2 SYNOPSIS

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

Name of Finished Product:
N.A.

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

Volume:

Page:</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="3">Title of Study: EFFICACY AND SAFETY OF ACLIDINIUM BROMIDE AT TWO DOSE LEVELS V S PLACEBO WHEN A DMINISTERED TO PATIENTS WITH MODERATE TO SEVERE CHRONI C OBSTRUCTIVE PULMONARY DISEASE (COPD)</td></tr>
<tr><td colspan="3">Investigators:</td></tr>
<tr><td colspan="3">Study sites:</td></tr>
<tr><td colspan="3">Publication (reference):
None</td></tr>
<tr><td colspan="2">Studied period (years):
Date study initiated (first screening):
07 October 2009
Date study finalised (last patient last visit):
08 November 2010</td><td>Phase of development: IIIa</td></tr>
<tr><td colspan="3">Objectives:
• To assess the long term bronchodilator efficacy of inhaled aclidinium bromide 200 µg and 400 µg, both administered twice a day (BID), compared to placebo in COPD patients.
• To assess the benefits of aclidinium bromide 200 µg and 400 µg, both administered BID, compared to placebo, in disease-related health status, COPD symptoms and COPD exacerbations.
• To evaluate the long term safety and tolerability of inhaled aclidinium bromide 200 µg and 400 µg, both administered BID, compared to placebo in the same target population.</td></tr>
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Methodology:
This was a prospective, randomised, parallel group, placebo-controlled, double-blind, multinational and multicentre, clinical study of repeated BID administration of inhaled aclidinium bromide (200 µg or 400 µg) or matching placebo in patients with moderate to severe stable COPD.

The study consisted of a Screening Visit (Visit 1) conducted after signature of the informed consent form, where medical history, COPD severity stage, physical examination, and baseline laboratory, spirometry and electrocardiogram (ECG) assessments were conducted. Patients fulfilling inclusion/exclusion criteria at the time of the Screening Visit were entered into a run-in period of 14±3 days to assess patient's disease stability. Patients who still met entry criteria at Visit 2 were randomised according to a randomisation ratio of 1:1:1 to aclidinium bromide 200 µg BID, aclidinium bromide 400 µg BID or placebo BID for a period of 24 weeks.

During the double-blind treatment period, patients visited the site to assess clinical efficacy and safety on seven occasions (from Visit 2 to Visit 8) and after treatment completion; a follow-up contact was performed 2 weeks later. Patients completing the study were those patients on treatment up to Visit 8, even if they did not complete the follow-up contact.

A subgroup of 20% of patients at selected sites took part in a 12-hour serial spirometry study.

Number of patients (planned and analysed):
Planned: A total of 1,250 patients were planned to be screened to achieve a total number of 810 randomised patients; that is 270 patients to each of three treatment groups.
Screened: 1061
Randomised: 828
Completed study: 736
Completed treatment: 737
Evaluated for safety: 819
Evaluated for efficacy (Intent-to-Treat [ITT] analysis): 819
Evaluated for efficacy (Per Protocol [PP] analysis): 759
Evaluated for efficacy (serial spirometry sub-study): 191

Diagnosis and main criteria for inclusion:

- Adult male or female patients aged 40 years or older with stable moderate to severe COPD (as defined by Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines).
- Current or ex-smokers of ≥10 pack years.
- Post-salbutamol forced expiratory volume in one second (FEV_1) ≥30% and <80% of predicted normal value and FEV_1/forced vital capacity (FVC) <70%.
- No history or current diagnosis of asthma.
- No signs of COPD exacerbation within 6 weeks prior to the Screening Visit.
- No evidence of clinically significant respiratory and/or cardiovascular conditions or laboratory abnormalities.
- No contraindication to use of anticholinergic drugs such as known symptomatic prostatic hypertrophy, bladder neck obstruction, acute urinary retention or narrow-angle glaucoma.
- No previous participation in studies involving aclidinium bromide.

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Test product, dose and mode of administration, batch number, expiry date:
Name: Aclidinium bromide
Administration route: Oral inhalation by Genuair® multi-dose dry powder inhaler
Dosage form: Inhalation powder
Dose and regimen: 1 puff of 200 µg or 400 µg in the morning (08:00-10:00) and in the evening (20:00-22:00).
Batch numbers: DPI038-L3 (200 µg); DPI047-L4 (400 µg) Expiry date: May 2011

Duration of treatment:
The planned treatment duration for this study was 24 weeks.

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Placebo to aclidinium bromide
Administration route: Oral inhalation by Genuair® multi-dose dry powder inhaler
Dosage form: Inhalation powder
Dose and regimen: 1 puff of placebo in the morning (08:00-10:00) and in the evening (20:00-22:00).
Batch numbers: DPI031-L1 Expiry date: May 2011

Criteria for evaluation:

Efficacy:

Primary Efficacy Variable:

- Change from baseline in morning pre-dose (trough) FEV_1 at Week 24 for the European Union (EU) filing and Week 12 for the United States (US) filing.

Secondary Efficacy Variables:

- Change from baseline in peak FEV_1 at Week 24 for the EU filing and Week 12 for the US filing.
- Number (%) of patients achieving a clinically relevant improvement (≥1 unit) in Transition Dyspnoea Index (TDI) focal score at Week 24.
- Number (%) of patients achieving a clinically relevant improvement (≥4 units) compared to baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score at Week 24.

Additional Efficacy Variables (Main additional variables are listed):
Pulmonary function tests (FEV_1, FVC and inspiratory capacity [IC]) at trough, peak, and by time point including time points from 12-hour serial spirometry sub-study, normalised area under the curve (AUC) from 0 to 3 hours (AUC_{0-3h}); TDI focal score, SGRQ total score, EXACT (Exacerbations of Chronic Pulmonary Disease Tool) respiratory symptoms (E-RS) captured in the EXACT–Patient Reported Outcome (EXACT-PRO), night-time and morning COPD symptoms, daily use of relief medication, EQ-5D questionnaire, COPD exacerbations based on Health Resource Utilisation (electronic Case Report Form [eCRF]) and COPD exacerbations derived from EXACT-PRO.

Safety:
Safety assessments included eliciting of adverse events (AEs) and serious AEs (SAE), the monitoring of haematology, blood biochemistry, urine values and theophylline levels, physical examinations including blood pressure (BP) measurement and recording of 12-lead ECGs. Pregnancy tests were performed in females of child-bearing potential.

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Statistical methods:

All efficacy analyses were performed on the ITT population, using last-observation-carried-forward (LOCF) if missing value was present. For the primary variable, a mixed-effects model for repeated measures based on observed cases and a per-protocol analysis based on LOCF were performed as sensitivity analyses of the ITT population and missing data approach, respectively.

For the primary variable, Hochberg multiplicity adjustment was applied for the two aclidinium bromide doses versus placebo. Secondary efficacy variables were tested if the primary variable was significant in both treatment comparisons (aclidinium bromide 200 µg BID versus placebo and aclidinium bromide 400 µg BID versus placebo). The testing procedure for secondary variables was performed in a sequential manner as follows:

- Change from baseline in peak FEV_1 at Week 24 for EU filing and Week 12 for US filing;
- Percentage of patients achieving a clinically relevant improvement (≥1 unit) in TDI focal score at Week 24; and
- Percentage of patients achieving a clinically relevant improvement (≥4 units) compared to baseline in the SGRQ total score at Week 24.

The change from baseline in peak FEV_1 was examined first applying the Hochberg procedure at the 5% level of significance. The process for moving in the sequential procedure was the following: testing continued with the next variable if at least one null hypothesis of the two treatment comparisons was rejected, otherwise the sequential testing procedures stopped for inferential purposes. If both doses (treatment comparisons) were significant then Hochberg's procedure was used to correct for multiple treatment comparisons; otherwise no correction was applied and the discarded dose could not be inferentially tested anymore in any of the remaining secondary variables in the sequence.

The primary efficacy variable (change from baseline in morning pre-dose FEV_1) and secondary variable (change from baseline in peak FEV_1) were analysed by means of an analysis of covariance (ANCOVA) model which included sex and treatment group as factors along with baseline FEV_1 value and age as covariates. The dichotomous secondary variables were analysed by means of logistic regression models with baseline, age, sex, and treatment as explanatory variables.

Safety outcomes were analysed on the Safety population.

Safety outcomes (AEs, laboratory parameters, vital signs, and 12-lead ECG) were summarised by means of descriptive statistics across time by treatment group. For the last three safety outcomes, potentially clinically significant post-baseline values were tabulated by treatment group.

SUMMARY – CONCLUSIONS

Disposition: A total of 1061 patients were screened, of whom 828 patients were assessed as eligible and were randomised into the study. Overall, 89.0% of randomised patients completed the treatment; 84.1% of patients in the placebo group, and 90.4% and 92.6% of patients in the aclidinium bromide 200 µg and 400 µg groups, respectively. A higher percentage of patients were discontinued from the placebo group (14.9%), than from the aclidinium bromide 200 µg group (8.6%), and aclidinium bromide 400 µg group (6.3%).

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Number of patients

	Placebo	AB 200 µg BID	AB 400 µg BID	Total
	N=276	N=280	N=272	N=828
	n (%)	n (%)	n (%)	n (%)
Screened	—	—	—	1061
Safety	273 (98.9)	277 (98.9)	269 (98.9)	819 (98.9)
Intent-to-Treat	273 (98.9)	277 (98.9)	269 (98.9)	819 (98.9)
Per Protocol	248 (89.9)	261 (93.2)	250 (91.9)	759 (91.7)

AB=aclidinium bromide; BID=twice daily; N=total number of randomised patients, n=number of patients in the specified category.
Screened Population included all patients who signed a written informed consent form and received a screening number.
Randomised Population included all patients in the Screened Population who were randomised to a treatment group.
Safety Population included all patients in the Randomised Population who took at least 1 dose of double-blind treatment.
ITT Population included all patients in the Safety Population who had a baseline and at least 1 postbaseline FEV_1 assessment.
Per-Protocol Population included all patients who met the main inclusion/exclusion criteria, attained a sufficient compliance to the treatment received, and did not present with relevant protocol deviations that could interfere with the efficacy assessments.

Demographic and Baseline Characteristics: The treatment groups were comparable with respect to mean demographic and baseline data.

Efficacy Results:

Primary Endpoint: At baseline the morning pre-dose (trough) FEV_1 was 1.500 L in the placebo group, and 1.514 L and 1.508 L in the aclidinium bromide 200 µg and 400 µg groups, respectively. A statistically significant greater adjusted mean change from baseline morning pre-dose (trough) FEV_1 was observed for aclidinium bromide 200 µg (0.077 L; p-value=0.0001) and aclidinium bromide 400 µg (0.105 L; p-value<0.0001) groups compared to placebo after 12 weeks of treatment. At Week 24, a statistically significant greater adjusted mean change from baseline morning pre-dose (trough) FEV_1 was observed for aclidinium bromide 200 µg (0.099 L; p-value<0.0001) and aclidinium bromide 400 µg (0.128 L; p-value<0.0001) groups compared to placebo. The bronchodilation provided by aclidinium bromide 400 µg was numerically greater than that provided by aclidinium bromide 200 µg at Week 12 (0.028 L; p-value=0.1671) and at Week 24 (0.029 L; p-value=0.1868) in the ITT population. Similar results were observed for the mixed model for repeated measures (MMRM) analysis and for comparisons in the PP population at Weeks 12 and 24, confirming the robustness of comparisons.

Secondary Endpoints:

Change from baseline in peak FEV_1: A statistically significant greater adjusted mean change from baseline in peak FEV_1 was observed for aclidinium bromide 200 µg (0.182 L; p-value<0.0001) and aclidinium bromide 400 µg (0.191 L; p-value<0.0001) groups compared to placebo after 12 weeks of treatment. Similarly, a statistically significant adjusted mean change from baseline in peak FEV_1 was observed for aclidinium bromide 200 µg (0.185 L; p-value<0.0001) and aclidinium bromide 400 µg (0.209 L; p-value<0.0001) groups compared to placebo after 24 weeks of treatment. The peak FEV_1 achieved in the aclidinium bromide 400 µg group was numerically greater than that achieved in the aclidinium bromide 200 µg at Week 24 (0.025 L; p-value=0.2919, ITT population). Similar results were

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observed for comparisons in the PP population at Weeks 12 and 24, confirming the robustness of comparisons.

Clinically relevant improvement (≥1 unit) in TDI focal score at Week 24: A statistically significant greater percentage of patients achieved a clinically relevant improvement in the TDI focal score in the aclidinium bromide 200 µg group (53.3% patients; odds ratio=1.47; p-value=0.0317) and the aclidinium bromide 400 µg group (56.9% patients; odds ratio=1.68; p-value=0.0038) compared to the placebo group (45.5% patients). These significant differences were already observed at Week 4 (odds ratio 1.46, p-value=0.0373 and odds ratio 1.89, p-value=0.0004 for the aclidinium bromide 200 µg and 400 µg group, respectively) and were maintained at Week 12. The percentage of patients with clinically relevant improvement in TDI focal score in the aclidinium bromide 400 µg group was always numerically larger than in the aclidinium bromide 200 µg group.

Clinically relevant improvement (≥4 units) in SGRQ total score at Week 24: A statistically significant greater percentage of patients achieved a clinically relevant improvement (≥ 4 units) in the SGRQ total score in the aclidinium bromide 200 µg group (54.9% patients; odds ratio=1.88; p-value=0.0004) and the aclidinium bromide 400 µg group (54.3% patients; odds ratio=1.77; p-value=0.0014) compared to the placebo group (39.5% patients). Adjusted treatment differences versus placebo were also observed at Week 12 (odds ratio 1.57, p-value=0.0119 and odds ratio 1.91, p-value=0.0004 for the aclidinium bromide 200 µg and 400 µg group, respectively).

Taking into account the multiplicity adjustment procedure, both aclidinium bromide 200 µg and 400 µg showed a significant effect compared to placebo for the primary and the secondary endpoints.

Additional Efficacy Variables:

All analyses of additional efficacy spirometric parameters based on FEV_1, FVC and IC were statistically significant for both the aclidinium bromide 200 µg and 400 µg groups versus placebo at Day 1 (where assessed), Weeks 1, 4, 8, 12, 18 and 24 (all time points). Based on these parameters, the aclidinium bromide 400 µg group was always numerically greater than the aclidinium bromide 200 µg group except for peak FVC at Week 12. The adjusted mean change from baseline in spirometry variables for aclidinium bromide 200 µg and 400 µg versus placebo at Weeks 12 and 24 is presented in the table below:

Adjusted mean change from baseline in spirometric efficacy parameters for aclidinium bromide 200 µg and 400 µg versus placebo

Endpoints		Adjusted Mean Differences (L) of Aclidinium Bromide 200 µg BID versus Placebo			Adjusted Mean Differences (L) of Aclidinium Bromide 400 µg BID versus Placebo		
		Range: Day 1 to Week 24	Week 12	Week 24	Range: Day 1 to Week 24	Week 12	Week 24
FEV_1	Trough	0.077, 0.105	0.077	0.099	0.105, 0.140	0.105	0.128
	AUC_{0-3h}	0.155, 0.183	0.170	0.183	0.180, 0.210	0.187	0.210
	Peak	0.161, 0.185	0.182	0.185	0.187, 0.211	0.191	0.209
FVC	Trough	0.119, 0.159	0.119	0.159	0.184, 0.224	0.184	0.224
	Peak	0.242, 0.276	0.263	0.262	0.257, 0.295	0.257	0.292

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IC	Trough	0.057, 0.070	0.070	0.068	0.109, 0.133	0.133	0.119

AUC_{0-3h}=area under the curve from 0 to 3 hours immediately after morning IMP administration; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; IC=inspiratory capacity.

All treatment differences were statistically significant (p-value≤0.0001 for FEV_1, p-value<0.001 for FVC, and p-value<0.05 for IC) compared to placebo.

In the 12-hour sub-study, bronchodilation provided by aclidinium bromide 200 µg and 400 µg was numerically greater and generally statistically significant superior to that provided by placebo over the entire 12-hour period on Day 1 and Weeks 12 and 24.

TDI focal score: At week 24, the placebo adjusted mean change from baseline in TDI focal score was statistically significant in the aclidinium bromide 200 µg group (0.60 unit, p-value =0.0387) and in the aclidinium bromide 400 µg group (1.00 unit, p-value=0.0006). The treatment effect in the aclidinium bromide 400 µg group was already present at Weeks 4 and 12 (approximately 0.90 units, p-value<0.010 for both weeks). The adjusted mean difference in the aclidinium bromide 200 µg group was 0.65 unit (p-value=0.0073) at Week 4 and 0.36 unit (p-value=0.1807) at Week 12.

SGRQ total score: At Week 24, the placebo adjusted mean change from baseline in SGRQ total score was -3.57 (p-value=0.0009) and -4.29 (p-value<0.0001) for the aclidinium bromide 200 µg and 400 µg groups respectively. The treatment effect in the aclidinium bromide 400 µg group was already present at Weeks 4 and 12 (-2.31 at Week 4 and -3.97 at Week 12, both p-values<0.010). The treatment effect in the aclidinium bromide 200 µg group was -0.56 (p-value=0.5020) at Week 4 and -3.06 (p-value=0.0015) at Week 12.

E-RS Total Score, Breathlessness, Chest and Cough and Sputum domain scores: Compared to placebo, aclidinium bromide 200 µg and aclidinium bromide 400 µg decreased the E-RS Total score assessed over the study period by 1.3 units (p-value=0.0002) and 2 units (p-value<0.0001), respectively. Aclidinium bromide 200 µg and aclidinium bromide 400 µg decreased the Cough and Sputum score by 0.21 units (p-value=0.0322) and 0.44 units (p-value<0.0001), respectively: The decreases in Breathlessness score were equal to 0.80 units (p-value<0.0001) and 1.05 units (p-value<0.0001) for the aclidinium bromide 200 µg and aclidinium bromide 400 µg groups, respectively. The decreases in Chest Symptom score were equal to 0.33 units (p-value<0.0031) and 0.52 units (p-value<0.0001) for the aclidinium bromide 200 µg and aclidinium bromide 400 µg groups, respectively.

Night-time and morning symptoms: Compared to placebo, aclidinium bromide 200 µg and aclidinium bromide 400 µg decreased the percentage of days with any morning COPD symptoms over the study period by 5.0% (p-value=0.0013) and 5.8% (p-value=0.0002), respectively. Compared to placebo, aclidinium bromide 400 µg decreased the percentage of days with any night-time COPD symptoms over the study period by 7.2% (p-value=0.0005); the decrease in the aclidinium bromide 200 µg was borderline significant (4.0%, p-value=0.0517). Morning and night-time lung condition significantly improved in both aclidinium bromide doses compared to placebo (p-value<0.05) and morning time disturbance significantly decreased in the aclidinium bromide 400 µg group (p-value=0.0011). No significant improvement in sleep disturbance was detected in either of the aclidinium bromide groups.

Relief Medication: Assessed over the study period, the placebo adjusted mean reduction from baseline in the daily use of relief medication was statistically significant for the aclidinium bromide 400 µg group (0.95 puffs reduction, p-value=0.0045), the placebo adjusted mean reduction in the aclidinium bromide 200 µg group was borderline significant (0.61 puffs reduction, p-value=0.0663). When assessed as

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change from baseline in the percentage of full days without relief medication over the study period, the adjusted mean difference between the aclidinium bromide 200 µg group and placebo was of 11.0% (p-value=0.0003) and the adjusted mean difference between the aclidinium bromide 400 µg group and placebo was 11.1% (p-value=0.0003).

EQ-5D questionnaire: The adjusted mean change from baseline in EQ-5D weighted score for the aclidinium bromide 400 µg group compared to the placebo group was statistically significant at Week 24 (0.03, p-value=0.0414); no other effect was statistically significant for this variable. The adjusted mean change from baseline in EQ-5D VAS score was also statistically significant at Week 24 (3.13, p-value=0.0047) for the 400 µg group.

COPD Exacerbations based on Health Resource Utilisation (eCRF): A numerically smaller percentage of patients experienced at least one COPD exacerbation (mild, moderate, or severe) in the aclidinium bromide 200 µg group (15.9%) and in the aclidinium bromide 400 µg group (14.1%) than in the placebo group (20.5%). Compared to placebo, the percent reduction in odds was 27% (p-value=0.1676) and 36% (p-value=0.0513) for the aclidinium bromide 200 µg and 400 µg doses, respectively. When assessed as exacerbation rates per patient-year, the percent reduction was approximately 30% (p-value<0.05 for both doses).

A numerically smaller percentage of patients experienced at least one moderate or severe COPD exacerbation in the aclidinium bromide 200 µg group (13.0%) and aclidinium bromide 400 µg group (12.3%) than in the placebo group (16.1%). Compared to placebo, the percent reduction in odds was 22% (p-value=0.3173) and 27% (p-value=0.2063) in the 200 µg and 400 µg dose, respectively. When assessed as exacerbation rates per patient-year, the percent reduction was 26% (p-value=0.0845) and 28% (p-value=0.0629) for the 200 µg and 400 µg dose, respectively.

Exacerbations based on EXACT-PRO questionnaire. A numerically smaller percentage of patients experienced at least one COPD exacerbation in the aclidinium bromide 200 µg group (30.0%) and aclidinium bromide 400 µg group (29.0%) than in the placebo group (36.6%). Compared to placebo, the percent reduction in odds was 25% (p-value=0.1067) and 29% (p-value=0.0644) for the 200 µg and 400 µg dose, respectively. When assessed as exacerbation rates per patient-year, the percent reduction was approximately 30% (p-value<0.05 for both doses).

Safety Results:

Adverse Events:
A total of 1199 treatment-emergent adverse events (TEAEs) were reported for 55.1% of patients. Overall, treatment-emergent SAEs were reported for 5.0% of patients and TEAEs leading to withdrawal were reported for 3.7% patients, which were similar between treatment groups. One fatal TEAE was reported in each of the treatment groups. No treatment- or dose-related trend was observed in the number of patients with at least one TEAE, number of patients with treatment-emergent SAEs, or the number of patients with TEAEs leading to withdrawal.

The majority of TEAEs were mild (35% of patients) or moderate (36% of patients). Most TEAEs were not related to the study medication (only 6% of patients reported related events). In these respects, treatment groups were similar. The most frequently occurring AE in all treatment groups was COPD (exacerbation), although the incidence was lower in the aclidinium bromide groups than in the placebo group: 20.5% in placebo, 15.9% in aclidinium 200 µg and 14.1% in aclidinium bromide 400 µg. Other

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TEAEs reported at incidences >10% were headache and nasopharyngitis.

Treatment-emergent AEs reported in 2% or more of patients and reported at a higher incidence in both active treatment groups compared to the placebo group were headache, nasopharyngitis, diarrhoea, cough and toothache. Treatment groups were comparable with respect to the incidence of severe TEAEs (reported in 8.3% of patients overall), except for severe events of COPD (exacerbation), which were reported in a higher number of patients in the placebo group (10 [3.7%] patients) than in the 200 µg and 400 µg aclidinium bromide groups (3 [1.1%] patients and 2 [0.7%] patients, respectively).

Overall, treatment-emergent SAEs were reported for 5.0% patients. In general, the number of SAEs and number of patients with SAEs were similar between the treatment groups. Overall, the most common SAE by PT was COPD (exacerbation) (16 events in 1.8% of patients).

The incidence of cardiac events overall was low (33 events in 28 [3.4%] of patients). A higher incidence of cardiac events was noted in the active treatment groups (4.3% and 4.1% in the aclidinium bromide 200 µg and 400 µg groups, respectively), than in the placebo group (1.8% of patients), with cardiac events leading to discontinuation being reported in the active treatment groups only (3 [1.1%] and 1 [0.4%] of patients in the aclidinium bromide 200 µg and 400 µg groups, respectively). One patient in the aclidinium bromide 400 µg group had a severe cerebral haemorrhage 4 days after the last dose of study medication. The patient recovered from the event with sequelae.

Three (treatment-emergent) deaths; one in each treatment group were reported during the treatment period (myocardial infarction in one patient in the aclidinium bromide 200 µg group, cardiac failure acute in one patient in the aclidinium bromide 400 µg group, and road traffic accident in one patient in the placebo group), none of which were considered related to the study medication. Both patients in the active treatment groups who died due to cardiac events, had a previously history of cardiovascular disorders.

The overall incidence of potential anticholinergic TEAEs were low. There were no pregnancies during the study.

Safety laboratory results:
Changes from baseline in mean values for all haematology and biochemistry parameters and urine parameters were generally small, with no treatment-related or dose-related changes observed at endpoint (Week 24). No treatment- or dose-related trends were observed in any notable abnormalities, and notable abnormalities associated with AEs were observed in low number of subjects.

Vital signs (blood pressure):
The mean changes in mean values of SBP and DBP values were generally small, with no treatment- or dose-related trends observed over time. Notable changes from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were observed in less than 1% of patients, with similar numbers of subjects having notable increases and decreases from baseline.

12-lead electrocardiogram:
The mean changes from baseline in 12-lead ECG parameters were generally small, with no apparent treatment- or dose-related trend in the change from baseline in any parameters, at any time point post-dose.

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CONCLUSIONS: **DATE OF REPORT:** Final, 12 April 2011		