had achieved a clinically meaningful improvement in TDI and the likelihood of achieving such an improvement was more than twice as high with aclidinium bromide 200 µg than with placebo. The NNT to achieve a clinically meaningful improvement in TDI was approximately 5 at Week 52.

Rescue Medication Use and COPD Symptoms
No differences between treatments were seen for use of rescue medication or patient-recorded daily symptom scores for breathlessness, cough, sputum production or wheezing.
Global Assessment of Efficacy
At each visit where a global assessment of efficacy was made (Weeks 12, 28, 44 and 52), treatment with aclidinium bromide 200 µg was rated as statistically significantly more effective than treatment with placebo.
Safety Results:
COPD exacerbations were included in the efficacy evaluation and were not reported as AEs unless they were life-threatening or fatal.
The proportion of patients treated with aclidinium bromide 200 µg reporting TEAEs was similar to the proportion of patients treated with placebo who reported TEAEs: 355 patients (56.6%) treated with aclidinium bromide 200 µg and 128 patients (59.3%) treated with placebo reported TEAEs. A total of 1784 TEAEs were reported, 1357 in patients treated with aclidinium bromide 200 µg and 427 in patients treated with placebo. When adjusted for differences in patient exposure, the incidence rate of TEAEs (expressed as number of patients with an event/1000 patient years) was numerically lower for aclidinium bromide 200 µg (615.08) than for placebo (678.38). In addition, COPD exacerbations (included as part of the efficacy evaluation and not reported as AEs unless life-threatening or fatal), were reported in 188 patients (30.5%) in the aclidinium bromide 200 µg group and 64 patients (30.5%) in the placebo group in the ITT population; these were reported more commonly than any specific TEAE.
The types of TEAEs reported were generally similar for aclidinium bromide 200 µg and placebo. The most commonly reported events (those reported by more than 5% of patients in either treatment group) in both treatment groups were nasopharyngitis (reported by 102 patients [16.3%] in the aclidinium bromide 200 µg group and 31 patients [14.4%] in the placebo group) and headache (71 patients [11.3%] in the aclidinium bromide 200 µg group and 27 patients [12.5%] in the placebo group). No other TEAEs were reported by more than 5% of patients in either treatment group. The incidence rates per 1000 patient years were 176.73 and 164.30, respectively for nasopharyngitis and 123.02 and 143.10, respectively for headache. No patients discontinued the study prematurely because of these TEAEs. In both treatment groups, the majority of these TEAEs were considered by the Investigator to be not related to study treatment and there was no apparent difference between treatments in the severity of these events.
Treatment-emergent AEs that were reported by at least 2% and <5 % of patients in either treatment group and which were reported by a higher proportion of patients (>1% more) in the aclidinium bromide 200 µg group than the placebo group were diarrhoea (17 patients, 2.7% versus 1 patient, 0.5%), arthralgia (17 patients, 2.7% versus 1 patient, 0.5%), influenza (21 patients, 3.3% versus 4 patients, 1.9%), pharyngolaryngeal pain (21 patients, 3.3% versus 3 patients, 1.4%) and gamma glutamyl transferase increased (13 patients, 2.1% versus 2 patients, 0.9%). No patients discontinued study treatment prematurely due to any of these TEAEs.
The majority of TEAEs were of mild or moderate intensity and there was no evidence of an increase in the severity of TEAEs for aclidinium bromide 200 µg compared with placebo: TEAEs of severe intensity were experienced by 73 patients (11.6%) treated with aclidinium bromide 200 µg and 28 patients (13.0%) treated with placebo. Headache was the only TEAE reported to be of severe intensity in more than 1% of patients in the aclidinium bromide 200 µg group: headache was reported as severe by 1.9% of patients in both treatment groups. Pneumonia and respiratory failure were each of severe intensity in 1.4% of patients in the placebo group compared with 0.8% and 0.0%, respectively in the aclidinium bromide 200 µg group.
TEAEs considered by the Investigator to be treatment-related were reported in 42 patients (6.7%) in the aclidinium bromide 200 µg group and 15 patients (6.9%) in the placebo group. Dry mouth was the only TEAE reported to be treatment-related in at least 1% of patients in the aclidinium bromide group (reported in 6 patients [1.0%] in the aclidinium bromide 200 µg group and 2 patients [0.9%] in the placebo group).
Eleven patients died after randomisation to the study, seven (1.1%) in the aclidinium bromide group and four (1.9%) in the placebo group. The proportion of patients with fatal SAEs was similar for aclidinium bromide 200 µg and placebo. No fatal events were considered by the Investigator to be related to study treatment. Sudden cardiac death was the only fatal SAE experienced by more than one patient in the study: two patients, both in the aclidinium bromide 200 µg group, experienced this event.
Serious adverse events (fatal and non-fatal, including fatal and life-threatening COPD exacerbations) were experienced by a smaller proportion of patients treated with aclidinium bromide 200 µg (8.0%) than treated with placebo (10.2%). Fatal or life-threatening COPD exacerbations were experienced by 2 patients (0.3%) in the aclidinium bromide 200 µg group and 2 patients (0.9%) in the placebo group.

Severe COPD exacerbations (exacerbations requiring hospitalisation), which were part of the efficacy evaluation and which were not considered as SAEs unless they were fatal or life-threatening, were reported in 40 patients (6.5%) in the aclidinium bromide 200 µg group and 14 patients (6.7%) in the placebo group in the ITT population.

A total of 105 SAEs (excluding non-fatal and non-life-threatening COPD exacerbations reported as part of the efficacy evaluations) were experienced, 70 SAEs in the aclidinium bromide 200 µg group and 35 in the placebo group. Pneumonia was the only SAE experienced by at least 1% of patients in the aclidinium bromide 200 µg group and was reported in similar proportions of patients in each group (1.3% of patients in the aclidinium bromide 200 µg group and 1.4% of patients in the placebo group). No SAEs of pneumonia were considered by the Investigator to be related to study treatment. The remaining SAEs were reported in no more than two patients in the aclidinium bromide 200 µg group and the types of SAEs were generally similar for aclidinium bromide and placebo treatments. Only two patients, both treated with aclidinium bromide 200 µg, experienced SAEs that were considered by the Investigator to be treatment-related. These SAEs were angle closure glaucoma and open angle glaucoma. Both patients discontinued treatment and the glaucoma recovered.

The proportion of patients who experienced a TEAE that led to discontinuation was lower in the aclidinium bromide 200 µg group (3.2%) than in the placebo group (5.6%). Pneumonia (reported in 2 patients [0.3%] in the aclidinium bromide 200 µg group and 3 patients [1.4%] in the placebo group), sudden cardiac death (reported in 2 patients [0.3%] treated with aclidinium bromide 200 µg) and COPD (reported in one patient [0.2%] in the aclidinium bromide 200 µg group and two patients [0.9%] in the placebo group) were the only TEAEs that led to discontinuation of more than one patient in either treatment group. Three-quarters of TEAEs that led to discontinuation were SAEs. No pattern was discernible in the types of TEAEs that led to discontinuation.

Few patients in either treatment group reported possible anticholinergic side effects during the study. The only possible anticholinergic TEAEs that were reported by at least 1% of patients in the aclidinium bromide 200 µg group were palpitations (1% in the aclidinium bromide group and 1.4% in the placebo group) and dry mouth (1% in the aclidinium bromide group and 0.9% in the placebo group). Constipation (0.6%) and tachycardia (0.5%) were each reported by more than one patient in the aclidinium bromide 200 µg group and no patients in the placebo group. Other possible anticholinergic TEAEs were either reported at a similar incidence in the two treatment groups or were reported in only one patient.

There was no evidence observed for an increase in cardiovascular TEAEs following treatment with aclidinium bromide 200 µg compared with placebo. The proportion of patients reporting TEAEs that were Cardiac Disorders or Vascular disorders was lower in the aclidinium bromide 200 µg group than in the placebo group. The incidence of cerebrovascular accident/ischaemic stroke was very low and similar in the two groups (1 patient in each treatment group).

Clinical laboratory tests, vital signs and 12-lead ECGs (including assessments of QTc intervals) were similar to placebo and did not reveal any safety signals. Results of Holter monitoring performed in a subgroup of patients were also similar in the two treatment groups.

CONCLUSIONS:

DATE OF REPORT:
12 October 2009