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 S tudy: 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 P ATIENTS WITH MODERATE TO SEVERE, STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Investigators:

[redacted]

Study centre (s):

[redacted]

Publication (reference):
None

Studied period (years): Date study initiated (first screening): 10 August 2006 Date clinical phase ended (last patient last visit): 9 June 2008	**Phase of development:** III

Objectives:
The objectives of the study were:
(1) to as sess the lo ng term bronchodilator efficacy of aclidinium bromide 200 µg a dministered once daily by inhalation (via Almirall 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 as sess the benefit in terms of exacerbation control and disease-related health status and other additional outcomes for up to 52 weeks compared to placebo in the same target population;
(3) to eva luate the long term safety and tolerability of aclidinium bromide 200 µ g administered once daily for 52 weeks by inhalation (via Almirall 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: 1456 patients
Randomised: 804 (600 patients to aclidinium bromide 200 µg and 204 patients to placebo)
Completed study: 564 (70.1%) (aclidinium bromide 200 µg: 446 [74.3%]; placebo: 118 [57.8%])
Evaluated for safety: 804 (100%) (aclidinium bromide 200 µg: 600 [100%]; placebo: 204 [100%])
Evaluated for efficacy (Intention-to-Treat [ITT] population): 795 (98.9%) (aclidinium bromide 200 µg: 594 [99.0%]; placebo: 201 [98.5%])
Evaluated for efficacy (Per protocol [PP] population): 738 (91.8%) (aclidinium bromide 200 µg: 553 [92.2%]; placebo: 185 [90.7%])

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) ratio 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 Almirall multidose dry powder inhaler (Almirall 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 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 Almirall multidose dry powder inhaler (Almirall 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 in the ITT population using a mixed model for repeated measures for which no data were imputed.

There were two secondary efficacy variables defined in the study: 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 decrease from baseline in SGRQ total score at 52 weeks of treatment. For the time to first moderate or severe COPD exacerbation, the hazard ratio between treatment groups (aclidinium bromide 200 µg / placebo), its 95% CI, and p-value were provided 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 decrease from baseline in SGRQ total score at 52 weeks of treatment were dichotomised into success (decrease from baseline in SGRQ total score ≥4 units) and failure (decrease 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 was slightly higher in the aclidinium bromide 200 µg group (1.213 L; SD=0.486; 95% CI=1.174 to 1.252 L) than in the placebo group (1.156 L; SD=0.479; 95% CI=1.090 to 1.223 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 and the adjusted mean differences between treatment groups (0.063 L and 0.059 L, respectively) were statistically significant at both time points ($p<0.0001$ and $p=0.0002$, respectively). After 12 weeks the adjusted mean trough FEV_1 was 1.233 L for aclidinium bromide 200 µg and 1.171 L for placebo. After 28 weeks, the adjusted mean trough FEV_1 was 1.220 L for aclidinium bromide 200 µg and 1.162 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, 197 patients (33.2%) in the aclidinium bromide 200 µg group and 80 patients (39.8%) 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 a statistically significant difference between treatments in the time to first moderate or severe exacerbation in favour of aclidinium bromide 200 µg with a 30% reduction in the risk of experiencing a moderate or severe exacerbation at any time in the study compared with placebo (HR=0.7; 95% CI=0.55 to 0.92; p=0.0100).
There were 224 patients (39.0%) in the aclidinium bromide 200 µg group and 64 patients (32.8%) 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 1.38 times more likely than patients treated with placebo to get a decrease of at least 4 units in SGRQ total score but this difference failed to reach statistical significance (odds ratio 1.375; 95% CI=0.970 to 1.949; p=0.0737).
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 between 0.051 L and 0.078 L from Day 2 up to 1 year. Peak FEV_1 values were also significantly higher for aclidinium bromide 200 µg than for placebo throughout the study with adjusted treatment differences of over 0.150 L at most visits. 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 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 0.133 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 1 hour 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 $AUC_{(0\text{-}3\ hours)}$. For FVC, mean differences in trough values ranged from 0.083 to 0.148 L and mean differences in peak values were at least 0.259 L at all visits. For IC, mean differences in trough values ranged from 0.064 to 0.135 L and mean differences in peak values were at least 0.171 L at all visits. Morning and evening PEF were also significantly higher following treatment with aclidinium bromide 200 µg than placebo.

Exacerbations

Exacerbation rates during the study for exacerbations of any severity were statistically significantly lower (p=0.0114) for aclidinium bromide 200 µg (0.63 exacerbations per patient year) than for placebo (0.86 exacerbations per patient year). A statistically significant difference between treatments was also seen in the analysis of the rate of severe exacerbations (p<0.0001) as well as the rate of moderate and severe exacerbations (p=0.0046). Analysis of the rate of moderate exacerbations just failed to achieve statistical significance (p=0.0567). No significant difference was seen between treatments in the likelihood of a patient experiencing at least one COPD exacerbation of any severity. However, patients treated with aclidinium bromide 200 µg were approximately 50% less likely than patients treated with placebo to experience at least one severe COPD exacerbation (OR 0.502; CI=0.289 to 0.871; p=0.0143). As for the secondary efficacy variable of time to first moderate or severe exacerbation, there was a statistically significant difference between treatments in the time to first exacerbation of any severity (p=0.0129). The proportion of patients withdrawn due to a COPD exacerbation was small (3.7% in the aclidinium bromide 200 µg group and 5.0% in the placebo group) and there was no difference in the time to withdrawal due to a COPD exacerbation.

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 -2.21 to -3.54. Differences between treatments were statistically significant at all assessment time points (p≤0.0211). Patients treated with aclidinium bromide 200 µg were significantly more likely than patients treated with placebo to achieve a decrease of at least 4 units in SGRQ total score after 12, 28 and 44 weeks of treatment (p≤0.0057).
Small improvements in health status as measured by both the EuroQol weighted healthy state index and the VAS were seen during the study, but no statistically significant differences between treatments were observed at most time points.

Evaluation of Dyspnoea

Statistically significant mean improvements in dyspnoea, as measured by the TDI, were observed for aclidinium bromide 200 µg compared with placebo at Weeks 12, 28 and 44 but not at Week 52. Mean

differences between the two treatments were clinically meaningful (difference >1 unit) at Week 28 and Week 44.

Rescue medication use and COPD symptoms

Some statistically significant differences between treatments in favour of aclidinium bromide 200 µg were seen for rescue medication use and patient-recorded daily symptom scores for breathlessness, cough, sputum production or wheezing but no clear pattern was apparent.

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: 479 patients (79.8%) treated with aclidinium bromide 200 µg and 154 patients (75.5%) treated with placebo reported TEAEs. A total of 2778 TEAEs were reported, 2107 in patients treated with aclidinium bromide 200 µg and 671 in patients treated with placebo. The incidence rate of TEAEs (expressed as number of patients with an event/1000 patient years of treatment) was numerically lower for aclidinium bromide 200 µg (957.64) than for placebo (1042.86). In addition, COPD exacerbations (included as part of the efficacy evaluation and not reported as AEs unless life-threatening or fatal) were reported in 216 patients (36.4%) in the aclidinium bromide 200 µg group and 85 patients (42.3%) in the placebo group in the ITT population; these were were reported more commonly than any specific TEAE. The COPD exacerbation rate was 0.63 exacerbations per patient year for aclidinium bromide 200 µg and 0.86 exacerbations per patient year for placebo.

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 the aclidinium bromide group) were headache (reported by 14.2% of patients in the aclidinium bromide 200 µg group and 12.7% of patients in the placebo group), nasopharyngitis (12.7% of patients in the aclidinium bromide 200 µg group and 11.3% in the placebo group), upper respiratory tract infection (10.8% of patients in the aclidinium bromide 200 µg group and 9.8% in the placebo group), diarrhoea (7.0% in the aclidinium bromide 200 µg group and 3.9% in the placebo group) and back pain (6.7% in the aclidinium bromide 200 µg group and 7.4% in the placebo group). No other TEAEs were reported by more than 5% of patients in the aclidinium bromide 200 µg group. Diarrhoea was seen at a higher incidence rate in the aclidinium bromide 200 µg group than in the placebo group; the incidence rates per 1000 patient years were 83.97 and 54.17, respectively. The other TEAEs reported by more than 5% of patients, when incidence rate was adjusted for patient exposure, were seen at a lower incidence for aclidinium bromide than for placebo. The majority of commonly reported TEAEs were considered by the Investigator to be not related to study treatment for both treatment groups and there was no apparent difference between treatments in the intensity of these events, with the exception of diarrhoea. No episodes of diarrhoea led to the premature discontinuation of the patient from study treatment. The only commonly reported TEAE that led to discontinuation was headache (discontinuation of 1 patient [0.2%] in the aclidinium bromide 200 µg group).

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 hypertension (27 patients, 4.5% versus 6 patients, 2.9%), arthralgia (24 patients, 4.0% versus 5 patients, 2.5%), pain in extremity (23 patients, 3.8% versus 4 patients, 2.0%), abdominal pain (20 patients, 3.3% versus no patients), musculoskeletal pain (19 patients, 3.2% versus 3 patients, 1.5%), myalgia (18 patients, 3.0% versus 3 patients, 1.5%), oedema peripheral (18 patients, 3.0% versus 2 patients, 1.0%), contusion (14 patients, 2.3% versus 1 patient, 0.5%), toothache (12 patients, 2.0% versus 2 patients, 1.0%) and pyrexia (12 patients, 2.0% versus 1 patient, 0.5%). Two patients (0.3%) in the aclidinium bromide 200 µg group discontinued the study prematurely due to myalgia and 1 patient (0.2%) in the aclidinium bromide 200 µg group discontinued the study because of pyrexia. No other patients discontinued study treatment prematurely due to these TEAEs.

The majority of TEAEs were of mild or moderate intensity and generally there was no evidence observed for an increase in the intensity of TEAEs for aclidinium bromide 200 µg compared with placebo: TEAEs of severe intensity were experienced by 105 patients (17.5%) treated with aclidinium bromide 200 µg and 42 patients (20.6%) 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: this TEAE was severe for 1.3% of patients in the aclidinium bromide 200 µg group and 2.0% in the placebo group. Back pain, cough and dyspnoea were each of severe intensity in 1.5% of patients in the placebo group compared with 1.0%, 0.3% and 0.8%, respectively in the aclidinium bromide 200 µg group. There was some evidence that the intensity of diarrhoea and arthralgia was greater in patients treated with aclidinium bromide 200 µg than in those treated with placebo. Diarrhoea and arthralgia were of severe intensity in few patients, 0.8% and 0.7% of patients, respectively in the aclidinium bromide 200 µg group and no patients in the placebo group. Diarrhoea and arthralgia were of moderate intensity in a higher proportion of patients in the aclidinium bromide 200 µg group (3.8% and 2.2%, respectively) than in the placebo group (1.5% and 1.0%, respectively).

TEAEs considered by the Investigator to be treatment-related were reported in 72 patients (12.0%) in the aclidinium bromide 200 µg group and 16 patients (7.8%) in the placebo group. Headache was the only TEAE reported to be treatment-related in more than 1% of patients in the aclidinium bromide group (reported in 16 patients [2.7%] in the aclidinium bromide 200 µg group and 3 patients [1.5%] in the placebo group).

Nine patients died after randomisation to the study, six (1.0%) in the aclidinium bromide group and three (1.5%) 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. Acute respiratory failure/respiratory failure was the only fatal SAE experienced by more than one patient in the study: 2 patients (0.3%), 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 similar proportion of patients treated with aclidinium bromide 200 µg (10.3%) and with placebo (11.3%). Fatal or lifethreatening COPD exacerbations were experienced by no patients in the aclidinium bromide 200 µg group and 2 patients (1.0%) in the placebo group. Severe COPD exacerbations (exacerbation requiring hospitalisation) which were part of the efficacy evaluation and not considered as SAEs unless they were fatal or life-threatening, were reported in 36 patients (6.1%) in the aclidinium bromide 200 µg group and 23 patients (11.4%) in the placebo group in the ITT population.

A total of 132 SAEs were reported (excluding non-fatal and non-life-threatening COPD exacerbations reported as part of the efficacy evaluations), 83 in the aclidinium bromide group and 49 in the placebo group. Pneumonia and myocardial infarction were the most commonly reported SAEs. Pneumonia or lobar pneumonia were reported by similar proportions of patients in the two treatment groups: 1.3% in the aclidinium bromide group and 1.5% in the placebo group. Myocardial infarction or acute myocardial infarction was reported in 1.2% of patients in the aclidinium bromide 200 µg group and 0.5% of patients in the placebo group. These were the only SAEs experienced by more than 1% of patients in the aclidinium bromide 200 µg treatment group. Only six patients, 4 (0.7%) treated with aclidinium bromide 200 µg and 2 (1.0%) treated with placebo experienced SAEs that were considered by the Investigator to be related to study treatment. In the aclidinium bromide 200 µg group, the treatment-related SAEs were: atrial fibrillation and sick sinus syndrome, atrial flutter, myocardial infarction and pneumonia. In the placebo group, the treatment-related SAEs were cerebellar infarction (which occurred after discontinuation of study treatment), headache and rash (headache and rash were experienced by the same patient).

The proportion of patients who experienced a TEAE that led to discontinuation was lower in the aclidinium bromide 200 µg group (4.8%) than in the placebo group (5.9%). Dyspnoea (reported in 2 patients [0.3%] in the aclidinium bromide 200 µg group and 1 patient [0.5%] in the placebo group), myocardial infarction (2 patients [0.3%] in the aclidinium bromide 200 µg group) and myalgia (2 patients [0.3%] in the aclidinium bromide 200 µg group) were the only TEAEs that led to discontinuation of more than one patient in either treatment group. Over half 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 TEAEs 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 urinary tract infection (4.8% in the aclidinium bromide group and 4.9% in the placebo group) and constipation (2.2% in the aclidinium bromide group and 2.0% in the placebo group) and these were reported in a similar proportion of patients in the two treatment groups. Dry eye (0.8%), atrial fibrillation (0.5%) and ventricular extrasystoles (0.5%) were 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. Dry mouth was reported by fewer patients in the aclidinium bromide group (2 patients [0.3%]) than in the placebo group (3 patients [1.5%]).

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 was lower in the aclidinium bromide 200 µg group than in the placebo group (6.8% versus 8.3%). The proportion of patients reporting Vascular Disorders was similar for aclidinium bromide 200 µg and placebo (5.7% versus 5.9%). Nine patients (7 patients [1.2%] in the aclidinium bromide 200 µg group and 2 patients [1.0%] in the placebo group) reported cerebrovascular accident/cerebral infarction/transient ischaemic attack.
Clinical laboratory test, vital sign and 12-lead ECG (including assessments of QTc intervals) data were similar to placebo and did not reveal any safety signals. Results of Holter monitoring performed in a small subgroup of patients were also similar in the two treatment groups.

CONCLUSIONS:

[redacted]

DATE OF REPORT:
19 October 2009